

## Immunonutrition in Critical Illness

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Immunonutrition is an emerging therapy that has been the focus of a number of clinical trials. Manipulation of the immune system has the substantial potential to modify disease outcome, particularly in regard to infectious complications. Many studies have examined the effects of nutritional formulas supplemented with arginine, n-3 fatty acids, structured lipids, and nucleotides compared with standard enteral feeding. Unfortunately, because of marked heterogeneity between studies, only limited consensus has been reached. Some randomized studies have shown that immune-enhanced nutritional formulas can reduce postoperative infectious complications in surgical patients with gastrointestinal or head and neck cancer and may be effective when provided preoperatively as well. A few studies show no benefit, but none demonstrated higher infection rates in this population, which is reinforced by the finding from three separate meta-analyses of overall benefit.<sup>1-3</sup> Therefore, for surgical patients with gastrointestinal/head and neck cancer, the evidence is reasonably strong in favor of the use of immunonutrition, particularly in malnourished patients.

In trauma and critically ill patients, the data are less clear, and no overall recommendation in favor of immunonutrition was made recently by Dr Heyland<sup>4</sup> in a review of the evidence (this issue of *NCP*). There are three large published studies in intensive care unit (ICU) patients, all using the same immune-enhancing diet, which differ in many ways, with only one showing a significant improvement in morbidity and mortality overall.<sup>5-7</sup> There was a clear trend toward increased mortality with the immune-enhancing diet in the earliest study.<sup>5</sup> Dr Heyland makes important points in his review of immunonutrition in the critically ill population. He describes in some detail potential deleterious effects

of using arginine as one component of the immunonutrition formula. It is true that pro-inflammatory mediators may be enhanced using arginine, with its propensity to increase nitric oxide generation. However, increased nitric oxide has not been consistently demonstrated *in vivo* to result from nutritional increase in arginine.<sup>8,9</sup> In currently available immunonutrition solutions, potential pro-inflammatory effects of arginine are balanced by anti-inflammatory sequelae of n-3 fatty acids. It is not unreasonable to consider that the two most likely immune-enhancing ingredients to have beneficial clinical effects are arginine and  $\omega$ -3 fatty acids, the former on the basis of its known impact on immune parameters and the latter on the basis of its clinically documented efficacy in reducing inflammatory responses. It is also interesting to note that most of the studies that show immunonutrition to be beneficial have used a concentration of arginine approximating 12 g/L (~4% energy) along with 1 g n-3 fatty acids per 1000 kcal, as is found in Impact (Novartis, Basel, Switzerland) and Immunaid (B. Braun, Irvine, CA). In contrast, immunonutrition solutions without benefit above control (or showing increased mortality in one unpublished study) used arginine 6 g/L (~2% energy).

If we confine ourselves to the three published studies in critically ill patients, what can be made of these data? The quoted unpublished study with increased mortality referenced by Dr Heyland perhaps should not be discussed at all, because there was a gross defect in randomization (which may explain why it remains unpublished). Significantly more patients in the treatment group ( $p < .005$ ) had pneumonia at randomization; most of the deaths occurred in patients with pneumonia. Dr Heyland makes a strong recommendation for an intention to treat analysis of the three published studies in critically ill patients, which we endorse. This is certainly the gold standard, but it is difficult to demonstrate efficacy if only 31% of the patients receive quantitatively significant amounts of the experimental diet (>821 kcal/d as determined in a post hoc analysis in the Bower et al study).<sup>5</sup> In this group, Bower et al found improved outcome (decreased length of stay) with no difference in mortality (2/39 versus 2/46). Such an analysis is the weakest form of evidence for the reasons stated by Dr Heyland. However, in the study by Atkinson et

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al,<sup>6</sup> a stronger inference can be drawn, although it must be noted that no benefits at all were realized in the treated group as a whole. The authors determined *a priori* that those patients receiving >833 kcal/d would be looked at as a subgroup. There was a significant improvement in morbidity (length of stay, ventilator time) without an impact on mortality (21/50 *versus* 19/51) in this subgroup. Although this is an interesting result from which to generate hypotheses, analysis of all randomized patients, irrespective of tolerance to the therapy, is mandatory for evaluation of effectiveness that would lead to a level 1 recommendation.

In the most recently published study in intensive care patients,<sup>7</sup> a significant improvement in overall mortality (17/89 *versus* 28/87) was demonstrated *versus* isonitrogenous control nutrition solution. Interestingly, the average energy intake was 1230 ± 410 kcal/d, which would mean that approximately 84% of patients would have had an intake of 820 kcal/d or greater. In conjunction with the suggestion from the subgroup analysis of the Atkinson et al study, amount of feeding may be the principal reason why the results of Galban et al<sup>7</sup> were positive. To be a candidate for this study, a minimum APACHE II score of 10 was required. On subgroup analysis, only the group with APACHE II scores between 10 and 15 had a significant improvement. Although not separately analyzed by the authors, in patients with APACHE II scores between 10 and 20, survival was significantly better in the immunonutrition group (8/67 *versus* 18/67). In fact, any grouping of APACHE scores would have positive results, because the overall analysis was significant, and the only group with arithmetically worse outcomes was the group with APACHE >25, which had a trivial difference (5/10 *versus* 4/9).

If inability to advance enteral feeds beyond minimal amounts is a major reason for failure of many immunonutrition trials to show benefit over control, one might propose that money for clinical research would be better spent finding ways to deliver adequate nutrition. Happily, recent papers have demonstrated that aggressive, nurse-directed protocols to advance feeding rates can be successful in the majority of those fed by nasogastric feeding. The allowance of larger residuals (up to 200 mL) should result in most ICU patients attaining goal feeding rates.<sup>10</sup> It is interesting to note that all of the Impact (Novartis) and Immunaid (B. Braun) trials in trauma and postoperative patients have used jejunal feeding where adequate intakes are more likely, whereas the three Impact trials in ICU patients have been with nasogastric feeding. One might also equally well hypothesize that feeding only small amounts of immunonutrition (as seen in the Bower et al study<sup>5</sup>) is a potential reason for the increase in deaths in the experimental group. The bulk of the increased mortality in this study was in the group that received the least amount of nutrition, randomized to immunonutrition.

In summary, although a beneficial outcome can not be assumed, it would not be unreasonable to feed these formulas in the ICU to at least the moderately ill on the basis of present evidence. One must be certain to attempt to reach a minimal critical volume in most patients. However, it should not be overlooked that maintenance of tight glucose homeostasis in the critically ill who are being adequately fed by either enteral or parenteral nutrition may be even more important in the determination of clinical outcome in terms of morbidity and mortality<sup>11</sup> than dietary composition. Therefore, we would certainly agree with Dr Heyland that no definitive recommendation can be made for the use of immune-enhancing diets in all populations of critically ill patients at the present time. On a background of higher numbers of patients achieving goal feeding rates, benefits of immunonutrition might be more readily apparent in future studies, which will of course be necessary before definitive recommendations can be made.

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