Immunonutrition in High-Risk Surgical Patients: A Systematic Review and Analysis of the Literature

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Immunonutrition in High-Risk Surgical Patients: A Systematic Review and Analysis of the Literature

Paul E. Marik, MD, FCCM1; and Gary P. Zaloga, MD, FCCM, FACN2

Financial disclosure: Dr Zaloga declares that he is a paid employee of Baxter Healthcare, Inc. Baxter Healthcare does not manufacture any of the enteral immune-modulating diets that are mentioned in the article.

Background: Immunomodulating diets (IMDs) have been demonstrated to improve immune function and modulate inflammation. However, the clinical benefit of these diets in patients undergoing elective surgery is controversial. The goal of this meta-analysis was to determine the impact of IMDs on the clinical outcomes of high-risk patients undergoing elective surgery. Methods: The review included prospective, controlled, clinical trials that compared the clinical outcome of elective surgical patients who were randomized to receive an IMD or a control enteral diet. Studies were stratified according to the type of IMD and the timing of the initiation of the IMD. Data were abstracted on study design, study size, patient population, and IMD used. The outcomes of interest were the acquisition of new infections, wound complications, length of hospital stay (LOS), and mortality. Meta-analytic techniques were used to analyze the data. Results: Twenty-one relevant studies were identified, which included a total of 1918 patients. Immunonutrition significantly reduced the risk of acquired infections, wound complications, and LOS. The mortality rate was 1% in both groups. The treatment effect was similar regardless of the timing of the commencement of the IMD. The benefits of immunonutrition required both arginine and fish oil. Conclusions: An immunomodulating enteral diet containing increased amounts of both arginine and fish oil should be considered in all high-risk patients undergoing major surgery. Although the optimal timing cannot be determined from this study, it is suggested that immunonutrition be initiated preoperatively when feasible. (JPEN J Parenter Enteral Nutr. 2010;34:378-386)

Keywords: immunonutrition; surgery; arginine; omega 3 fatty acids; enteral nutrition; wound complications; infections

Malnutrition is an important risk factor for the occurrence of postoperative complications, most notably infections and poor wound healing.1-3 Malnutrition decreases both cell-mediated and humoral immune responses, which are restored with refeeding. The early initiation of enteral nutrition has been demonstrated to decrease infectious complications and hospital length of stay (LOS) in patients undergoing abdominal surgery.4 Consequently, enteral nutrition is considered an essential part of the perioperative management of malnourished and high-risk surgical patients. An increased understanding of the effects of different nutrients on disease processes has led to the development of specialized enteral nutrition formulas. Immunomodulating diets (IMDs) are characterized by increased quantities of nutrients that improve immune cell function and modulate inflammation.5,7 Immune-modulating nutrients that have been added to IMDs include arginine, ω-3 polyunsaturated long-chain fatty acids (PUFAs), RNA, and antioxidants (such as ascorbic acid and selenium).

Although the biological properties of immunonutrients have been well studied in experimental models, the role of IMDs during routine clinical care is controversial.8-10 The Canadian Clinical Practice Guidelines for Nutrition Support in Critically Ill Patients recommend “that diets supplemented with arginine and other select nutrients not be used for critically ill patients.”11 In contrast, the European Society for Parenteral and Enteral Nutrition guidelines for intensive care state, “Immune modulating formulae (formulae enriched with arginine, nucleotides, and omega-3 fatty acids) are superior to standard enteral formula.”12 Although IMDs represent a class of specialized nutritional formulas, the formulas differ substantially from each other in both composition and physiologic actions. In addition, it is likely that the clinical response varies according to the patient’s disease state. Arginine has been shown to...
Nitric oxide, a major metabolite of arginine, is higher in patients following surgical trauma compared with sepsis and surgical trauma regulate arginine metabolism abrogated with the addition of arginine. Patients with sepsis and surgical trauma regulate arginine metabolism differently. Arginine levels are lower and arginase activity is higher in patients following surgical trauma compared with sepsis. Nitric oxide, a major metabolite of arginine, is elevated in sepsis and decreased following surgical trauma. Because metabolism of arginine differs in surgical vs nonsurgical patients, the effects of arginine supplementation in these patients is also likely to differ. Thus, both arginine and FO may have important immunomodulating properties that affect clinical outcomes in noninfected patients undergoing elective surgery. To test this hypothesis, we performed a systematic review and meta-analysis of studies that investigated the benefit of an IMD supplemented with arginine and FO either alone or in combination in patients undergoing major surgery. A priori we stratified patients according to the type of IMD and the timing of the initiation of the IMD.

Methods

Identification of Trials

Our aim was to identify all relevant randomized controlled clinical trials that investigated the clinical outcomes of IMDs containing arginine and FO either alone or in combination in patients undergoing major elective surgery. We included only studies that randomized patients to an IMD or a control enteral formula that was similar in composition to the IMD except for the specific immunonutrients that were being tested. There was no restriction as to the type of patient or the clinical setting where the study was performed. We used a multimethod approach to identify relevant studies for this review. Both authors independently searched the National Library of Medicine’s MEDLINE database for relevant studies in any language published from 1966 to December 2008 using the following Medical Subject Headings (MeSH) and keywords: immunonutrition, arginine, ω-3 fatty acid, and fish oil. The search was limited by the following terms: randomized clinical trial or controlled clinical trial and surgery or perioperative complications/care. In addition we searched Embase and the Cochrane Database of Systematic Reviews. Bibliographies of all selected articles and review articles that included information on IMDs were reviewed, and experts in the field were contacted to identify additional relevant studies. This search strategy was done iteratively, until no new potential citations were found. We performed this meta-analysis according to the guidelines proposed by the QUOROM group.

Study Selection and Data Extraction

In keeping with previous meta-analyses on immunonutrition, we included studies that reported 1 or more of the following clinical outcomes: (1) number of patients with new infections, (2) wound complications (fistula, anastomosis, or incision dehiscence), (3) hospital LOS, and (4) mortality. Outcomes were recorded according to intention-to-treat analysis. Both authors independently abstracted data from all eligible studies using a standardized form. Data were abstracted on study design, study size, study setting, patient population, timing of initiation of immunonutrition, and enteral formulation used. We recorded the method of randomization, blinding, and concealment. A priori the studies were grouped according to the type of IMD as follows: (a) arginine supplementation alone, (b) FO supplementation alone, or (c) both.

We used the fixed effects models using Comprehensive Meta-analysis 2.0 (Biostat, Englewood, NJ) and Review Manager 5.016 (Cochrane Collaboration, Oxford, UK) for all analyses and considered P ≤ .05 (2 sided) as significant. We report binary outcomes as odds ratios (ORs) and continuous outcomes as weighted mean differences (measure of absolute change). Summary effects estimates are presented with 95% confidence intervals (CIs). We assessed heterogeneity between studies for each outcome using the Cochran Q statistic, with P ≤ .10 indicating significant heterogeneity, and I² with suggested thresholds for low (25%–49%), moderate (50%–74%), and high (>75%) values.

Results

Trail Flow

The initial search strategy generated 42 citations; of these 22 studies were excluded because the intervention/control group received parenteral nutrition, the study did not include a group that received a control diet, the study did not report a prespecified clinical outcome, or the study was not relevant to our review. A review of the bibliographies of the selected articles, meta-analyses, and review articles failed to identify additional studies. An additional study was identified by an expert reviewer.
Study Characteristics and Outcomes

Twenty-one studies met the inclusion criteria and were included in the meta-analysis. In all, 1918 patients were randomized to an immunomodulating or standard diet and their clinical outcomes were reported. These studies are summarized in Table 1. Of the 21 studies, 18 used an IMD with added arginine and FO, 2 studies used added arginine alone, and 1 study used FO alone. Impact (Novartis Nutrition, Bern Switzerland), which contains added arginine, FO, RNA, and selenium, was used in 16 studies, whereas Stresson (Nutricia, The Netherlands), which contains added arginine, FO, and selenium, was used in 2 studies. In 15 studies, the IMD was given postoperatively, whereas 5 studies used the IMD during the perioperative (both preoperative and postoperative) period, and 1 study used preoperative immunonutrition alone. Fifteen studies enrolled patients undergoing abdominal surgery for a gastrointestinal (GI) malignancy, 2 studies evaluated patients undergoing general abdominal surgery, 3 studies evaluated head/neck surgery patients undergoing resection for malignancy, and 1 study enrolled high-risk cardiac surgery patients.

Infectious complications were reported in all studies, LOS in 17 studies, and wound complications in 11 studies. Immunonutrition significantly reduced the risk of acquired infections (OR 0.49; 95% CI, 0.39–0.62, P < .0001). This benefit was noted in the postoperative and perioperative subgroups that received an IMD with both arginine and FO (Figure 1). Similarly, the risk of infection was lower in those studies that enrolled patients with GI malignancy (OR 0.44; 95% CI 0.34–0.59) as well as those without GI malignancy (OR 0.50; 95% CI 0.32–0.77). There was a trend toward a lower infection rate in the arginine-only group (n = 2) as well as the preoperative group that received arginine and FO (n = 1); however, given the small number of patients (and studies), this did not reach statistical significance. In terms of infectious complications, the data suggest that the benefit of immunonutrition required both arginine and FO. Furthermore,
Figure 1. Effect of immunomodulating diets (IMDs) on acquisition of new infections, stratified by both the type of IMD and the time of initiation of the experimental diet. Weight is the relative contribution of each study to the overall treatment effect (odds ratio and 95% confidence interval [CI]) on a log scale assuming a fixed effects model. FO, fish oil; A-F, arginine and fish oil; M-H, Mueller-Hinton.
the treatment effect did not appear to depend on the timing of the initiation of the IMD. In most studies, wound infections, pneumonia, and other postoperative infections were grouped together as “infectious complications,” and we were unable to break down the infections complications by site. Wound complications (OR 0.60; 95% CI 0.40–0.91, \( P = .02 \)) and LOS (−3.03 days; 95% CI −3.43 to −2.64 days, \( P < .0001 \)) were significantly reduced in the patients who received an IMD (Figures 2 and 3). The mortality rate was 1% in both groups. There was significant heterogeneity between studies for the LOS analysis; however, the Q statistic was insignificant for the analysis of infectious and wound complications.

**Discussion**

This meta-analysis demonstrates that immunonutrition formulas with added arginine and FO reduce the risk of acquired infections, reduce wound complications, and shorten hospital LOS in high-risk patients undergoing elective surgery. Although the majority of studies included in this review enrolled patients with GI malignancies, 2 studies enrolled patients undergoing general abdominal surgery, 3 studies enrolled patients with head/neck malignancy, and 1 study enrolled high-risk patients undergoing cardiac surgery (age >70 years, ejection fraction <40% or mitral valve replacement). The treatment benefit was noted among all patient groups. The data suggest that patients at high risk of postoperative complications (malnourished and high-risk patients) may benefit from an immunonutrition enteral diet.

Although an IMD with added arginine failed to improve outcomes in trauma patients and patients with sepsis,\(^{15}\) this analysis reports that these IMDs are beneficial in high-risk elective surgery patients. The biological explanation for these differences in clinical outcomes is unclear. It is likely that in patients with trauma and sepsis, arginine supply and metabolism are adequate for arginine action and that additional arginine has no effect. It has also been postulated that arginine may augment inflammatory responses in these patients. For example, conversion of arginine to nitric oxide is increased in patients with sepsis. In contrast, arginine levels are decreased and arginine degradation (via arginase) is increased in patients with surgical trauma. In high-risk surgical patients, arginine may restore depressed humoral and cell-mediated immunity and promote wound healing. In experimental studies, L-arginine improved wound healing, restored postoperative depressed macrophage function and lymphocyte responsiveness, and augmented resistance to infection.\(^{14,16,53}\) Improved indices of cell-mediated immunity have been demonstrated in postoperative patients who received an arginine-containing IMD.\(^{31,34,50,4,56}\) Tepaske et al\(^{50}\) demonstrated that patients treated preoperatively with an arginine-containing IMD had increased expression of human leukocyte antigen–DR epitopes on monocytes and significantly lower levels of serum interleukin-6.\(^{50}\) These patients had an improved delayed hypersensitivity response to recall antigens, which
Figure 3. Effect of immunomodulating diets (IMDs) on length of hospital stay (LOS). Weight is the relative contribution of each study to the overall treatment effect (fixed effects model of weighted mean difference with 95% confidence interval [CI]). A–F, arginine + fishoil; IV.

Surgery induces a potent local and systemic inflammatory response manifest by changes in plasma concentrations of various acute-phase proteins and proinflammatory cytokines.\(^{56,59}\) Elevation of these substances is associated with an increased risk of infectious complications and overall morbidity.\(^ {60}\) ω-3 PUFAs found in FO have potent anti-inflammatory properties.\(^ {5,6}\) These anti-inflammatory effects are mediated through a variety of mechanisms that include alterations in membrane structure and function, modulation of signaling pathways, suppression of proinflammatory transcription factors such as nuclear factor-κB, alterations in

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>IMD Mean</th>
<th>IMD SD</th>
<th>IMD Total</th>
<th>Control Mean</th>
<th>Control SD</th>
<th>Control Total</th>
<th>Mean Difference IV, Fixed, 95% CI Year</th>
<th>Mean Difference IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>3.2.1 Arginine</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>de Luis 2005</td>
<td>22.8</td>
<td>11.8</td>
<td>23</td>
<td>31.2</td>
<td>19</td>
<td>24</td>
<td>-8.4 (-17.40, 0.60) 2005</td>
<td></td>
</tr>
<tr>
<td>Casas-Rodera 2008</td>
<td>22.4</td>
<td>9.4</td>
<td>15</td>
<td>18.2</td>
<td>7.5</td>
<td>15</td>
<td>4.20 (-1.89, 10.29) 2008</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>38</td>
<td>0.6%</td>
<td>39</td>
<td>0.25</td>
<td>[4.79, 5.29]</td>
<td></td>
<td></td>
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</tbody>
</table>

Heterogeneity: $\chi^2 = 5.17, df = 1 (P = 0.02); I^2 = 81%$
Test for overall effect: $Z = 0.10 (P = 0.92)$

**3.2.2 A-F preoperative**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>IMD Mean</th>
<th>IMD SD</th>
<th>IMD Total</th>
<th>Control Mean</th>
<th>Control SD</th>
<th>Control Total</th>
<th>Mean Difference IV, Fixed, 95% CI Year</th>
<th>Mean Difference IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xu 2005</td>
<td>9.0</td>
<td>2.2</td>
<td>30</td>
<td>12</td>
<td>3.7</td>
<td>30</td>
<td>-3.00 (-4.54, -1.46) 2006</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>30</td>
<td>0.5%</td>
<td>30</td>
<td>-3.00 [-4.54, -1.46]</td>
<td>2006</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Not applicable
Test for overall effect: $Z = 3.82 (P = 0.0001)$

**3.2.3 A-F postoperative**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>IMD Mean</th>
<th>IMD SD</th>
<th>IMD Total</th>
<th>Control Mean</th>
<th>Control SD</th>
<th>Control Total</th>
<th>Mean Difference IV, Fixed, 95% CI Year</th>
<th>Mean Difference IV, Fixed, 95% CI</th>
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<tr>
<td>Daly 1992</td>
<td>18.8</td>
<td>11.1</td>
<td>41</td>
<td>20.4</td>
<td>9.6</td>
<td>44</td>
<td>-1.60 (-6.03, 2.83) 1992</td>
<td></td>
</tr>
<tr>
<td>Daly 1993</td>
<td>16.0</td>
<td>0.9</td>
<td>30</td>
<td>22</td>
<td>2.9</td>
<td>30</td>
<td>-13.11 (-7.09, -9.11) 1995</td>
<td></td>
</tr>
<tr>
<td>Schilling 1996</td>
<td>14.7</td>
<td>4.0</td>
<td>14</td>
<td>20.3</td>
<td>3.5</td>
<td>14</td>
<td>-5.60 (-12.72, 1.52) 1996</td>
<td></td>
</tr>
<tr>
<td>Braga 1996</td>
<td>13.6</td>
<td>6.1</td>
<td>20</td>
<td>15.5</td>
<td>3.5</td>
<td>20</td>
<td>-1.90 (-4.98, 1.18) 1996</td>
<td></td>
</tr>
<tr>
<td>Gianotti 1997</td>
<td>16.1</td>
<td>6.2</td>
<td>87</td>
<td>19.2</td>
<td>7.9</td>
<td>87</td>
<td>-3.50 (-5.21, -0.90) 1997</td>
<td></td>
</tr>
<tr>
<td>Senkal 1997</td>
<td>27.2</td>
<td>2.3</td>
<td>77</td>
<td>30.5</td>
<td>3.1</td>
<td>77</td>
<td>28.80 (-44.46, -2.74) 1997</td>
<td></td>
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<tr>
<td>Braga 1999</td>
<td>13.7</td>
<td>4.8</td>
<td>55</td>
<td>16.1</td>
<td>5.9</td>
<td>55</td>
<td>-2.40 (-4.41, -0.39) 1999</td>
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<tr>
<td>Snyderman 1999</td>
<td>15.3</td>
<td>9.1</td>
<td>82</td>
<td>17.4</td>
<td>11.9</td>
<td>47</td>
<td>1.00 (-6.03, 8.03) 1999</td>
<td></td>
</tr>
<tr>
<td>Di Carlo 1999</td>
<td>16.3</td>
<td>6.2</td>
<td>33</td>
<td>17.8</td>
<td>6.9</td>
<td>35</td>
<td>-1.50 (-4.81, 1.81) 1999</td>
<td></td>
</tr>
<tr>
<td>Farreras 2006</td>
<td>13.2</td>
<td>3.0</td>
<td>30</td>
<td>15</td>
<td>2</td>
<td>30</td>
<td>15.1% (-3.01, -0.99) 2006</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>469</td>
<td>61.5%</td>
<td>439</td>
<td>-3.48 [-3.98, -2.98]</td>
<td>2005</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 34.25, df = 9 (P < 0.0001); I^2 = 74%$
Test for overall effect: $Z = 13.60 (P < 0.0001)$

**3.2.4 A-F perioperative**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>IMD Mean</th>
<th>IMD SD</th>
<th>IMD Total</th>
<th>Control Mean</th>
<th>Control SD</th>
<th>Control Total</th>
<th>Mean Difference IV, Fixed, 95% CI Year</th>
<th>Mean Difference IV, Fixed, 95% CI</th>
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</thead>
<tbody>
<tr>
<td>Braga 1999</td>
<td>11.1</td>
<td>4.4</td>
<td>102</td>
<td>12.9</td>
<td>4.6</td>
<td>104</td>
<td>-1.80 (-3.03, -0.57) 1999</td>
<td></td>
</tr>
<tr>
<td>Senkal 1999</td>
<td>22.2</td>
<td>4.1</td>
<td>78</td>
<td>25.8</td>
<td>3.8</td>
<td>76</td>
<td>-3.60 (-4.85, -2.35) 1999</td>
<td></td>
</tr>
<tr>
<td>Braga 2002</td>
<td>12.0</td>
<td>3.8</td>
<td>50</td>
<td>15.3</td>
<td>4.1</td>
<td>50</td>
<td>-3.30 (-4.85, -1.75) 2002</td>
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<tr>
<td>Heiminen 2007</td>
<td>10.0</td>
<td>4.0</td>
<td>50</td>
<td>9.5</td>
<td>5</td>
<td>50</td>
<td>4.59 (0.77, 2.27) 2007</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>280</td>
<td>31.4%</td>
<td>280</td>
<td>-2.24 [-2.94, -1.54]</td>
<td>2007</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 19.65, df = 3 (P = 0.0002); I^2 = 85%$
Test for overall effect: $Z = 13.60 (P < 0.0001)$

**Total (95% CI)**

<table>
<thead>
<tr>
<th>IMD Mean</th>
<th>IMD SD</th>
<th>IMD Total</th>
<th>Control Mean</th>
<th>Control SD</th>
<th>Control Total</th>
<th>Mean Difference IV, Fixed, 95% CI Year</th>
<th>Mean Difference IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>817</td>
<td>788</td>
<td>100.0%</td>
<td>-3.03 [-3.43, -2.64]</td>
<td>2007</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 68.66, df = 16 (P < 0.00001); I^2 = 77%$
Test for overall effect: $Z = 15.14 (P < 0.00001)$
Test for subgroup differences: $\chi^2 = 9.58, df = 3 (P = 0.02), I^2 = 66.7%$

persisted until hospital discharge. Arginine is metabolized by arginase into urea and ornithine.\(^ {57}\) Ornithine is subsequently converted to proline, the backbone of collagen, and polyamines, essential regulators of cell proliferation. Farreras and coauthors\(^ {46}\) randomized patients undergoing abdominal surgery to receive an IMD supplemented with arginine and ω-3 PUFA or a control diet.\(^ {46}\) In this study, patients fed with the arginine/ω-3–supplemented formula had higher local hydroxyproline levels in their surgical wounds and developed fewer surgical wound complications.
gene expression, and modulation of eicosanoid production. FO has been shown to reduce arachidonic acid and increase eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) levels in membrane phospholipids. The increased concentrations of EPA in phospholipids compete with arachidonic acid for cyclooxygenase and 5-lipoxygenase binding sites, reduce eicosanoid formation from arachidonic acid, and thereby reduce tissue inflammation without compromising mononuclear cell function. These effects may play important roles in suppressing the generalized inflammatory response and subsequent immunosuppression and capillary leakage after major surgery. In addition, resolvins and protectins are novel ω-3 fatty acid products derived from EPA and DHA following neutrophil–endothelial interactions. These lipid mediators are reported to play an important role in the resolution of inflammation and promotion of wound healing.

In this meta-analysis, we report improved clinical outcomes (infection rates, wound complications, LOS) in elective surgery patients receiving an enteral diet supplemented with arginine and ω-3 polyunsaturated fatty acids. In contrast, in our previous meta-analysis of 8 studies of trauma patients admitted to the ICU, we reported no improvement in mortality, infections, or length of hospital stay using similar formulations. It is unclear why trauma patients do not respond to these diets in the same manner as elective surgery patients. However, the metabolic response to traumatic tissue injury may be different than surgical tissue injury. In addition, the trauma patients had multiple organ injuries that differ from the isolated tissue effects of elective surgery (ie, removal of malignant tissue). Further studies are required to delineate the different metabolic responses of these 2 patient populations.

The results of our meta-analysis suggest that both perioperative and postoperative immunonutrition reduces secondary infections, wound complications, and hospital LOS. The treatment effect did not depend on the timing of the initiation (ie, preoperatively, postoperatively) of the enteral formula. However, it is probable that the benefit of an IMD takes a number of days to manifest. In our previous meta-analysis of septic patients, we reported no differences in mortality, infections, or length of hospital stay using similar formulations. It is unclear which formulations are optimal for the surgical patient with an infection. We postulate that these patients are similar to elective surgery patients in terms of low arginine and high arginase activity. However, a randomized clinical trial will be required to define the optimal nutrition formulations for such patients.

The majority of studies in this meta-analysis were performed with the product Impact (Novartis Nutrition, Bern, Switzerland). This enteral formulation contains added antioxidants and nucleotides. It is unclear whether the clinical benefits of the formulation result from 1 or more of the supplemented nutrients. It is also unclear whether the effects from this formulation can be extrapolated to other immune formulations that differ in composition. Further study is required to address these issues. The strength of our meta-analysis includes the fact that we used several methods to reduce bias (comprehensive literature search, duplicate data abstraction, pre-specified criteria for analysis) and analyzed standardized and clinically important clinical outcomes (by intention-to-treat analysis). The major limitation of our study was the small number of studies in certain subgroups according to type of IMD used.

We have demonstrated that IMDS have important beneficial effects on clinical outcomes in both malnourished and nonmalnourished high-risk surgical patients. Furthermore, our study suggests that arginine and ω-3 PUFAs may act synergistically to improve outcomes in noninfected surgical patients. Although the optimal time to initiate immunonutrition (ie, preoperatively vs postoperatively) could not be determined from this meta-analysis, both experimental and clinical data support the concept that immunonutrition may be more effective when initiated prior to the surgical insult. We recommend starting at least 5 days prior to surgery and continuing into the postoperative period, when such initiation is feasible.
References


