Editorial

What is the best nutritional support for critically ill patients?

L. John Hoffer[1], Bruce R. Bistrian[2]

[1]Lady Davis Institute for Medical Research, Jewish General Hospital, McGill University, Montreal, Quebec, Canada; [2]Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA

Correspondence to: L. John Hoffer, MD, PhD. Lady Davis Institute for Medical Research, 3755 Cote Ste Catherine, Montreal, QC H3T 1E2, Canada. Email: l.hoffer@mcgill.ca.

Abstract: Optimum nutritional support in critical illness remains controversial. A recent review of nutritional interventions in the ICU concluded that few of them improved clinical outcomes. In our view, it is a serious shortcoming of these trials that they focused on calories, falling far short of current recommendations for protein provision. Well designed clinical trials that ensure sufficient protein provision are urgently needed if we are to improve the quality of nutritional support in the ICU.

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What nutritional support is best for critically ill patients? A recently published review article (1) provides a useful analysis of this important question. This article analyzed old and recent high quality randomized clinical trials (RCTs) of different nutritional interventions in the ICU with the goal of answering several specific questions about the benefits of nutritional support. Because almost none of the novel interventions demonstrated important clinical benefits, the conclusions were modest and very limited, namely, that the currently common practice of hypocaloric enteral feeding is appropriate for up to 7 days in patients who are well-nourished at the time of admission to an ICU. It was also concluded that, unlike what was indicated by earlier RCTs in which excessive calorie provision induced severe hyperglycemia, modern lower-calorie parenteral nutrition (PN) appears not to increase the risk of infections (1).

In our opinion, these are valid conclusions regarding currently used nutritional regimens in well nourished patients, but they leave a host of important questions unanswered.

The issue we would like to raise about this review has to do with the validity of the RCTs its conclusions are based on. The purpose of evidence-based medicine is to guide the design, conduct and interpretation of clinical trials with the minimum of bias, so the review correctly addressed questions of internal validity, as determined by details of design and conduct like randomization, blinding, and intention-to-treat analysis.

But a more fundamental kind of validity also has to be ascertained when designing and interpreting clinical trials, namely the physiological soundness and plausibility of the therapeutic hypothesis that the RCT is testing. All therapeutic trials—especially nutritional ones, owing to their variety and complexity—need to be founded on physiologically sound premises (2,3). Therapies that lack a biologically sound premise (homeopathy, blood-letting to treat fever, or vitamin B_{12} injections to treat iron-deficiency anemia come to mind as examples) must be regarded skeptically. How does one go about determining which candidate nutritional therapies are plausible enough to justify the effort and expense of a large, high quality RCT? By mastering the underlying physiological principles and reviewing all the available scientific evidence pertinent to it. The selection and analysis of basic and non-RCT clinical evidence should be as objective and unbiased as the selection of which RCTs to include in a systematic review or meta-analysis. It should go without saying that cherry picking evidence—basic and non-RCT clinical evidence included—that supports a preferred hypothesis while willfully ignoring evidence that contradicts it violates the rules of science.

The therapeutic hypothesis tested by the RCTs analyzed in this review was that calories are the quintessential

macronutrient in critical illness. The review's authors explain why they regard this hypothesis as biologically plausible. Failure to provide calories can lead to a cumulative calorie deficit that contributes to skeletal muscle wasting and its associated adverse consequences—and, since muscle atrophy occurs extremely rapidly in protein-catabolic critical illness, it could be especially important to provide calories in this situation. Secondly, a large number of observational studies have linked worse clinical outcomes with more deficient calorie provision. Since causal inference is questionable in observational studies, prospective RCTs are necessary to test the "not enough calories" hypothesis.

In our opinion, this hypothesis is highly implausible. While it is true that a high rate of calorie provision (without protein) may temporarily mitigate skeletal protein wasting, it does so at the cost of visceral protein loss and impaired immunity; in fact, the existing biological data suggest rather strongly that high energy, protein-deficient nutrition is harmful (4-6).

Rather, an enormous amount of basic and clinical research data have been published which, in the aggregate, provides solid support for the proposition that the macronutrient that is most lacking in critical illness—and whose provision is most likely to be of benefit—is protein. Sufficient exogenous protein provision mitigates skeletal muscle atrophy and supplies amino acids for the synthesis of proteins involved in wound healing and immune function (7). It is because of this accumulated evidence that all nutritional care guidelines in critical illness recommend a level of protein or amino acid provision that is much higher than the daily requirement of a healthy person. A healthy adult requires 0.8 g of high quality protein/kg per day, whereas the commonest recommendation for protein provision in critical illness is 1.5 g/kg/day (7). In fact, extensive metabolic data (and some clinical trial evidence) suggest that the early provision of 1.5-2.5 g protein/kg per day could be optimal in critical illness (3,7). Even as little as approximately 84 g protein/day (1.2 g/kg) could be enough to improve some clinical outcomes (8).

Calorie provision greater than about 50% of measured energy expenditure leads to only very slight further improvements in nitrogen balance (9), especially in critical illness (10-12). The problem with aiming for 100% of energy expenditure is the risk of inadvertent energy overfeeding with little or no compensating benefit. A minimum amount of energy may be important in critical illness, but it is unlikely to exceed 50% to 70% of energy expenditure, as long as protein provision is increased to compensate for the mild impairment of protein retention induced by the hypocaloric state (3,7).

The commonest argument used to justify the "not enough calories" hypothesis—stated again in the recent review—is that observational studies show a relationship between deficient calorie provision and poor clinical outcomes. But calorie-deficient diets are protein-deficient! The observational studies upon which the "not enough calories" hypothesis is founded are more rationally interpreted as supporting the "not enough protein" hypothesis (3,13).

It should come as no surprise, therefore, that so many recent RCTs of nutritional support in the ICU have been disappointing. The amount of protein provided in all but two of them—both of which reported better outcomes in the protein-supplemented patients (8,14)—was dramatically less than what the best available evidence suggests it ought to be (7). Unlike the authors of this review, most experts now call for high quality RCTs to test the benefits of suitably generous protein provision, such as 1.5 to 2.0 g protein [equivalent to 1.8 to 2.4 g mixed free amino acids (15)] per kg of normalized dry body weight per day in protein-catabolic critically ill patients (3,7,16-20).

Why have clinical trial experts ignored the problem of protein starvation in the ICU for so long? The answer may lie in human cognitive frailty. In the early years of nutritional support, PN was routinely enriched with high-energy dextrose to boost the protein-anabolic effect of the co-infused amino acids. As it became increasingly clear that calorie overfeeding is poorly tolerated, and enteral nutritional products and procedures for delivering them improved, PN fell into disfavor and EN became the standard of care in the ICU. The problem with existing enteral products is that they are designed for normal people, not critically ill patients. It is nearly impossible to deliver suitably generous amounts of protein to critically ill patients without calorie-overfeeding them. Actually, in practice, EN usually progresses so slowly that patients are deficient in calories and doubly deficient in protein for the first week or longer of their ICU admission. Yet these physiologically irrational products now represent the standard of care in the ICU, against which other, physiologically implausible regimens are compared in clinical trials (3). Another reason why protein has been ignored is that many critical care investigators, lacking a formal background in clinical nutrition, somehow allowed the concept of "nutrition" to morph into "calories," fostering the aberrant notion that the only significant ingredient in food is its calories. Most of the recent critical care literature routinely uses the words "nutrition" and "calories" interchangeably, as if they mean

the same thing!

The disappointing results of the many nutritional interventions that have focused narrowly on calories should heighten our awareness of the near-absence of high quality data addressing the question of protein requirements in critical illness. Implementation of the recommendations endorsed in this recent review would continue to guarantee drastic protein starvation for the first week or longer of an ICU stay (7). Is this clinically harmful? We suspect it is, but at present we just don't know. Fortunately, we hope to see, in the near future, the publication of physiologically well-designed and properly carried out RCTs of nutritional regimens that provide suitably generous amounts of protein to protein-catabolic critically ill patients.

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References

1. Casaer MP, Van den Berghe G. Nutrition in the acute phase of critical illness. N Engl J Med 2014;370:1227-36.
2. Tonelli MR, Curtis JR, Guntupalli KK, et al. An official multi-society statement: the role of clinical research results in the practice of critical care medicine. Am J Respir Crit Care Med 2012;185:1117-24.
3. Hoffer LJ, Bistrian BR. Why critically ill patients are protein deprived. JPEN J Parenter Enteral Nutr 2013;37:300-9.
4. Moldawer LL, Trerice MS, Flatt JP, et al. A protein sparing model in the rat during hypocaloric feeding: factors determining preservation of visceral protein function. J Surg Res 1978;25:424-32.
5. Moldawer LL, Bistrian BR, Blackburn GL. Factors determining the preservation of protein status during dietary protein deprivation. J Nutr 1981;111:1287-96.
6. Sandström R, Drott C, Hyltander A, et al. The effect of postoperative intravenous feeding (TPN) on outcome following major surgery evaluated in a randomized study. Ann Surg 1993;217:185-95.
7. Hoffer LJ, Bistrian BR. Appropriate protein provision in critical illness: a systematic and narrative review. Am J Clin Nutr 2012;96:591-600.
8. Heidegger CP, Berger MM, Graf S, et al. Optimisation of energy provision with supplemental parenteral nutrition in critically ill patients: a randomised controlled clinical trial. Lancet 2013;381:385-93.
9. Dickerson RN. Hypocaloric feeding of obese patients in the intensive care unit. Curr Opin Clin Nutr Metab Care 2005;8:189-96.
10. Behrendt W, Bogatz V, Giani G. The influence of posttraumatic parenteral calorie and nitrogen supply upon the cumulative nitrogen balance. Infusionstherapie 1990;17:32-9.
11. Frankenfield DC, Smith JS, Cooney RN. Accelerated nitrogen loss after traumatic injury is not attenuated by achievement of energy balance. JPEN J Parenter Enteral Nutr 1997;21:324-9.
12. Japur CC, Monteiro JP, Marchini JS, et al. Can an adequate energy intake be able to reverse the negative nitrogen balance in mechanically ventilated critically ill patients? J Crit Care 2010;25:445-50.
13. Allingstrup MJ, Esmailzadeh N, Wilkens Knudsen A, et al. Provision of protein and energy in relation to measured requirements in intensive care patients. Clin Nutr 2012;31:462-8.
14. Botrán M, López-Herce J, Mencía S, et al. Enteral nutrition in the critically ill child: comparison of standard and protein-enriched diets. J Pediatr 2011;159:27-32.e1.
15. Hoffer LJ. How much protein do parenteral amino acid mixtures provide? Am J Clin Nutr 2011;94:1396-8.
16. Verbruggen SC, Coss-Bu J, Wu M, et al. Current recommended parenteral protein intakes do not support protein synthesis in critically ill septic, insulin-resistant adolescents with tight glucose control. Crit Care Med 2011;39:2518-25.
17. Singer P, Cohen JD. To implement guidelines: the (bad) example of protein administration in the ICU. JPEN J Parenter Enteral Nutr 2013;37:294-6.
18. Choban P, Dickerson R, Malone A, et al. A.S.P.E.N. Clinical guidelines: nutrition support of hospitalized adult patients with obesity. JPEN J Parenter Enteral Nutr 2013;37:714-44.
19. Plank LD. Protein for the critically ill patient--what and when? Eur J Clin Nutr 2013;67:565-8.
20. Singer P, Hiesmayr M, Biolo G, et al. Pragmatic approach to nutrition in the ICU: expert opinion regarding which calorie protein target. Clin Nutr 2014;33:246-51.

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