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Protein Requirement in Critical Illness

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Abstract

How much protein do critically ill patients require? For the many decades that nutritional support has been used there was a broad consensus that critically ill patients need much more protein than required for normal health. Now, however, some clinical investigators recommend limiting all macronutrient provision during the early phase of critical illness. How did these conflicting recommendations emerge? Which of them is correct? This review explains the longstanding recommendation for generous protein provision in critical illness, analyzes the clinical trials now being claimed to refute it, and concludes with suggestions for clinical investigation and practice.

Key Words

Bias

Calories

Critical care

Critical illness

Energy

Enteral Nutrition

Nutritional support

Nutrition requirements

Parenteral nutrition

Protein requirements

Introduction

How much protein do critically ill patients require? For most of the more than 40 years that effective nutritional support therapy has been used there was a broad consensus that critically ill patients require much more protein than people in normal health. Now, however, some clinical investigators recommend that we not interfere with the early catabolic phase of critical illness by administering large amounts of any macronutrient (Casaer and van den Berghe 2014). As one of them (Rice 2013) put it, “Nutrition may be another treatment in the intensive care unit (ICU) where less is more.” How did these conflicting recommendations emerge?

Nutritional pathophysiology of critical illness

Let's start by reviewing the original recommendation that critically ill patients benefit from the early provision of large amounts of protein. The body cell mass (BCM) consists of a peripheral compartment, skeletal muscle, which accounts for ~ 80% of the BCM of a healthy young adult, and a central compartment (splanchnic and other organs, blood cells, immunocytes and plasma proteins) which makes up the rest. Severe tissue injury precipitates a systemic inflammatory storm that dramatically increases endogenous muscle protein catabolism, releasing amino acids into the circulation for delivery to the rapidly turning over central compartment for protein synthesis at sites of tissue injury and elsewhere to regulate inflammatory and immune responses (Hoffer and Bistrian 2012). Left unchecked, skeletal muscle catabolism can rapidly lead to severe muscle atrophy and deplete the body of the amino acids it needs for wound healing and immune regulation. These considerations strongly predict that generous protein provision can

improve clinical outcomes in protein-catabolic states. The recommended protein intake for normal people is 0.8 g/kg per day, whereas the commonest official recommendation in critical illness is 1.5g/kg normal dry body weight per day (Ziegler 2009; Hoffer and Bistrian 2013a). A large amount of metabolic data, and some preliminary clinical trial evidence, suggests that the early provision of 1.5 - 2.5 g protein/kg per day could be optimal (Hoffer and Bistrian 2012; Hoffer and Bistrian 2013b; Hoffer and Bistrian 2014). No high-quality clinical trials have been carried out to identify what the requirement actually is (Ziegler 2009; Hoffer and Bistrian 2012; Hoffer and Bistrian 2013a).

The problem with recommendations based on recent clinical trials

The recommendation that “less nutrition is better” emerged from recent randomized clinical trials (RCTs) of early nutritional interventions in the ICU (Rice 2013; Casaer and van den Berghe 2014; Preiser et al. 2015). An analysis of five of them led to the conclusion that supplemental nutrition does not improve clinical outcomes, and a sixth RCT published shortly afterward was consistent with this view (Harvey et al. 2014).

Did these RCTs disprove the hypothesis that generous protein provision is beneficial in the ICU? Actually they did not, because they are flawed by a serious design problem: *they focused on the wrong nutrient*. All therapeutic trials – especially nutritional ones, given their variety and complexity – should be founded on physiologically sound premises (Tonelli et al. 2012; Hoffer and Bistrian 2013a). The physiologically implausible premise of all the RCTs whose results are being cited to justify the recommendation that “less nutrition is better in the ICU” is that calories

are the only important macronutrient in critical illness. *All of these clinical trials were calorie interventions.*

I calculated the amounts of energy and protein provided in six recent, large-enrollment RCTs: the EDEN trial (n = 1000) (The National Heart Lung and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network. 2012), the Early PN trial (n = 1372) (Doig et al. 2013), the EpaNIC trial (n = 4640) (Casaer et al. 2011), the SPN trial (n = 305) (Heidegger et al. 2013) the TICACOS trial (n = 130) (Singer et al. 2011) and the CALORIES trial (n = 2388) (Harvey et al. 2014). Five of these RCTs were carried out to test the benefits of early calorie supplementation in critical illness; the sixth (Harvey et al. 2014) tested for differences in clinical outcomes when equivalent nutrition was provided either as enteral nutrition (EN) or parenteral nutrition (PN). The RCTs were successful in the sense that the early calorie supplementation groups in five of the RCTs did receive significantly more calories: 1300 versus 400 kcal/day (The National Heart Lung and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network. 2012); 1400 versus 800 (Doig et al. 2013); 1900 versus 700 (Casaer et al. 2011); 2000 versus 1500 (Heidegger et al. 2013); and 2100 versus 1500 (Singer et al. 2011); and calorie provision was equivalent (1400 versus 1400) in the PN versus EN trial (Harvey et al. 2014). These articles only inconsistently mention protein, but information about it can be calculated by studying the original data, figures, and supporting documents. Calculated either as average daily protein provision rate during protocol days 1 through 6 or 7, or as the maximum protein dose administered on any day (usually the final day of the protocol), protein provision was grossly deficient in the conventional care groups of every trial, and – important to appreciate – it was nearly as deficient in the intervention groups of every trial, usually failing to attain even

half the commonest formal recommendation for critically ill patients (Ziegler 2009), except for one trial (Heidegger et al. 2013). Thus, the rates of protein provision in the conventional care and supplemental nutrition groups of these RCTs were approximately as follows (as a percentage of the commonest formal recommendation for protein provision in critical illness, 1.5 g/kg per day (Ziegler 2009)): 15% versus 45% (The National Heart Lung and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network. 2012); 29% versus 45% (Doig et al. 2013); 7% versus 47% (Casaer et al. 2011); 53% versus 80% (Heidegger et al. 2013); 43% versus 63% (Singer et al. 2011); and 53% versus 41% (Harvey et al. 2014). Actually, one of the trials indicated some clinical benefit from the intervention (Chertow and O'Grady 2013) – it was the one that provided the most protein, even though the amount provided was still inadequate (Heidegger et al. 2013). These recent RCTs plainly demonstrate that calorie supplemented, protein-deficient nutrition does not improve clinical outcomes. They do not support the recommendation against early nutritional interventions *of any kind*.

Cognitive biases

Why have so many RCTs been carried out to test the hypothesis that critically ill people need more *calories*, knowing as we do that 95% of them already have adequate or excessive calories stored in their adipose tissue, but not more *protein*, knowing as we do that the majority of them receive drastically less protein than has long been formally recommended? The scientific reasoning used to justify these trials was explained as follows (Casaer and van den Berghe 2014). EN is currently strongly preferred to PN, but in practice EN advances so slowly that it falls short of recommended goals for most ICU patients. Since critical illness increases energy expenditure

and negative energy balance promotes muscle wasting, providing more calories to critically ill patients could spare their muscle mass. Furthermore, observational studies have linked worse clinical outcomes to more deficient calorie provision. In conclusion, this reasoning goes, the provision of more calories to critically ill patients could improve their clinical outcomes.

Both arguments are incorrect. While it's true that energy expenditure increases roughly proportionately to the intensity of the protein-catabolic response, calorie provision that exceeds ~50% of energy expenditure improves nitrogen balance very little further (Dickerson 2005), especially in critical illness (Behrendt et al. 1990; Frankenfield et al. 1997; Japur et al. 2010), even as it increases the risk of hyperglycemia and other adverse outcomes. Some level of non-protein calorie provision may indeed be important in the early phase of critical illness, but it is unlikely that total calorie provision has to exceed 50 to 70% of energy expenditure in the early phase of critical illness as long as protein provision is increased to compensate for the mild reduction in the efficiency of protein retention induced by the hypocaloric state (Hoffer and Bistrian 2012; Hoffer and Bistrian 2013a). The existing biological data actually suggest that high energy, protein-deficient nutrition of the kind that was tested in these RCTs is harmful (Moldawer et al. 1978; Moldawer et al. 1981; Sandstrom et al. 1993).

The second argument is simply misconstrued. It's true that there's a relationship between low rates of calorie provision and poor clinical outcomes in the ICU, but calorie-deficient diets are invariably even more seriously *protein* deficient. Leaving aside the problem of causal inference that always confounds observational studies, the evidence cited by these clinical trial experts to

justify the physiologically implausible claim that critically ill patients don't get enough *calories* is much more plausibly interpreted as evidence that they don't get enough *protein*.

In response to such criticism, a post hoc analysis was carried out that suggested the possibility that patients who received less protein had better clinical outcomes (Preiser et al. 2015). Post hoc analyses of this kind are notoriously untrustworthy, and they are particularly unreliable in this situation, because the protein intakes that were analyzed are well below a plausible threshold for detecting a physiological effect.

How did such simplistically flawed scientific reasoning ever gain currency? I suggest two explanations: the first is a complacent ignorance of the details of nutritional physiology, perhaps justified by the misconception that since physiological insight is not “evidence” it can be disregarded when designing clinical trials (Tonelli et al. 2012; Hoffer and Bistrian 2013a); the second is cognitive bias. One such bias arises from a process of stereotypical thinking that regards “calories” as a synonym for “nutrition.” Even a casual reading of the modern critical care literature turns up nearly countless examples of this conflation bias. For example, three of the six RCTs that were analyzed for this article formally describe themselves as “calories” trials (Singer et al. 2011; Heidegger et al. 2013; Harvey et al. 2014), but they are now being interpreted as “nutrition” trials. When someone starts thinking that “calories” and “nutrition” mean the same thing, it's easy to forget about the other components of a nutritional regimen.

A second bias, known as the streetlight effect, arises from an emotional disinclination to acknowledge any variable that's not in plain view (Lernmark 2015). In the early years of

nutritional support, PN was enriched with high-energy dextrose in a misguided effort to boost the anabolic effect of the infused amino acids. As the toxicity of calorie overfeeding became evident and EN products and procedures improved, EN became the standard of care. Unfortunately, it went unnoticed that the enteral products that have replaced PN are designed for normal people and hence are protein-deficient for critically ill patients. The current situation requires the treating team to choose between two adverse consequences: severe protein deficiency during the first 7 to 10 days in the ICU, or toxic calorie overfeeding as the cost of providing a suitable amount of protein. Because of the streetlight bias, these physiologically irrational EN products represent the current standard of care in modern ICUs, against which other, equally irrational regimens were compared in recent RCTs (Hoffer and Bistrian 2013a; Hoffer and Bistrian 2014).

Need for better clinical research and practice

Fortunately, the disappointing results of these several large, calorie-focused RCTs appears to have increased awareness of the complete absence of high quality evidence addressing the truly important question of protein requirements (Preiser et al. 2015). One hopes to see, in the near future, the publication of physiologically literate RCTs of nutritional regimens that provide early and suitably generous amounts of protein to critically ill protein-catabolic patients, such as 1.5 to 2.0 g protein – equivalent to 1.8 to 2.4 g mixed free amino acids (Hoffer 2011) – per kg of normalized dry body weight per day without calorie overfeeding (Verbruggen et al. 2011; Hoffer and Bistrian 2012; Hoffer and Bistrian 2013a; Singer and Cohen 2013; Choban et al. 2013; Plank 2013; Singer et al. 2014).

The design of these trials will benefit from insights derived from the study of the obese critically ill patients who make up a large proportion of modern ICU patients. Current guidelines recommend providing obese critically ill patients with 2.0-2.5 g protein/kg normalized dry body weight per day while limiting energy provision to 50-70% of energy expenditure (Choban et al. 2013). These well-reasoned recommendations should be rigorously tested, not only in obese patients, but in all protein-catabolic patients whose body fat store is reasonably adequate (Hoffer and Bistrian 2015).

Conclusion

We have more than enough information from sophisticated RCTs that tested the implausible hypothesis that critically ill patients need more calories but not much protein, with predictably negative results. We may safely conclude that less “calories” is better in the ICU. We may not conclude that less “nutrition” is better. The correct amount of protein to provide critically ill patients remains an urgent, unanswered question.

Take home points

1. For many decades there was a broad consensus that critically ill patients need much more protein than required for normal health. Some clinical investigators now recommend that all macronutrient provision be restricted during the early phase of critical illness.

2. The view that protein requirements are increased in protein-catabolic critical illness is supported by a vast amount of consistent physiological and metabolic research, but no high quality randomized clinical trial (RCT) has ever been carried out to verify whether providing the amounts of protein recommended actually improves clinical outcomes. Several recent large RCTs of intensified nutritional support in the early phase of critical illness now show no evidence of benefit from such interventions.

3. These RCTs have been described by their authors as nutritional interventions, but in reality they were calorie interventions. Except for one of them, the amounts of protein provided were well below a plausible threshold for detecting any clinical benefit. The recommendation that all macronutrients (including protein) be restricted in critical illness is not justified by the results of these clinical trials.

4. Many RCTs have now tested the biologically implausible hypothesis that critically ill patients – most of whom already have ample or more than ample fat stores – need more calories, but no clinical trials have been carried out to test the extremely plausible hypothesis that protein-catabolic patients – most of whom are severely protein deprived – would benefit from generous protein provision. There is an urgent need for such clinical trials.

Conflict of interest statement

The author declares that there are no conflicts of interest.

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References

Behrendt, W., Bogatz, V., and Giani, G. 1990. The influence of posttraumatic parenteral calorie and nitrogen supply upon the cumulative nitrogen balance. *Infusionstherapie* **17**: 32-39.

Casaer, M.P., Mesotten, D., Hermans, G., Wouters, P.J., Schetz, M., Meyfroidt, G., Van Cromphaut, S., Ingels, C., Meersseman, P., Muller, J., Vlasselaers, D., Debaveye, Y., Desmet, L., Dubois, J., Van Assche, A., Vanderheyden, S., Wilmer, A., and van den Berghe, G. 2011. Early versus late parenteral nutrition in critically ill adults. *N. Engl. J. Med.* **365**: 506-517.

Casaer, M.P. and van den Berghe, G. 2014. Nutrition in the acute phase of critical illness. *N. Engl. J. Med.* **370**: 1227-1236.

Chertow, D.S. and O'Grady, N.P. 2013. ACP Journal Club: in critically ill adults, supplemental parenteral nutrition reduced nosocomial infections. *Ann. Intern. Med.* **158**: JC3.

Choban, P., Dickerson, R., Malone, A., Worthington, P., Compher, C., and American Society for Parenteral and Enteral Nutrition 2013. A.S.P.E.N. Clinical guidelines: nutrition support of hospitalized adult patients with obesity. *JPEN J. Parenter. Enteral Nutr.* **37**: 714-744.

Dickerson, R.N. 2005. Hypocaloric feeding of obese patients in the intensive care unit. *Curr. Opin. Clin. Nutr. Metab. Care* **8**: 189-196.

Doig, G.S., Simpson, F., Sweetman, E.A., Finfer, S.R., Cooper, D.J., Heighes, P.T., Davies, A.R., O'Leary, M., Solano, T., Peake, S., and Early PN Investigators of the ANZICS Clinical Trials Group 2013. Early parenteral nutrition in critically ill patients with short-term relative contraindications to early enteral nutrition: a randomized controlled trial. *JAMA* **309**: 2130-2138.

Frankenfield, D.C., Smith, J.S., and Cooney, R.N. 1997. Accelerated nitrogen loss after traumatic injury is not attenuated by achievement of energy balance. *JPEN J. Parenter. Enteral Nutr.* **21**: 324-329.

Harvey, S.E., Parrott, F., Harrison, D.A., Bear, D.E., Segaran, E., Beale, R., Bellingan, G., Leonard, R., Mythen, M.G., Rowan, K.M., and CALORIES, T., I 2014. Trial of the route of early nutritional support in critically ill adults. *N. Engl. J. Med.* **371**: 1673-1684.

Heidegger, C.P., Berger, M.M., Graf, S., Zingg, W., Darmon, P., Costanza, M.C., Thibault, R., and Pichard, C. 2013. Optimisation of energy provision with supplemental parenteral nutrition in critically ill patients: a randomised controlled clinical trial. *Lancet* **381**: 385-393.

Hoffer, L.J. 2011. How much protein do parenteral amino acid mixtures provide? *Am. J. Clin. Nutr.* **94**: 1396-1398.

Hoffer, L.J. and Bistran, B.R. 2012. Appropriate protein provision in critical illness: a systematic and narrative review. *Am. J. Clin. Nutr.* **96**: 591-600.

Hoffer, L.J. and Bistrian, B.R. 2013a. Why critically ill patients are protein deprived. JPEN J. Parenter. Enteral Nutr. **37**: 300-309.

Hoffer, L.J. and Bistrian, B.R. 2013b. Why critically ill patients are protein deprived. JPEN J. Parenter. Enteral Nutr. **37**: 441.

Hoffer, L.J. and Bistrian, B.R. 2014. What is the best nutritional support for critically ill patients? Hepatobiliary Surg. Nutr. **3**: 172-174.

Hoffer, L.J. and Bistrian, B.R. 2015. Energy deficit is clinically relevant for critically ill patients: no. Intensive Care Med. **41**: 339-341.

Japur, C.C., Monteiro, J.P., Marchini, J.S., Garcia, R.W., and Basile-Filho, A. 2010. Can an adequate energy intake be able to reverse the negative nitrogen balance in mechanically ventilated critically ill patients? J. Crit. Care **25**: 445-450.

Lernmark, A. 2015. The streetlight effect – is there light at the end of the tunnel? Diabetes **64**: 1105-1107.

Moldawer, L.L., Bistrian, B.R., and Blackburn, G.L. 1981. Factors determining the preservation of protein status during dietary protein deprivation. J. Nutr. **111**: 1287-1296.

Moldawer, L.L., Tseric, M.S., Flatt, J.P., Bistrian, B.R., and Blackburn, G.L. 1978. A protein sparing model in the rat during hypocaloric feeding: factors determining preservation of visceral protein function. J. Surg. Res. **25**: 424-432.

Plank, L.D. 2013. Protein for the critically ill patient – what and when? Eur. J. Clin. Nutr. **67**: 565-568.

Preiser, J.C., van Zanten, A.R., Berger, M.M., Biolo, G., Casaer, M.P., Doig, G.S., Griffiths, R.D., Heyland, D.K., Hiesmayr, M., Iapichino, G., Laviano, A., Pichard, C., Singer, P., van den Berghe, G., Wernerman, J., Wischmeyer, P., and Vincent, J.L. 2015. Metabolic and nutritional support of critically ill patients: consensus and controversies. *Crit Care* 2015;19:35.

Rice, T.W. 2013. Gluttony in the intensive care unit: time to push back from the consensus table. *Am. J. Resp. Crit. Care Med.* **187**: 223-224.

Sandstrom, R., Drott, C., Hyltander, A., Arfvidsson, B., Schersten, T., Wickstrom, I., and Lundholm, K. 1993. The effect of postoperative intravenous feeding (TPN) on outcome following major surgery evaluated in a randomized study. *Ann. Surg.* **217**: 185-195.

Singer, P., Anbar, R., Cohen, J., Shapiro, H., Shalita-Chesner, M., Lev, S., Grozovski, E., Theilla, M., Frishman, S., and Madar, Z. 2011. The tight calorie control study (TICACOS): a prospective, randomized, controlled pilot study of nutritional support in critically ill patients. *Intensive Care Med.* **37**: 601-609.

Singer, P. and Cohen, J.D. 2013. To implement guidelines: the (bad) example of protein administration in the ICU. *JPEN J. Parenter. Enteral Nutr.* **37**: 294-296.

Singer, P., Hiesmayr, M., Biolo, G., Felbinger, T.W., Berger, M.M., Goeters, C., Kondrup, J., Wunder, C., and Pichard, C. 2014. Pragmatic approach to nutrition in the ICU: Expert opinion regarding which calorie protein target. *Clin. Nutr.* **33**: 246-251.

Tonelli, M.R., Curtis, J.R., Guntupalli, K.K., Rubenfeld, G.D., Arroliga, A.C., Brochard, L., Douglas, I.S., Gutterman, D.D., Hall, J.R., Kavanagh, B.P., Mancebo, J., Misak, C.J., Simpson, S.Q., Slutsky, A.S., Suffredini, A.F., Thompson, B.T., Ware, L.B., Wheeler, A.P., Levy, M.M.,

and ACCP/ATS/SCCM Working Group 2012. An official multi-society statement: the role of clinical research results in the practice of critical care medicine. *Am. J. Resp. Crit. Care Med.* **185**: 1117-1124.

Verbruggen, S.C.A.T., Coss-Bu, J., Wu, M., Schierbeek, H., Joosten, K.F.M., Dhar, A., Van Goudoever, J.B., and Castillo, L. 2011. Current recommended parenteral protein intakes do not support protein synthesis in critically ill septic, insulin-resistant adolescents with tight glucose control. *Crit. Care Med.* **39**: 2518-2525.

Ziegler, T.R. 2009. Parenteral nutrition in the critically ill patient. *N. Engl. J. Med.* **361**: 1088-1097.

Draft