Immune-Enhancing Diets: Improving Outcomes in Multiple Trauma and Gastrointestinal Cancer Resection

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ABSTRACT Immune-enhancing diets are nutritionally complete enteral nutrition formulations that contain supplemental doses of arginine, glutamine, omega-3 fatty acids, nucleotides, and beta carotene. The components in these formulations have been demonstrated to stimulate immune function and down-regulate the stress response to injury and infection. There are now sufficient data to demonstrate improved clinical outcomes in patients who receive these products in the post-injury period of multiple trauma or post-surgical period following gastrointestinal cancer resection.

Critical illness or major surgery usually results in hypermetabolism, hypercatabolism, immunosuppression, and erosion of body cell mass. Some patients suffering from these metabolic alterations can develop sepsis, septic shock, and multiple organ dysfunction syndrome, resulting in increased utilization of health care resources from prolonged stays in the intensive care unit (ICU) and hospital. Administration of specialized nutrition support as parenteral or enteral nutrition can maintain or improve some nutritional indices such as serum proteins and nitrogen balance in critically ill patients. However, traditional specialized nutritional support does not preserve body cell mass or help to attain an immunocompetent state.

Some investigators have suggested that the route of specialized nutrition support is important in determining which patients will be subjected to septic morbidity. Most of these data favor the enteral route for the delivery of nutritional support during critical illness, and this route should be used whenever possible. There is still a subset of patients, however, who do not tolerate enteral nutrition even when access is obtained. These patients must receive parenteral nutrition or a combination of both enteral and parenteral nutrition to meet nutritional needs until an oral diet can be safely achieved.

NUTRITIONAL COMPONENTS AND AVAILABLE PRODUCTS

Recently, there has been widespread interest in the use of specific nutrients to enhance immune function, especially in critically ill patients. Specifically, diets enhanced with glutamine, arginine, omega-3 fatty acids, nucleotides, or antioxidants (e.g., vitamins A, C, and E) have been used in basic and clinical research studies. Glutamine has been shown to stimulate enterocyte function in the gastrointestinal tract and to enhance the ability of neutrophils to fight antimicrobial infections. Bone marrow transplant patients given glutamine-supplemented parenteral nutrition had a reduced incidence of infection and shortened hospital stays when compared to controls receiving parenteral nutrition without glutamine. Arginine supplementation results in increased secretion of human growth hormone, insulin-like growth factor-1, and insulin, and leads to improved immune function. Healthy elderly males and females supplemented with arginine for 14 days prior to being subjected to small subcutaneous wounds demonstrated increased hydroxyproline accumulation and total protein content in the wound catheter, as well as improved in vitro lymphocyte nitogen stimulation tests. Immunosuppressive eicosanoids (e.g., PGE_{2}) are synthesized when omega-6 fatty acids compose the entire portion of lipid in the diet. Replacement of some omega-6 fatty acids with omega-3 fatty acids results in eicosanoids that are much less suppressive. Supplemental nucleotides might improve natural killer cell activity; vitamins A, C, and E enhance immune function through their antioxidant properties.

There are now several commercially available enteral nutrition formulas, referred to as immune-enhancing diets (IEDs), that contain combinations of the nutrients that affect immunocompetence (Table 1). The IEDs are nutritionally complete and can be used as the sole source of nutrition support in patients; however, they are substantially more expensive than standard enteral formulas. Most of the clinical trials to date have had critically ill trauma or burn patients, or patients with upper gastrointestinal malignancies. This review focuses on the clinical studies of IEDs that have been published in peer-reviewed journals and assessed measurement of clinical outcomes, and two recent meta-analyses that have been published addressing the use of these products.

CRITICAL CARE

The first study in the critical series (Table 2) was prospective, randomized, and double-blinded; it came from the Shriners Burns Institute in Cincinnati, Ohio. Fifty patients with thermal injuries (10–89% of total body surface area) were randomized to receive either a modular tube feeding formula developed by this group or one of two control formulas. The modular tube feeding formula contained enhanced concentrations of arginine, omega-3 fatty acids, cysteine, histidine,
Immune-Enhancing Diets

A prospective, randomized clinical trial was conducted in 37 multiple trauma patients assigned to either an IED or a control formula with added protein to make them nearly isonitrogenous. The IED in this study was supplemented with arginine, omega-3 fatty acids, and nucleotides, or a standard elemental formula. The patients randomized to the IED demonstrated a significantly lower incidence of intra-abdominal abscess and multiple organ dysfunction syndrome; they also showed improved measurements of immune function. The enteral formulas in this unblinded study were not isonitrogenous because arginine and glutamine were added. Therefore, it was not possible to attribute the clinical benefit to the IED because of differences in nitrogen intake.

A prospective, randomized clinical trial was conducted in 37 multiple trauma patients assigned to either an IED or a control formula with added protein to make them nearly isonitrogenous. The IED in this study was supplemented with arginine, omega-3 fatty acids, and beta carotene. The patient group receiving the IED had fewer infections compared to the group receiving the control formula (3/19 vs. 10/18). The patients in the IED group had more patients with jejunostomy tubes (8/19 vs. 1/18) and they were given enteral nutrition sooner than the control group (3.5 vs. 5 days from admission). These two variables might have contributed to the positive results in clinical outcome.

Another study conducted with an IED included 326 patients, from eight centers, who either sustained multiple trauma, underwent a major surgical operation, or were severely injured. Thirty of these ICU patients were excluded, leaving 168 to receive the IED (arginine, omega-3 fatty acids, nucleotide supplementation) and 158 to receive the standard enteral formula. This was a prospective, randomized, double-blinded clinical trial. The rate of enteral feeding was advanced to 60 mL/hr, after which time it was adjusted based on indirect calorimetry. There was no significant difference in mortality rate between the two groups. The length of hospital stay decreased from 29 to 21 days in the group receiving an IED—they actually received an average of 821 mL/d when compared to a similar group of control patients.

IED patients who had sepsis (according to the American College of Chest Physicians/Society for Critical Care Medicine [ACCP/SCCM] guidelines) at study entry had a significant decrease in hospital stay—from 28 to 18 days—when compared to septic patients receiving the control formula. The ACCP/SCCM guidelines were developed to help standardize definitions of disease states and clinical conditions such as pneumonia, sepsis, and acute respiratory distress syndrome.

Length of hospital stay also decreased significantly in septic patients receiving at least 821 mL/d of an IED when compared to a similar group of control patients (28.5 to 17 days). Positive findings in clinical outcome were demonstrated only after extensive subgroup analysis (e.g., patients with sepsis who actually received close to the prescribed rate over a seven-day period benefited from the IED). Also, the IED contained more nitrogen than the control formula because arginine had been added to it.

Kudsk et al. conducted a prospective, randomized, double-blinded study of 35 trauma patients who had an abdominal trauma index of 25 or greater or an injury severity score of less than or equal to 21. These very ill patients were fed by jejunostomy and randomized to either an IED containing supplemental glutamine, arginine, omega-3 fatty acids, and nucleotides, or to an isonitrogenous control. A group of 19 patients who would have qualified for the study but did not have jejunostomies placed served as a delayed-feeding control group.

The percentage of patients with major infections was significantly lower in the IED group (6%) compared to the isonitrogenous controls (41%) and the delayed-feeding controls (58%). This study was better controlled than the first one in trauma patients because bronchoalveolar lavage was used for the diagnosis of pneumonia, and an isonitrogenous group and a delayed-feeding group were both available for comparative analysis. Several other clinical outcome measurements approached statistical significance, so an increased number of patients would have strengthened the conclusions if the same trends continued.

A prospective, randomized, blinded study design was used to examine the effects of IED on several clinical outcome measurements in 59 trauma patients. There were no significant differences between groups in mortality, length of hospital stay, or length of ICU stay. This study suffered from a small number of evaluable patients (22 in the experimental group and 21 in the

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control group) and used patients enrolled in other clinical trials, including one studying the use of antioxidants.

Saffle et al.\textsuperscript{16} reported on the use of IED in 50 thermally injured patients. This prospective, randomized, double-blinded study reported similar clinical outcomes; however, there were several flaws in the methods of this relatively small study. Non–fiber-containing enteral formulas were used for the first three months and fiber-containing formulas were used for the remainder of the study. In addition, the control enteral formula contained substantial amounts of glutamine and omega-3 fatty acids. Both children and adults were used in this study; children tolerated thermal injury better than the adults and their nutritional needs were adjusted according to body weight.

Three hundred ninety-eight patients hospitalized in an ICU were randomized to an IED or an isocaloric, isonitrogenous control enteral formula.\textsuperscript{17} Of these 398 patients, 390 were retained and received some enteral nutrition. A group of 101 patients who received more than 2.5 liters over the first 72 hours comprised the early enteral nutrition group. There was no significant difference between groups in terms of mortality; however, the early enteral nutrition group receiving the IED was reported to have a significantly decreased length of hospital stay and decreased time receiving mechanical ventilation.

In a small study involving 29 trauma patients, those who received IEDs had a significant decrease in the amount of systemic inflammatory response syndrome and lower multiple organ failure scores when compared to patients receiving control enteral formulas.\textsuperscript{18} No other significant difference in clinical outcome measurements (i.e., length of stay, days of mechanical ventilation, or infectious disease) was observed between the two groups. Interestingly, both groups of patients received parenteral nutrition, which has been shown to be immunosuppressive independent of the primary disease process. This confounding variable and the small number of patients in the study might have masked any potential differences between the two groups.

A high-fat, low-carbohydrate enteral formula enhanced with fish oil (eicosapentaenoic acid) and borage oil (gamma linolenic acid) was compared with a standard high-fat, low-carbohydrate enteral formula in patients receiving mechanical ventilation who were predisposed to developing acute respiratory distress syndrome (ARDS).\textsuperscript{19} These fatty acids are known to be less inflammatory than omega-6 fatty acids. This prospective, randomized, double-blinded, multicenter trial reported on 146 ICU patients. Only 98 of the patients were evaluable because some were unable to receive enteral nutrition for at least four days and others had pretreatment oxygenation measurements that were outside the required range. Data on clinical outcomes were analyzed both in evaluable patients and by intention-to-treat analysis. In both analyses, patients receiving the enteral formulations with fish and borage oil demonstrated superior oxygenation, spent less time receiving mechanical ventilation, and had fewer organ failures.

Galban et al.\textsuperscript{20} recently reported on 181 septic ICU patients who were randomized to either an IED or a control formula similar in total calories and nitrogen. After five patient exclusions, 89 patients received the IED and 87 received the control formula. The mortality rate was significantly lower in moderately ill patients who received the IED. Fewer patients in the IED group had bacteremia when compared to controls. There was no significant change in length of hospital stay or number of days of mechanical ventilation.

### Gastrointestinal Cancer

The formulations for nutrition support were isocaloric and isonitrogenous. Immune markers were significantly better in the group receiving the IED. There have also been several clinical trials in which IEDs were used during the postoperative management of patients who had surgery for upper or lower gastrointestinal tract carcinoma (Table 3). In many of these trials, jejunostomy tubes were surgically placed following the carcinoma resection.

Eighty-five patients who were operated on for upper gastrointestinal malignancy and jejunostomy placement were randomized to an IED supplemented with arginine, omega-3 fatty acids, and nucleotides or to a control formula.\textsuperscript{21} In this prospective, randomized clinical trial, the group receiving the IED demonstrated a significantly decreased percentage of patients with infectious/wound complications compared to the control patients (11% vs. 37%). The length of hospital stay was significantly shorter for the patients receiving the IED when compared to the controls (15.8 ± 5.1 vs. 20.2 ± 9.4 days). The patients in the experimental group received significantly more nitrogen because of the added arginine, and had a better nitrogen balance when it was measured. Also, clinical outcomes such as pneumonia and wound infections were not as precisely defined as in other studies. It was not possible to assess whether the improvements in clinical outcome in this study were caused by the IEDs or the increased nitrogen doses received by the patients in the experimental group.

Daly et al.\textsuperscript{22} studied 60 adult patients with upper gastrointestinal tract malignancy using an IED and an isonitrogenous control formula. This was a prospective, randomized, clinical trial, in which patients were assigned one of the two enteral

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**Table 1 Immune-Enhancing Enteral Formulas Available in the U.S.**

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Kcal/ mL</th>
<th>g protein/L</th>
<th>Immune-Enhancing Components</th>
</tr>
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<tbody>
<tr>
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<td>94.2</td>
<td>arginine, fish oil</td>
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<td>56</td>
<td>arginine, fish oil, nucleotides</td>
</tr>
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</tr>
<tr>
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</tr>
<tr>
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<td>arginine, glutamine, alpha-linolenic acid</td>
</tr>
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<td>62.5</td>
<td>borage oil, fish oil</td>
</tr>
<tr>
<td>Perative</td>
<td>1.3</td>
<td>51.2</td>
<td>arginine, alpha-linolenic acid, beta carotene</td>
</tr>
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</table>
formulas after surgical resection and jejunostomy tube placement. The IEDs contained supplemental arginine, omega-3 fatty acids, and nucleotides. Only 10% of patients receiving an IED had infectious/wound complications, compared to 43% of the patients receiving the control formula. Mean length of hospital stay was reduced in the group receiving IEDs when compared to controls (16 vs. 22 days). The investigators of this study used an isonitrogenous control formula, which strengthened the earlier observations by this same group.21

Fifty adult patients who had upper gastrointestinal tract malignancy and were scheduled for resection and jejunostomy placement were randomized to either a standard control formula or an IED supplemented with a fish oil.23 This was a prospective, randomized, double-blinded study using isonitrogenous formulas. There was a 50% decrease in gastrointestinal complications and infections in the group receiving the IED diets. Also, renal and hepatic function appeared to improve in the group receiving the IED. The dropout rate (30% of all patients, mainly because of gastrointestinal intolerance) was quite high, although the patients in this particular study were older than those in the studies involving patients with trauma or burns. This same group confirmed that patients with upper gastrointestinal malignancy resections, and who were given enteral nutrition formulas containing fish oil, had a profound decrease in eicosanoid production.24

In a prospective, randomized, controlled study, 164 patients with upper gastrointestinal malignancy requiring resection were given IEDs containing arginine, fish oil, and nucleotides or an isocaloric, isonitrogenous control formula.25 One hundred and fifty patients remained after patients who withdrew and those who were not receiving the required enteral nutrition dose were dropped. There were 77 patients remaining in each group. Late postoperative complications were significantly lower in the group receiving the IEDs, but there was no significant difference in mortality. Lengths of stay in the ICU and the hospital were shorter for the group receiving the IEDs; however, the difference was not statistically significant.

Heslin et al.26 randomized 195 patients with upper gastrointestinal malignancies to either postoperative enteral nutrition with an IED or intravenous crystallloid and gradual introduction of fluids. The IEDs contained supplemental arginine, omega-3 fatty acids, and nucleotides. Only 10% of patients receiving an IED had infectious/wound complications, compared to 43% of the patients receiving the control formula. Mean length of hospital stay was reduced in the group receiving IEDs when compared to controls (16 vs. 22 days). The investigators of this study used an isonitrogenous control formula, which strengthened the earlier observations by this same group.21

Fifty adult patients who had upper gastrointestinal tract malignancy and were scheduled for resection and jejunos-
of an oral diet. The authors reported no significant differences between groups in mortality, length of stay, and infectious complications. It is notable in this study that the patients were not undernourished, whereas in most of the other clinical trials, these types of patients suffered substantial weight loss or had low serum protein concentrations.

Two hundred sixty patients with either gastric or pancreatic cancer were studied in a prospective, randomized clinical trial. Patients were assigned to one of three treatment groups following surgical resection: enteral nutrition with an IED, enteral nutrition with a standard control formula, or parenteral nutrition. Length of stay was significantly shorter in the IED group when compared to the other two groups. The infectious complication rate was lower in the IED group and approached statistical significance. This same group reported in a follow-up study of patients with cancer of the colon, stomach, or pancreas. After surgical resection, the patients were randomized to receive 1,000 mL of either an IED or a standard enteral formula by mouth daily. Infectious complications and length of hospital stays were both significantly reduced in the group receiving the IEDs.

CONCLUSION

Most of these IED studies have demonstrated improved clinical outcomes in a primarily surgical population. Each clinical study had some flaws in design and conduct; however, when these trials are viewed together, the data are nevertheless compelling. The studies that have used isonitrogenous controls and confirmed that the improvement in clinical outcome in patients receiving IEDs are more likely caused by the formulations. When there is a substantial difference in protein intake in two comparable groups, it is impossible to differentiate the impact of the respective formulas from the difference in protein intake. For instance, Alexander et al demonstrated several years ago that a high protein intake in thermally injured pediatric patients resulted in improvements of many measurements of immune function when compared to similar patients given standard protein doses. Two recent meta-analyses of these products have supported the notion that IED decreases length of hospital stay and postoperative infectious complications. There does not appear to be a major effect on overall mortality from using these products. These data would suggest that the increased cost of these products can be justified. Patients who would have met the criteria for entry into these studies (e.g., major trauma, major thermal injury, major surgery for carcinoma) should be considered candidates for IEDs, especially when early access to the gastrointestinal tract is obtained. Further research can identify other patient populations who will benefit nutritionally, immunologically, and clinically from IEDs.

REFERENCES