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P. Jolliet
C. Pichard

Immunonutrition in the critically ill

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P. Jolliet (✉)
Division of Medical Intensive Care, University Hospital, Geneva, Switzerland

C. Pichard
Clinical Nutrition and Diet Therapy, University Hospital, Geneva, Switzerland

Mailing address:
Division des soins intensifs de Médecine,
Hôpital Cantonal Universitaire, 1211 Geneva 14, Switzerland
e-mail: jolliet@cmu.unige.ch
Tel. + 41 (22) 372 90 93
Fax + 41(22)372 91 05

Introduction

Critical illness is associated with important protein breakdown and severe catabolism resulting in wasting of endogenous protein stores, mass reduction of muscle and viscera, and a decrease in the immune response. Translated into clinical terms, the combination of these factors can lead to prolonged ventilator dependency and stay in the intensive care unit (ICU), with a heightened susceptibility to nosocomial infection. The latter represents a major cause of mortality in ICU patients, as it often leads to septic shock and multiple organ failure (MOF).

It is presently accepted that the early institution of nutritional support can modulate the extent of metabolic abnormalities by altering the cytokine-driven response to stress and infection and attenuate critical illness-related wasting. Furthermore, using enteral rather than parenteral nutrition can maintain the gut's structural and functional integrity. This point is of particular importance, since gut atrophy caused by the absence of enteral feeding has been shown to induce increased permeability to bacteria and endotoxins, thereby increasing the risk of infection and systemic metabolic abnormalities. Nonetheless, it is all too clear that in spite of these favorable effects much progress remains to be made in attempting to reduce the rate of nosocomial infection. A novel approach in that direction, developed over the past decade, consists of enriching standard feeding preparations with various nutrients aimed at enhancing the host's immune status. Indeed, most nutrients can alter the metabolic response and the cellular signaling initiated by the invasion of microbial intruders, but only a number of specific compounds have been shown in vitro and in vivo to increase cellular immune response to infectious stimuli, as well as to improve survival in animals submitted to a septic challenge. This approach has been termed "immunonutrition". Among the substances identified as potential components of immunonutrition, some are present in commercially available preparations, such as the combination of arginine, purine nucleotides, and ω-3 polyunsaturated fatty acids for enteral nutrition and glutamine for parenteral nutrition. Several trials exploring their potential clinical benefits have recently been published, three of which will now be reviewed briefly.

Atkinson S, Sieffert E, Bihari D, on behalf of the Guy's Hospital Intensive Care Group (1998) A prospective, randomized, double-blind, controlled clinical trial of enteral immunonutrition in the critically ill. Crit Care Med 26: 1164–1172

This rigorously designed prospective, randomized, controlled, double-blind single-center study evaluated the effects of enteral immunonutrition in 398 medical and surgical ICU patients. Within 48 h of admission, patients received either a commercially available enteral feed combining arginine, purine nucleotides, and ω-3 polyunsaturated fatty acids (Impact, Novartis Nutrition, Berne, Switzerland) or an isocaloric, isonitrogenous

control feed. When analyzed on an intention-to-treat basis, there was no significant difference between the two groups, whether in hospital mortality (immunonutrition group 48 %, control group 46 %), the study's primary endpoint, or in any of the secondary outcome measures. However, in a subgroup of 101 patients, defined a priori as those having achieved successful early enteral nutrition (i. e., > 2.5 l of feeding solution in the first 72 h after ICU admission), immunonutrition induced a reduction in the median duration of mechanical ventilation (6.0 vs 10.5 days, $p = 0.007$) and length of ICU (7.5 vs. 12 days, $p = 0.02$) and hospital (15.5 vs. 20 days, $p = 0.03$) stays. There was also a decrease in the median number of days during which the criteria for the diagnosis of systemic inflammatory response syndrome (SIRS) were fulfilled (3.0 vs. 6.0 days, $p = 0.03$). The authors conclude that, while immunonutrition did not influence mortality in this general ICU patient population, it did significantly reduce the morbidity of critical illness in those patients able to achieve early enteral feeding. This conclusion is very stimulating because most ICU patients can indeed tolerate a constant enteral flow of about 700 ml per day.

Weimann A, Bastian L, Bischoff WE et al. (1997) Influence of arginine, omega-3 fatty acids and nucleotide-supplemented enteral support on systemic inflammatory response syndrome and multiple organ failure in patients after severe trauma. Nutrition 14: 165–172

Thirty-two severe trauma patients (injury severity score > 20) were studied in this prospective, randomized, controlled, double-blind single-center trial. The primary endpoints were the incidence of SIRS and MOF, while secondary endpoints were parameters of acute phase and immune response, infection rate, hospital stay and mortality. Patients were randomized to receive either Impact or an isocaloric, isonitrogenous control feed, starting on day 2 after ICU admission. Initial feeding rate was 25 ml/h and was progressively increased daily by 25 ml/h, up to a maximum of 150 ml/h. To ensure a minimal protein-calorie supply from the onset, parenteral nutrition was initially administered simultaneously, until the final goal of 35–40 kcal/kg was met. Parenteral nutrition was subsequently progressively withdrawn as enteral feeding increased. In the immunonutrition group, there were significantly fewer days during which the diagnostic criteria for SIRS were met (mean ± SD 8.3 ± 6.3 vs 13.3 ± 6.7, $p < 0.05$) over a 28-day period, the difference being the most marked between days 8 and 14 (3.0 ± 2.5 vs 6.2 ± 0.9, $p < 0.001$). Likewise, the MOF score was lower in the immunonutrition group at day 3 and between days 8 and 11 ($p < 0.05$), while markers of the acute phase response such as serum levels of C-reactive protein and plasma fibrinogen, were also lower on days 2 and 12–14, respectively ($p < 0.05$). There was no difference between groups regarding infection rate, hospital stay, or mortality, although the latter was lower in the immunonutrition group (2/16 vs 4/13). The authors conclude that, even though the small number of patients precluded any significance being reached in outcome measurements, immunonutrition exerts a modulating effect on the parameters of the immune and inflammatory response which could prove clinically beneficial.

Griffiths RD, Jones C, Allan Palmer TE (1997) Six-month outcome of critically ill patients given glutamine-supplemented parenteral nutrition. Nutrition 13: 295–302

This prospective, block-randomized, controlled, double-blind, single-center study evaluated the effects of glutamine-supplemented parenteral nutrition in a general ICU patient population. Out of 156 ICU admissions, 84 patients in whom enteral feeding was contraindicated or could not be achieved over 48 h were randomized to receive either a glutamine-containing (25 g/l) or a non-glutamine containing isocaloric isonitrogenous control parenteral nutrition solution. Endpoints were morbidity, mortality, and cost at 6-month postnutritional intervention. Survival at 6 months was significantly improved in the glutamine-enriched group (24/42 vs 14/42, $p = 0.049$), while the total hospital cost per survivor was reduced by 50 %. A significantly higher number of deaths occurred in those patients requiring parenteral nutrition for > 10 days who were receiving the control formula ($p = 0.03$), the most frequent cause of death being MOF. The authors conclude that, in critically ill patients unable to receive enteral nutrition, using a glutamine-containing solution can reduce mortality, mostly in patients presenting with late-onset MOF, while decreasing hospitalization and posthospitalization costs for the surviving patient. In spite of some weakness in the data, this study's prolonged follow-up should be regarded as a unique approach correlating the impact of nutritional support not only with immediate morbidity factors but also with its effect on the global management of body reserves and function during the recovery phase of the disease.

Discussion

Although the ICU populations are not strictly comparable between the Atkinson et al. and Griffiths et al. trials (medical and surgical) and the Weimann et al. trial (trauma patients), results of the three studies do have a common message: immunonutrition can exert beneficial effects in at least some of these patients, possibly by reducing the duration and magnitude of the acute phase inflammatory response. Furthermore, this favorable im-

pact on biologic parameters can be translated into an improved outcome and cost. These encouraging results call for a few comments.

First, even though the global rationale behind the concept of immunonutrition is fairly straightforward in general terms – namely, enhancing the patients' immune status and resistance to infection – it is not quite clear which key mechanisms are actually implicated when such preparations are used. Indeed, each specific component participates in several crucial steps associated with the complex pathways of the inflammatory response. Arginine, a non-essential amino acid, is a potent stimulant of growth hormone, glucagon, prolactin, and insulin release, as well as a precursor of nitric oxide (NO) synthesis. NO has been shown to induce vasodilatation, regulate hepatic protein synthesis, generate free radicals, and exert antiinflammatory effects through the reduction of inflammatory mediator release. Nucleotides are essential structural units of DNA, RNA, adenosine triphosphate, and nicotinamide adenine dinucleotide, and hence participate in the fundamental processes maintaining cellular integrity and functionality, as well as stimulating natural killer cell activity. Compared to ω-6 fatty acids, ω-3 fatty acids contained in immunonutrition feeds shift the release of proinflammatory cytokines toward antiinflammatory cytokines, hence promoting a better control of the overall inflammation process. Glutamine, a non-essential amino acid, is the most abundant in the body and exerts multiple functions: it is a primary fuel source for lymphocytes, macrophages, and enterocytes, a precursor of the antioxidant glutathione, and helps to maintain acid-base balance. Thus, given the many roles played by these components and the numerous interactions between the pathways in which they participate, the exact mechanisms by which they can favorably act on the patients' immune response remain to be determined. Analysis is even more difficult when a feeding solution contains more than one specific immunonutrient, as used in the Atkinson et al. and Weimann et al. trials. Furthermore, animal models relied on severe depletion and subsequent substitution with such elements, which might often not reflect the situation in those ICU patients who are not malnourished to the same extent.

Second, one essential finding of the Atkinson et al. trial was that the beneficial effects of immunonutrition were observed only in those patients having achieved early enteral feeding. This finding seems logical, since the effects of any substance would only be expected if that substance were truly administered to the patients. However, another possibility is that the gut might be an important target of immunonutrition and that both the content of the feeding solution and its precocious delivery to the digestive tract are crucial for any benefit to be documented. Should this be the case, it would again underline the sound basis on which rests the presently accepted trend of using the gut early in such patients. Indeed, if, as suggested by some, the atrophic gut is an important motor of MOF due to increased permeability to endotoxin and bacteria, or through some as yet unknown mechanisms, timely feeding of this organ with immune-enhancing components might well make a difference.

Third, it seems that whatever the route of feeding, adding immunonutrients leads to a favorable modulation of the overall inflammatory response from the acute condition until recovery of health, as evidenced by the Griffiths et al. study. Naturally, given the multiple functions of glutamine outlined above, it is difficult to pinpoint where its main point of action was in these patients. However, the lower incidence of MOF in glutamine-treated patients suggests that sepsis, a key trigger for MOF, might have been less frequent or less severe. Since the study population consisted of patients without enteral nutrition, this suggests that the gut may not be the sole culprit in promoting MOF, which seems a fairly reasonable assumption. However, since glutamine is an important fuel for enterocytes and since the latter receive part of their nutriments from the blood supply, part of the beneficial effect might still be linked to improved gut function.

Fourth, the encouraging results of these and other studies, and the absence of documented side effects could lead to a "if it doesn't work at least it won't hurt" generalization approach, which could be premature at this time. Indeed, there seems to be a delicate balance between excess and insufficient inflammatory response in critically ill patients, the disruption of which either way can slowly evolve into sepsis and MOF. Hence, some patients might require an enhancement of their acute phase response, while in others a suppressive effect might be preferable. Thus, some caution would be in order as far as modulating the host's immune response goes.

In conclusion, evidence is mounting that immunonutrition can exert beneficial effects on parameters of the inflammatory response in critically ill patients and that these can favorably influence outcome. These encouraging results and their exciting perspectives should prompt further research with drug industry-like design into the specific mechanisms involved, as well as into which immunonutrients are the most potent, and which patients are the most likely to benefit from this approach. Finally, more research should be devoted to the potential side effects of this nutritional strategy, since immunonutrition is turning basic nutritional support into a form of therapy with side effects generally proportional to primary effects. Due to the added cost, cautious optimism and a careful assessment of these important issues are needed before wide-scale recommendations on the use of immunonutrition can be established.