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Immunonutrition in the critically ill: from old approaches to new paradigms

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In this issue of *Intensive Care Medicine*, Keift et al. [1] report the results of a multicenter, randomized, double-blind, controlled trial comparing an enteral formula enriched with arginine, glutamine, antioxidants and containing omega 3 fatty acids with an isocaloric, non-isonitrogenous standard enteral formula, in a mixed population of 597 critically ill patients. When analyzed both using an efficacy analysis (those fed for more than 48 h) and by an intention-to-treat analysis, the authors failed to demonstrate any difference in clinical outcomes in the overall analysis or several subgroup analyses. Mortality, infectious complications, ICU length of stay, and duration of mechanical ventilation were the same between the two groups. Although the lack of a treatment effect on clinical outcomes has been shown in other trials, given the highly controversial nature of the topic of immunonutrition in critically ill patients, this article is significant, particularly since this is the largest and one of the more robust randomized trials of immune-enhancing diets in an ICU population.

When the results of this large trial are added to the existing trials, in the form of a meta-analysis, the overall treatment effect is consistent with no effect on mortality (relative risk [RR] 1.05 and 95% confidence intervals [CI] 0.89, 1.25), infectious complications (RR 0.97, CI 0.81,1.15) or length of stay in ICU (weighted mean difference [WMD] -1.59 , CI $-3.25,0.08$) [2]. After 20 years of research, 18 randomized trials of 2,348 critically ill

patients, and countless millions of research dollars, why is it that we are unable to demonstrate a positive treatment effect associated with these immune-enhancing products? Do we need more trials like this one to prove the virtues of these special nutrients? Or, do we have to ask ourselves whether there are fundamental problems with our approach to proving the hypothesis that certain nutrients with immunologic and metabolic properties will improve the outcomes of critically ill patients? We have argued before that there are significant methodological limitations to the existing literature that limit the inferences we can make from these studies [3]. As we argue below, perhaps the problem is further compounded by the fact that multiple nutrients are combined into single nutritional products and tested in heterogeneous patient populations.

For any sick patient, “metabolic resuscitation” of the gastrointestinal tract by providing adequate nutrition, in general, and defined immuno-modulating substrates specifically, to maintain gut-barrier integrity and function and to reduce regional oxidative stress, will have to be considered as key therapeutic strategies. However, within a given patient over time or across different patient populations, the severity of “gut failure”, the amount of bacterial translocation, the degree of cellular immune dysfunction, the balance of inflammation/anti-inflammation, and the regional and systemic generation of reactive oxygen species will vary. Generally speaking, elective surgical patients experience minimal activation of cytokines and some degree of suppression of the cellular defense function following surgical stress, putting them at higher risk for acquired infectious morbidity and mortality. It follows that nutrients, such as arginine, that stimulate the cellular defense system may reduce infectious complications in the elective surgical patient. In contrast, the associated changes to the systemic inflammatory response accompanying critical illness are far more intense, complex, variable, and less well-defined, but best characterized by an over-amplified inflammatory

Table 1 Nutrients recommended for specific patient populations (*EN* enteral nutrition, *PN* parenteral nutrition, *ID* inadequate data to make a recommendation)

Nutrients	Population					
	Elective surgery	Critically ill				
		General	Septic	Trauma	Burns	Acute lung injury
Arginine	Benefit	No benefit	Harm	No benefit	No benefit	No benefit
Glutamine	Possible benefit	PN beneficial (? receiving EN)	ID	EN possibly beneficial	EN possibly beneficial	ID
Omega 3 fatty acids	ID	ID	ID	ID	ID	Possible benefit
Antioxidants	ID	Possible benefit	ID	ID	ID	ID

response, probably due to excess of nitric oxide, reactive oxygen species (ROS), and excessive availability of lipid mediators. Thus, nutrients that further stimulate the systemic inflammatory response, such as arginine, may be deleterious in critically ill patients. In fact, novel therapies that have been shown to be effective in the early phase of critical illness decrease the inflammatory response associated with critical illness; they do not stimulate it [4,5]. What is emerging in the critical care literature is the notion of hyper-inflammation and cellular immune dysfunction coexisting in the same patient or patient population at the same time [6]. Hence, for critically ill patients, nutrients that augment cellular defense (specific and nonspecific immune function) and ameliorate reactive oxygen species without a collateral increase in the inflammatory response are most likely to be beneficial. Thus, the treatment effect of various substrates or nutrients will vary depending on the underlying pathophysiology of the host and whether the substrate influences cellular immune function and/or the synthesis of inflammatory mediators and/or the generation of ROS. To combine these nutrients with immuno-enhancing effects into single products delivered to heterogeneous groups of patients seems fundamentally flawed. It is plausible that some of these nutrients, tested individually, may have some positive (or negative) therapeutic benefits in some groups of patients, but when combined together and exposed to heterogeneous groups of patients, as best illustrated by the current study [1], any signal of benefit (or harm) is lost.

When we developed the Canadian Clinical Practice guidelines for nutrition support in the mechanically ventilated patient [7], we attempted to isolate the effect of individual nutrients in specific homogenous critically ill patient populations (see Table 1). This was difficult, as there are no studies testing the effect of arginine alone in critically ill patients. We had to infer, from products that contained supplemental arginine and other supplemented nutrients, what the effect of arginine might be in critically ill patients. From our review of the literature, glutamine and antioxidant strategies are most likely to be beneficial

to critically ill patients [8,9]. What is most interesting in the studies included in these reviews is that they are testing the beneficial effect of single nutrients (such as glutamine or selenium) in a patient receiving balanced nutrition. In such a study, we are able to see the signal that the nutrients are responsible for an apparent mortality reduction, independent of the nutrition provided. This suggests that the way forward is to test single nutrients in large-scale, well-designed, randomized trials of homogenous patient populations.

Prior to doing so, we need to understand the optimal dose of such nutrients. Dose-finding studies in nutrition literature are very rare. Yet, an additional reason why some previous randomized trials have failed to demonstrate a treatment effect may relate to inadequate dosing. The results of the glutamine and antioxidant meta-analyses [8,9] seem to suggest that a higher dose of glutamine and selenium provided was associated with a greater treatment effect. When provided enterally and combined with the enteral nutrition product, given that these sick patients may have trouble tolerating their enteral feeds, reducing the intake of enteral feeds limits the intake of these key nutrients. Future studies should dissociate the study nutrients from the intended nutrition, so that, if there are issues with tolerance of standard nutrition support, the delivery of the study nutrients is not compromised. This is a unique concept that represents a major advance in the design of studies in this area.

In conclusion, the current approach to defining those key nutrients that may have positive effects in critically ill patients is not working. We need a new scientific paradigm to illuminate future prospects. This paradigm includes focusing on single nutrients dissociated from nutrition, tested in homogenous patient populations in large, rigorously designed randomized clinical trials. Perhaps the label, “immunonutrition” represents the “old” approach and “pharmakonutrition” could stand for the new paradigm?

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