



Perioperative Immunonutrition: Does One Size Fit All?

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Over the past twenty years, numerous articles have been published in the field of immune-modulating formulas, also called “immunonutrition.” Hailed for various beneficial effects, these formulas are typically high protein enteral formulations or oral supplements with high levels of “pharmakonutrients.” The most common of these immunonutrients are arginine, omega-3-fatty acids, glutamine, ribonucleic acids, selenium, and other antioxidants. These nutrients are often present in combination at levels many times higher than the levels found in standard nutritional products.

Stated goals of immunonutrition include attenuation of excessive inflammatory responses, supplementation of conditionally-essential nutrients that are rapidly depleted in certain stress states (eg, glutamine and arginine), and delivery of nutrients thought to aid recovery in specific disease and injury states. Examples of these strategies include the well-described supplementation of arginine and glutamine after abdominal operations for gastrointestinal disease, use of anti-inflammatory lipids (mixtures of omega-3 and borage oils) in Acute Respiratory Distress Syndrome (ARDS) patients, and the use of specialized supplements in patients after brain injury.

Arginine has been and continues to be the most highly touted of the immunonutrients. It has been shown to stimulate cell-mediated immunity with activation of T lymphocytes, upregulation of T-helper cell populations, improved phagocytosis, and respiratory burst generation.¹ Arginine specifically promotes healing by two additional mechanisms: increased nitric oxide production with subsequent tissue perfusion due to vasodilation, and augmented collagen production as a precursor to proline. Arginine depletion after surgery is well described due to upregulation of arginase, particularly more than 24 hours after surgery.² Previously unavailable in most supplements due to patent restrictions, the now more widely-available arginine precursor, citrulline, has the potential to replace arginine due to improved bioavailability, better tolerance, and the achievement of higher sustained arginine plasma levels.³

The omega-3 fatty acids docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) are the other premier ingredients in most immunonutrition products. However, how omega-3s result in improved surgical outcomes is less evident. They are known to reduce oxidative injury, modify endothelial expression of adhesion molecules such as E-selectin, inhibit inflammatory responses due to downregulation of arachidonic acid, and to generate resolvins and other novel anti-inflammatory modulators.⁴ High dose intravenous fish oil appears to modulate the inflammatory response in surgical patients, but oral fish oil supplementation at standard doses did not show benefit in a large cardiac surgery trial (Omega-3 Fatty Acids for Prevention of Postoperative Atrial Fibrillation [OPERA]).⁵

After arginine and fish oil, glutamine historically has been the most discussed immunonutrient. Recognized as the preferred fuel of the enterocyte and other rapidly dividing cells as well as the most abundant free amino acid with a significant antioxidant effect, glutamine supplementation has long been encouraged in surgical patients. Enthusiasm has waned since the large multinational REDUCING Deaths due to OXIDATIVE Stress (REDOXS) trial in critically ill patients (not all surgical) demonstrated a 5.2% increase in mortality due to high-dose parenteral



and enteral supplementation of glutamine.⁶ At a more practical dose, the European MetaPlus study failed to demonstrate any benefit from high glutamine enteral immunonutrition in critically ill patients (only some of which were surgical).⁷

In reviewing the literature regarding the application of immunonutrition to surgical patients, it is challenging to draw valid conclusions because of a lack of clarity in numerous aspects of study design, comparability of studies, and the role of combining multiple immunonutrients. Generally, it is thought that there is some synergism between the multiple immunonutrients that limits the efficacy of single immunonutrients and inhibits isolated clinical evaluation of any nutrient in isolation. Over time, nutrient compositions of commercial formulas have changed. Studies that evaluate various immunonutrition formulas in a variety of settings—before surgery (preoperative), after surgery (postoperative), and both before and after surgery (perioperative)—have been used to justify grandiose claims not always supported by study design or even by physiology. The literature is also unclear because many studies lack an isocaloric, isonitrogenous control. Without standard nutritional supplementation in the control group, these studies fail to distinguish the benefit of immunonutrients from the benefit of the supplemental protein, carbohydrate, and standard nutrients many traditional oral nutritional supplements provide.

A meta-analysis confirmed preoperative immunonutrition conferred no reduction in wound infections, infectious and non-infectious complications, or length of stay when compared to isonitrogenous standard high-protein oral nutritional supplements (Figure).⁸ However, when compared to an un-supplemented regular diet in the same meta-analysis, oral immunonutrition supplements resulted in lower infectious complications and over a two-day reduction in hospital length of stay ($P<0.01$).⁸

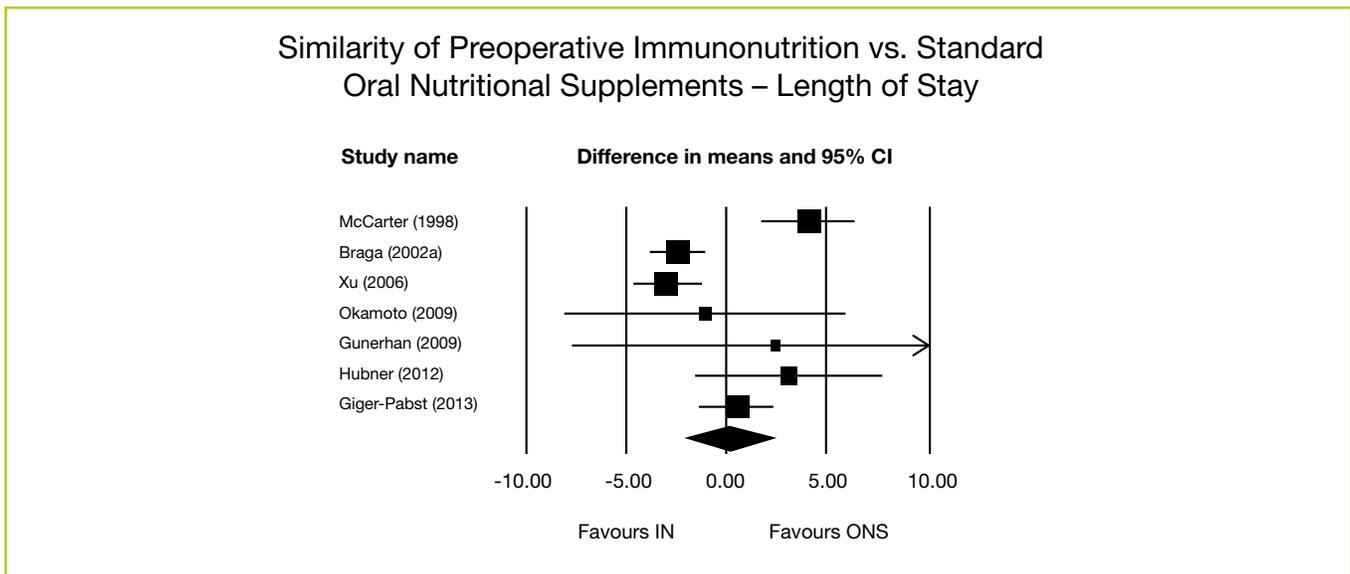


Figure. Comparison of preoperative immunonutrition vs standard oral nutritional supplements.⁸

Meta-analysis confirmed no reduction in length of stay between immunonutrition and standard high-protein oral nutritional supplements in the preoperative setting.

CI=Confidence Interval, IN=immunonutrition, ONS=oral nutritional supplement

Source: Hegazi RA et al. Preoperative standard oral nutrition supplements vs immunonutrition: results of a systematic review and meta-analysis. *J Am Coll Surg.* 2014;219(5):1078-1087.



Both American and European guidelines published in the 2000's made major recommendations for immunonutrition, but recent and emerging guidelines make only weak recommendations for immunonutrition.⁹ Despite limited evidence, quality improvement efforts based on the use of preoperative immunonutrition oral supplements are slowly proliferating in the United States. The precise immunonutrient profile, timing, dose and duration are all issues that need to be resolved before immunonutrition can be optimally prescribed to diverse clinical populations. In the future, immunonutrition may be tailored to target specific mechanistic derangements observed in specific clinical populations. Modulation of immune dysfunction is tricky business, and no successful pharmaceutical therapies have emerged from over a hundred human drug trials in this arena. Therefore, we must be cautious and not look to immunonutrition as a panacea. It does not appear to be a "one size fits all" solution.¹⁰

References

1. Kemen M, Senkal M, Homann HH, et al. Early postoperative enteral nutrition with arginine-omega-3 fatty acids and ribonucleic acid-supplemented diet versus placebo in cancer patients: an immunologic evaluation of impact. *Crit Care Med*. 1995;23(4):652-659.
2. Makarenkova VP, Bansal V, Matta BM, Perez LA, Ochoa JB. CD11b+/Gr-1+ myeloid suppressor cells cause T cell dysfunction after traumatic stress. *J Immunol*. 2006;176(4):2085-2094.
3. Wijnands KA, Vink H, Briede JJ, et al. Citrulline a more suitable substrate than arginine to restore NO production and the microcirculation during endotoxemia. *PLoS One*. 2012;7(5):e37439.
4. Evans DC, Martindale RG, Kiraly LN, Jones CM. Nutrition optimization prior to surgery. *Nutr Clin Pract*. 2014;29(1):10-21.
5. Mozaffarian D, Marchioli R, Macchia A, et al. Fish oil and postoperative atrial fibrillation: the Omega-3 Fatty Acids for Prevention of Post-operative Atrial Fibrillation (OPERA) randomized trial. *JAMA*. 2012;308(19):2001-2011.
6. Heyland D, Muscedere J, Wischmeyer PE, et al. A randomized trial of glutamine and antioxidants in critically ill patients. *N Engl J Med*. 2013;368(16):1489-1497.
7. van Zanten AR, Sztark F, Kaisers UX, et al. High-protein enteral nutrition enriched with immune-modulating nutrients vs standard high-protein enteral nutrition and nosocomial infections in the ICU: a randomized clinical trial. *JAMA*. 2014;312(5):514-524.
8. Hegazi RA, Hustead DS, Evans DC. Preoperative standard oral nutrition supplements vs immunonutrition: results of a systematic review and meta-analysis. *J Am Coll Surg*. 2014;219(5):1078-1087.
9. Gustafsson UO, Scott MJ, Schwenk W, et al. Guidelines for perioperative care in elective colonic surgery: Enhanced Recovery After Surgery (ERAS®) Society recommendations. *Clin Nutr*. 2012;31(6):783-800.
10. Evans DC, Hegazi RA. Immunonutrition in critically ill patients: does one size fit all? *JPEN. J Parenter Enteral Nutr*. 2015;39(5):500-501.