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IMMUNONUTRITION IN SURGERY AND CRITICAL CARE

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■ **Abstract** The benefits of specialty supplemented enteral diets administered to critically ill and critically injured patients and those undergoing major surgical procedures have been documented in a number of randomized prospective studies. It is unclear which nutrient or combination of nutrients causes the beneficial effects, but there are significant reductions in infectious complications depending upon the patient populations studied. It is imperative that the data be interpreted in the context of individual patient risk since specialty formulas appear most beneficial in patients at risk of subsequent complications or in those with significant pre-existing malnutrition. Although controversy exists regarding the use of specialty supplemented enteral diets in critically ill patients, they have been administered safely with minimal risk of adverse outcome in malnourished patients and in the critically ill and critically injured.

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INTRODUCTION

Over the past two and a half decades, a number of clinical trials have compared enteral nutrition to starvation (30, 35) or parenteral nutrition (28, 34, 36) following general surgery or after severe injury. In toto, these studies demonstrated significant reductions in septic morbidity in the enterally fed group associated with shorter lengths of stay and/or reduced costs. Although the mechanism(s) explaining this improvement are as yet unknown, these results are supported by a meta-analysis of the randomized trials (17). Although most early trials used elemental or semi-elemental enteral formulas to test the hypothesis of improved outcome with enteral feeding, more complex formulas containing fiber (which was shown not to clog small-bore feeding tubes) or other specialty nutrients appeared on the market. Many of these formulas were enriched with specialty nutrients including arginine and omega-3 fatty acids (obtained from canola or fish oil). Other formulas were supplemented with glutamine and/or nucleotides and/or beta-carotene and/or branched-chain amino acids (BCAAs) in addition to the omega-3 and arginine. This group of formulas is commonly referred to as immune-enhancing diets or immunonutrition. Although clear evidence of benefit with these diets exists in specific populations, studies with other patient populations show no benefit or deleterious effects (2, 19, 21). This review addresses the appropriate patient identification for use of these specialty nutrient solutions.

RATIONALE FOR INDIVIDUAL COMPONENTS IN COMMERCIALLY AVAILABLE FORMULAS

Omega-3 Fatty Acids

Omega-3 polyunsaturated fatty acids (PUFAs) obtained from either fish or canola oil replace a significant amount of the vegetable oil–derived omega-6 fatty acids for a lipid energy source. The PUFAs rapidly accumulate in cell membranes and plasma phospholipids (24). Their metabolic effects occur during stress when phospholipases cleave the PUFAs from the membrane for entry into metabolic pathways that produce specific products. Omega-6 fatty acids are precursors of the 2- and 4-series prostanoids, which are vasoconstrictive and induce platelet aggregation (18, 39). These immunosuppressive products impair cytotoxic T-lymphocyte function, cytokine secretion, leukocyte migration, and reticuloendothelial system function (18). Omega-3 PUFAs are metabolized to the 3-series of prostanoids and the 5-series of leukotrienes, which are less inflammatory and less immunosuppressive. Whether omega-6 fatty acids derived from fish oil or canola oil differ in their effects is less clear.

Arginine

Arginine becomes an essential amino acid during periods of stress due to its use in tissue repair and due to upregulation of arginase following trauma. Arginine serves as a precursor for proline, glutamate, and polyamines and is used for ammonia detoxification. Its role in nitric oxide synthesis (38) has generated controversy regarding its safety in critically ill or septic patients (2, 21). Depletion of arginine reduces wound healing and Kupfer cell function. Supplementation promotes proliferation of T-cells in vitro and increases natural killer cell cytotoxicity, macrophage tumor cytotoxicity, and cytolytic T-cell activity (25). It stimulates prolactin insulin-like growth factor, pituitary human growth hormone, and insulin.

Glutamine

Glutamine (GLN) (40, 43, 44) is the most abundant free amino acid in the cytosol. Although GLN and alanine comprise only 6%–8% of structural muscle protein, GLN and alanine constitute 70% of the amino acids released by skeletal muscle during stress and sepsis. During stress, serum and intracellular concentrations of GLN decrease, and under these conditions, it becomes an essential amino acid. GLN provides metabolic fuel for T-lymphocytes, enterocytes, and other rapidly proliferating cells. One drawback to GLN in feedings is the propensity for the free amino acid to degrade in solution into a toxic product—pyroglutamate—particularly during heat sterilization. Therefore, formulas with free glutamine amino acids are packaged dry and require reconstitution just prior to their administration. Recently, the use of proteins rich in glutamine eliminated toxicity issues in prepared liquid formulas.

Nucleotides (RNA)

Nucleotide deprivation inhibits T-cell and macrophage function and increases susceptibility to sepsis with *Staphylococcus aureus* and *Candida albicans* in animal models (32). Administration of RNA during refeeding reverses these defects.

Branched-Chain Amino Acids

BCAAs provide the primary fuel for skeletal muscle during stress and sepsis. The leucine, isoleucine, and valine are added to formulas as a metabolic source to supplement skeletal muscle metabolic needs during these metabolic states.

Overview of These Products in Commercial Products

Different commercial formulas vary in their combinations and concentrations of the individual components described above. Unfortunately, it is impossible to dissect the role of each component and combination since both the component and its concentration are relevant to their effect. However, the commercial formulas have a demonstrated clinical benefit in certain populations. There is also some evidence of potential harm due to augmented inflammatory responses.

CLINICAL EVIDENCE OF IMMUNONUTRITION EFFECTIVENESS (OR LACK OF EFFECTIVENESS)

The Importance of Stratification by Risk

The contradictory results noted in some clinical nutrition trials confound many clinicians. For example, of eleven published randomized prospective trials of perioperative nutrition, authors of six studies concluded that provision of nutrition support resulted in no benefit or poorer outcome, whereas five authors noted improvement (4, 5, 7, 10, 11, 13, 14, 16, 19, 41, 42). Studies that noted no improvement recruited a high percentage of well-nourished patients into the trials. Studies that demonstrated benefit included high numbers of malnourished patients. These studies typify the importance of identification and stratification by risk because administration of nutritional therapy to an individual who is not nutritionally "at risk" is unlikely to demonstrate any benefit.

In 1998, this author suggested that patients in trials and in practice should be stratified by the expected degree of operative stress or injury as well as by nutritional risk (27). Mild or moderate degrees of pre-existing malnutrition do not affect outcome in patients undergoing lesser surgical procedures, but pre-existing nutritional defects increase postoperative complications as the surgical stress increases from minor to moderate to high (e.g., hernia to colectomy to pancreatectomy to esophagectomy). This was first demonstrated in the Veterans Affairs Cooperative Study (41), which randomized 395 preoperative patients to 7–10 days of parenteral nutrition with ad libitum oral intake or to an oral ad libitum diet alone. Measurable but not statistically significant drops in noninfectious complications (such as wound dehiscence and anastomotic leaks) occurred in the parenteral group, but infectious complications in this group were significantly higher (14.1% versus 6.4%, $p < 0.05$). When patients were stratified by nutritional status and risk, results showed that the increase in infectious complications occurred in patients with borderline or mild malnutrition, with no beneficial effect on noninfectious complications in this group. However, parenteral nutrition given to severely malnourished patients reduced infectious complications (21.4% versus 15.8%; ns) and major noninfectious complications (42.9% versus 5.3%; $p < 0.01$), demonstrating that stratification by nutritional risk is important in the interpretation of clinical trials.

RISK STRATIFICATION IN TRAUMA TRIALS The concept of stratification by risk is particularly relevant to trauma trials. In a large randomized trial of enteral versus parenteral feeding (28), patients were stratified into populations at high risk and low risk for complications by two trauma-scoring systems. The systems—Injury Severity Score (ISS) and Abdominal Trauma Index (ATI)—had been validated in earlier trials (29). The ISS is an anatomic scoring system that divides the body into six regions (head/neck, face, thorax, abdomen/pelvic contents, extremities, and external tissues). The most severe injuries in each of the three most injured regions are used in the calculation. An ISS ≥ 20 represents a high risk of complications. One weakness of the system is the underestimation of risk when multiple severe injuries are isolated within one region (such as the abdomen). The ATI addresses this issue for the abdomen. Each abdominal organ carries a risk for septic complications. The higher the number, the greater the risk of sepsis if that organ is injured. The higher numbers are assigned to the pancreas (5), a major vascular injury (5), the duodenum (4), the liver (4), and the colon (4). These individual values are multiplied by a severity score of 1 (a simple contusion) to 5 (a major destructive injury), and the individual scores are summed. The higher the ATI, the greater the risk of complications. An ATI ≥ 25 reflects significantly increased risk. In an enteral versus parenteral trial (28), enterally fed patients sustained significantly fewer pneumonias (31% versus 12%; $p < 0.02$) and significantly fewer intra-abdominal abscesses (13% versus 2%; $p < 0.04$) than did the parenteral group, but the magnitude of injury played an important role. In patients with an ISS < 20 or an ATI < 25, there were no differences between the groups—nutrition was probably not necessary because the risk of complications was low. However, in patients randomized to TPN with an ISS ≥ 20 or an ATI >24, risk of infections increased 6.3 times ($p < 0.002$) and 7.3 times ($p < 0.005$), respectively, in comparison with enterally fed patients. In high-risk patients with both high ATI and high ISS scores, parenteral feeding increased the risk of infection 11.3 times ($p < 0.003$) compared with enteral feeding.

RISK STRATIFICATION IN NUTRITION AND SURGICAL TRIALS A comprehensive analysis of controlled clinical trials for nutrition support validates this concept of stratification by severity of risk and nutritional risk. Kondrup et al. (26) examined how severity of illness and nutritional risk affected results of the nutrition intervention trials. Degrees of severity of disease and malnutrition were defined as absent, mild, moderate, or severe and converted to a validated numeric score that increased as severity of nutrition risk increased. The results of these studies, which correlate nutritional risk with clinical outcome (positive or no effect), are shown in Figure 1. Increasingly positive results with nutrition support were noted if recruited populations had greater severity of illness and malnutrition. Of 75 studies with patients classified as nutritionally at risk (score ≥3), 43 showed a positive effect of nutrition support on outcome. Of 53 studies of patients not considered to be at risk by nutritional status and severity of illness (score <3), only 14 showed any positive effect ($p = 0.0006$).

We recently studied a group of surgical patients undergoing elective resection anastomosis of the esophagus, stomach, pancreas/duodenum, or colon and showed a strong inverse correlation between preoperative albumin and postoperative surgical complications (Figure 2) (31). To be included, all patients must have been capable of receiving preoperative nutrition, but the physician chose not to provide it. Esophageal and pancreatic procedures resulted in significantly higher complication rates than did colon or gastric procedures at all albumin levels below 3.5 g/dL. Patients undergoing elective colon resection sustained significantly fewer

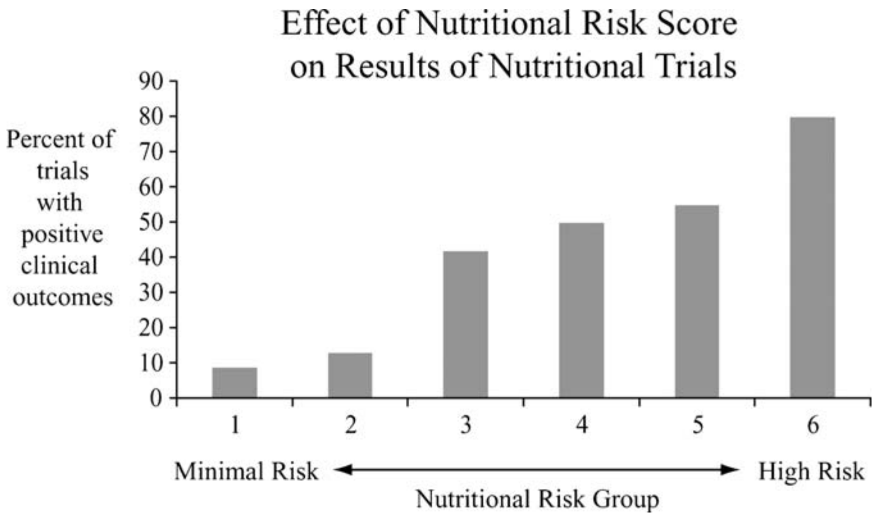

Figure 1 Nutritional trials were ranked by increasing nutritional risk of the patients recruited into the trials. Nutrition trials were most likely to demonstrate benefit with nutrition support if the populations recruited into the trials had increased nutritional risk. Trials with low-risk patients usually demonstrated no benefit with specialized nutrition support. Adapted from Kondrup et al. 2003 (26).

complications at any level. Resource utilization including postoperative stay and intensive care unit (ICU) stay correlated with these complications: Esophagus and pancreas procedures used the most resources (i.e., postoperative stay and ICU days), whereas colon procedures used the least at any albumin level. The data clearly showed descending risk of complications by surgical procedure at any given albumin level: esophagus > pancreas > stomach > colon. Therefore, this review interprets the existing immunonutrition data in the context of both surgical and nutritional risk.

Results of Immunonutrition Trials in Trauma Patients

In one of the earliest immunonutrition trials, Moore et al. (37) randomized patients requiring celiotomy with an ATI of 18–40 or an ISS of 16–45. This excluded many critically injured patients included in the enteral/parenteral trial (28). A nonisonitrogenous nonisocaloric elemental control diet was compared with a diet enriched in glutamine, arginine, omega-3 fatty acids, nucleotides, and BCAAs. Both diets were started postoperatively through a jejunostomy. Although length of stay, ICU stay, and ventilator days were shorter in the immunonutrition group, this did not reach statistical significance. However, significant reductions in intra-abdominal abscess ($p = 0.023$) and in the development of multiple organ

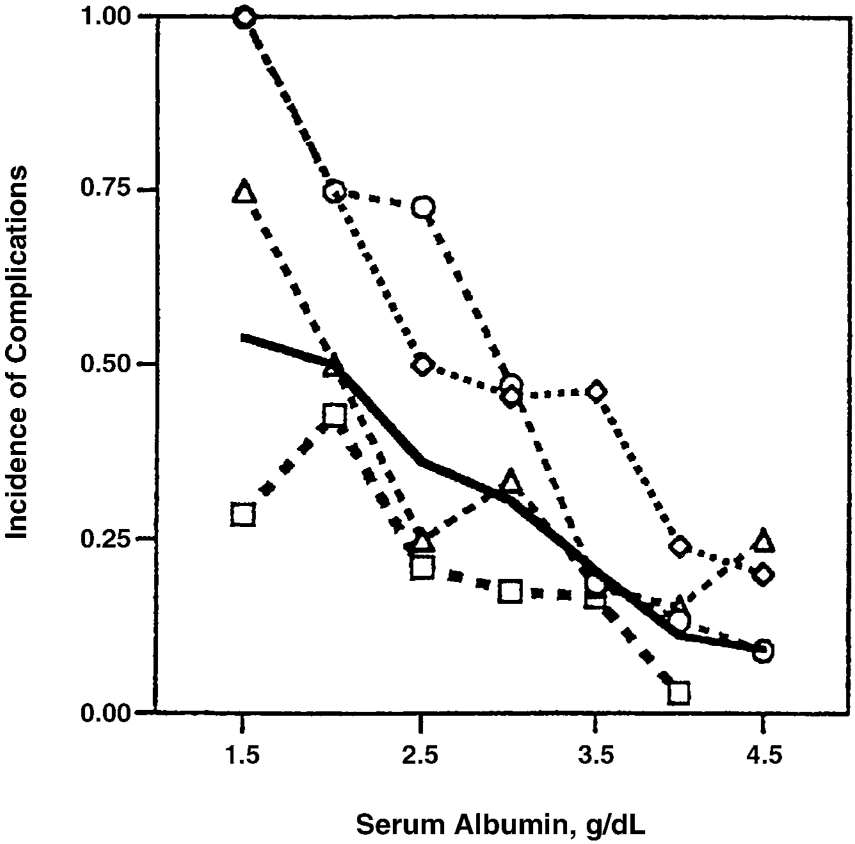

Figure 2 Complications increase as albumin drops in the combined group, but rates vary by surgical procedure. Esophageal and pancreatic procedures result in a higher rate of complications at lower albumin levels compared with colon procedures. Gastric surgery mirrored the complication rate of the combined group. ——, combined sample; --◊--, esophagus; --○--, pancreas; --Δ--, stomach; --□--, colon. Reprinted/adapted from Kudsk et al. 2003. Preoperative albumin and surgical site identify surgical risk for major postoperative complications. *JPEN J. Parenter. Enteral Nutr.* 27:1–9, with permission from the American Society for Parenteral and Enteral Nutrition (ASPEN). ASPEN does not endorse the use of this material in any form other than its entirety.

dysfunction syndrome ($p = 0.023$) occurred in the immunonutrition group. Approximately 100 patients were randomized in this trial.

Kudsk et al. (30) limited inclusion criteria to only patients with an ATI $\geq$25 or an ISS $\geq$20, the group that had responded to different nutrition regimens in the enteral/parenteral trial noted above (28). The same immunonutrition formula used by Moore et al. (37) was compared with an isonitrogenous, isocaloric control diet administered via a jejunostomy placed at the time of celiotomy. With only 32 patients randomized to the two groups (immune-enhancing diet, 15; control, 17), there was significant reduction in length of stay ($p = 0.03$), with a trend toward reduction in ICU stay ($p = 0.10$) and in ventilator days ($p = 0.10$). Immunonutrition significantly reduced major infections ($p = 0.02$) and intra-abdominal abscesses ($p = 0.05$) and use of therapeutic antibiotics (2.8 ± 1.6 days versus 7.1 ± 1.7 days, $p = 0.02$). Average charges for the immunonutrition and control groups were \$80,515 ± \$21,528 and \$110,599 ± \$19,132 ($p = 0.10$), respectively. Interestingly, an unfed group of patients who were not entered into the trial because enteral access had not been obtained at the time of celiotomy but who were eligible by severity of injury had the highest rate of infection, the greatest use of antibiotics, and the highest hospital charges. This work shows that restriction of entry criteria to at-risk patients reduces the numbers necessary to evaluate effectiveness of therapy.

Brown et al. (8) randomized 41 consecutive patients with major trauma receiving enteral feeding to a standard enteral formula or an enteral formula supplemented with arginine, linoleic acid, beta-carotene, and hydrolyzed protein. Patients receiving the supplemented diet developed fewer infectious complications than did those receiving the unsupplemented diet (3/19 versus 10/18; $p < 0.05$). These results correlated with improvement in the acute-phase protein, C-reactive protein, and the CD4:CD8 ratio. Unfortunately, a breakdown in randomization resulted in more successful enteral feeding due to significantly more jejunostomy tube placements in patients given the specialty enteral formula. No complications from the diet were noted.

An initial note of caution with immunonutrition in trauma patients was expressed by Mendez et al. (33). This group randomized a population of trauma patients who required enteral feeding and who had an ISS >13 to a standard diet or to a diet enriched in glutamine and arginine. Length of stay and ventilator days increased with the supplemented diet as adult respiratory distress syndrome (ARDS) appeared to increase from 18% to 45%. However, the majority of these patients had a pulmonary dysfunction and ARDS prior to institution of the diet; the onset of ARDS after starting the diet increased only slightly.

In summary, data from the trials suggest a significant reduction in infectious complications, most notably intra-abdominal abscess, in at-risk trauma patients administered immunonutrition compared with either starvation or a standard enteral formula. The issue of immunonutrition aggravating pulmonary inflammatory responses was not definitively addressed by the Mendez et al. study (33), but it warrants clinical consideration due to the work of Heyland & Novak (21) and Bertolini et al. (2), which is described below. There are insufficient data to make recommendations in closed head injury or burn patients.

Results of Immunonutrition Trials in General Surgical Patients

Accounts have been published on a number of perioperative trials using immunonutrition in general surgical populations, with the diets administered either postoperatively or preoperatively and postoperatively. The timing of administration affects who benefits from the formula and who does not.

POSTOPERATIVE USE OF IMMUNONUTRITION IN GENERAL SURGICAL PATIENTS A meta-analysis of immunonutrition appears to show significant benefit when it is administered postoperatively (22). However, close evaluation of the data suggests that certain populations do not benefit.

In 1992, Daly et al. (10) randomized patients undergoing esophagectomy, gastrectomy, or pancreaticoduodenectomy (and a few other operations) either to an immune diet enriched in arginine omega-3 fatty acids and nucleotides or to a non-isonitrogenous nonisocaloric standard diet. With a specialty diet, complication rates decreased from 36.4% to 12.1% ($p < 0.01$) and length of stay decreased from 20.2 to 15.9 days ($p < 0.004$). Because of criticism over the control diet, Daly et al. (11) recruited a similar group of patients and randomized them to an isonitrogenous control diet versus a same specialty diet. Complications dropped significantly, from 43% to 10% ($p < 0.05$), and length of stay was decreased from 22 to 16 days ($p = 0.03$). Most of the complications were infectious.

A subsequent study by Heslin et al. (19), published in 1997, painted a different picture, and initially confused the literature. In this study, patients undergoing resection of the esophagus, stomach/pancreas, and duodenum for malignancies were randomized to J-tube feeding with immunonutrition or to intravenous (IV) fluids alone. There were no differences in intra-abdominal abscesses, wound problems, leaks, or pneumonia, and major complications were similar between the two groups. Length of stay was 11 days for patients fed the specialty diet versus 10 days for those receiving IV fluids. One shortcoming of this trial was the relatively small amount of immunonutrition administered to the enterally fed group.

Although a casual review would suggest that IV fluids were comparable to specialty diets, a close investigation of the data demonstrates that the primary differences are probably secondary to the patients recruited (Table 1). In the Heslin et al. study (19), only 5% of the patients in one group and 6% of the patients in the other group sustained any preoperative weight loss at all, and there was no evidence of risk with a calculated Nutrition Risk Index. In the Daly et al. trials (10, 11), more than 30% of patients entered in the first trial (10) and more than 60% of those in the second trial (11) had a weight loss that was greater than 10%. The average albumin levels in the Heslin et al. study were 4.0 g/dL and 4.1 g/dL in the two groups, whereas the patients of Daly et al. had an average albumin level of 3.0–3.3 g/dL in the trials. In addition, more patients underwent esophagectomy (which is the highest-risk surgical operation) in the Daly trials, although a large number of patients underwent pancreaticoduodenectomy, another high-risk operation, in the Heslin et al. trial. Taking into account the risk of surgery and the risk of nutritional status, it appears clear that specialty diets are not effective postoperatively in well-nourished patients, but there are benefits when the specialty diets are given to malnourished patients undergoing major surgical procedures.

TABLE 1 A comparison of patients recruited for immunonutrition trials who demonstrated no effect of immunonutrition (19) or beneficial effects (10, 11)

	Reference 19		Reference 10		Reference 11	
	IED	**Fluids**	**IED**	**Standard diet**	**IED**	**Standard diet**
Surgery						
Esophagus	13	14	14	16	14	13
Stomach	30	41	12	3	6	5
Pancreas	54	43	6	12	6	9
Other	0	0	9	6	4	3
Nutritional status						
Weight loss	6 ± 0.7%	5 ± 0.6%	32%	32%	60%	67%
			>10% wt loss		>10% wt loss	
Albumin (g/dL)	4.0 ± 0.04	4.1 ± 0.04	3.3 ± 0.8	3.0 ± 1.2	3.3 ± 0.6	3.2 ± 0.5
NRI	No risk	No risk	N/D	N/D	N/D	N/D
Complications (wound or infection)	20.6%	23.5%	13.9%	51%	10%	42%
			(p = 0.02)		(p < 0.005)	
LOS	Median: 11 d	Median: 10 d	Avg: 15.8 ± 5. 20.2 ± 9.4d (p < 0.0004)		Avg: 16.9 ± 0.9d 22 ± 2.9d (p < 0.03)	

IED, immune-enhancing diet; LOS, length of stay; N/D, not done; NRI, Nutrition Risk Index = 1.59 × albumin (g/dL) = (0.417 × percent usual body weight).

PREOPERATIVE ADMINISTRATION IN THE GENERAL SURGICAL PATIENT A recent body of literature suggests that preoperative administration of supplemented diets for a week may improve the outcome of both well-nourished and malnourished patients undergoing major surgical procedures.

In a trial of preoperative feeding, Braga et al. (5) randomized malnourished patients only. One hundred fifty patients with weight loss ≥10% undergoing elective resection of the esophagus, pancreas, stomach, or colon and rectum for malignancy were randomized to a diet enriched in omega-3 fatty acids, arginine, and nucleotides preoperatively (1 liter per day) and postoperatively via jejunostomy (group 1); preoperatively (1 liter per day) with an enriched diet and postoperatively with a standard diet via jejunostomy (group 2); or to a standard isonitrogenous isocaloric diet administered via jejunostomy postoperatively only (group 3). The majority of patients underwent pancreas, gastric, or colorectal resections. The average weight loss was approximately 13% in all the groups, and the average albumin levels ranged from 3.4 to 3.5 g/dL in the three groups (Table 2). Very few patients required postoperative parenteral nutrition. Patients in group 3, who received the standard diet postoperatively developed significantly more major complications. Total complications were significantly reduced in group 1, which received the specialty diet both pre- and postoperatively, although group 2

TABLE 2 Demographics and outcome of perioperative immunonutrition

	Perioperative immunonutrition		
	Group I	**Group II**	**Group III**
Diet			
Preoperative	IED -1 L/d for 7 days	Same IED	Nothing
Postoperative	IED	Standard diet	Standard diet
Surgery			
Esophagus	1	3	2
Pancreas	21	20	18
Stomach	18	19	19
Colorectal	10	8	11
Nutritional status			
Weight loss	13.3 ± 4.1%	12.9 ± 3.3%	13.1 ± 3.6%
Albumin (g/dL)	3.4 ± 0.8	3.4 ± 0.6	3.5 ± 0.8
Complications	9 ($p < 0.05$ versus III)	14	21
LOS (days)	12.0 ± 3.8 ($p < 0.05$ versus II or III)	13.2 ± 3.5 ($p < 0.05$ versus III)	15.3 ± 4.1

IED, immune-enhancing diet; LOS, length of stay. Adapted from Reference 5.

patients approached statistical significance as well in comparison with group 3. Both groups that received the preoperative specialty diet had significantly shorter lengths of stay than did patients given the standard diet postoperatively. Group 1 patients who received the specialty both pre- and postoperatively had the shortest lengths
of stay.

Another intriguing study of preoperative preparation with the same specialty diet was published by Gianotti et al. (16). In this study, 305 well-nourished and malnourished patients undergoing resection of the stomach, pancreas, or colon and rectum were randomized to receive preoperatively one liter per day for five days of the same supplemented diet orally but no postoperative nutrition. A second group received the same nutrition both pre- and postoperatively. A final group received no nutrition support. In comparison with the final group, which received nutrition and postoperative IV fluids alone, the preoperative feeding reduced the septic complications from 30% to 14% (0.009) and length of stay from 14.0 ± 7.7 days to 11.6 ± 4.7 days. Complications and length of stay were also significantly lower in the group receiving both pre- and postoperative feedings compared with the unfed group. Complications dropped from 39% to 14% ($p = 0.05$) in the subpopulation of patients with pre-existing malnutrition. Similar results with preoperative nutrition occurred in patients resected for colorectal neoplasms (6).

TABLE 3 Mortality in subgroups of patients in intensive care unit in Bower et al. (3) 1995 trial

Immunonutrition in the intensive care unit		
	Immunonutrition	**Standard diet**
Met criteria	153	143
Received feeding	147	132
Mortality	23	10 ($p < 0.05$)
Septic	44	45
Mortality	11	4 ($p = 0.051$)
Critically ill	103	87
Mortality	12	6 ($p = 0.325$)

From Reference 3.

SUMMARY

Analyses of these trials support the postoperative use of immunonutrition in at-risk patients undergoing major surgical resections. Clinical trials showing that outcomes are improved in both well-nourished and malnourished patients who have received preoperative preparation with these specialty diets are intriguing.

Results in the Critically Ill Patient

In 1995, Bower et al. (3) published the results of a large of study of ICU patients randomized to a formula supplemented with arginine, nucleotides, and fish oil or to a standard enteral formula. Of 326 patients who met criteria and were enrolled in a trial (Table 3), most received their appropriate diet. Feedings were advanced to a target volume of 60 mL/hr by 96 hours. In a post hoc analysis, the hospital median length of stay was reduced by eight days ($p < 0.05$) in patients who received at least 821 mL/day of the supplemented formula. In a septic subpopulation of patients who received at least 821 mL/day of the supplemented formula, median length of stay dropped by 11.5 days in association with a reduction in acquired infections ($p < 0.05$). However, more patients in the group receiving the specialty diet died. While there was no significant increase in mortality in the subgroup of patients considered critically ill ($p = 0.325$), mortality increased from 9% to 25% ($p = 0.051$) in the group classified as septic. This study raised the first note of caution regarding potential deleterious effects of immunonutrition during sepsis.

Atkinson et al. (1) subsequently designed a prospective randomized double-blind controlled trial with the plan a priori to evaluate patients receiving at least 2.5 liters of immunonutrition over the first 72 hours. The diet was identical to that used in the Bower et al. (3) trial, and it was compared with an isonitrogenous, isocaloric control. There were no significant differences in hospital mortality rate between the two groups. Of the 101 patients who received >2.5 liters of formula in the first 72 hours, significant reductions in length of stay and ICU days and a nonsignificant reduction in ventilator days occurred with immunonutrition. This work demonstrated that it is difficult to provide adequate enteral feeding to critically ill patients, but if such feeding is successfully tolerated, outcome is improved.

Galban et al. (15) randomized 181 septic patients with indications for enteral feeding to an enteral diet enriched in arginine, nucleotides, and omega-3 fatty acids (from fish oil) or to a high-protein control diet. In this trial, mortality was significantly lower in the immunonutrition group. Both the bacteremia rate ($p = 0.01$) and the number of patients with more than one nosocomial infection ($p = 0.01$) dropped significantly with the specialty diet.

INCREASED MORTALITY IN SEPSIS WITH IMMUNONUTRITION? The issue of increased mortality with specialty diets in septic patients received significant attention after presentation of the "Ross trial" results, a multi-institutional trial led by Heyland and colleagues (12). In this trial, 170 critically ill patients with "similar demographics" were randomized to a diet supplemented with marginally increased arginine levels, omega-3 fatty acids, and beta carotene or to an isonitrogenous control diet. Unfortunately, specific demographics of the patient population remain unclear because the formal article remains unpublished and data are available only in abstract form or in summary reviews (12, 21, 23). In the trial, mortality increased significantly with the supplemented diet ($p = 0.03$). This mortality appeared to occur in patients septic with pneumonia. Unfortunately, a breakdown in randomization occurred and significantly more of the patients with pneumonia were randomized to the specialty diet group than to the control diet [26/87 (23%) and 8/83 (9%), respectively; $p = 0.03$). Most of the patients who died received fewer than three days of feeding or died after completion of the study several days after the diets had stopped. No indication was provided of how or why the patients died. Perhaps because of the significant breakdown in randomization, publication appears abandoned by the primary authors. However, given the results of Mendez et al. (33), Bower et al. (3), and a more recent study by Bertolini et al. (2), surgeons must be circumspect about using these formulas in certain populations.

The Bertolini et al. study (2) randomized patients requiring a higher level of care, ventilator support, and nutrition for at least four days to either parenteral nutrition ($n = 21$) or to an enteral diet supplemented with arginine ($n = 18$). Because of the Ross trial (12), an interim analysis of patients with severe sepsis and septic shock was performed after approximately 40 patients were recruited into the trial. There was no differences in age or 28-day mortality between the groups, but ICU mortality was higher in patients receiving the enteral arginine-supplemented diet. This reached statistical significance by the chi-square test ($p = 0.04$), but such a small population size should be analyzed by Fisher's exact test ($p = 0.07$, ns). No indication was provided of how or why the patients died. Nevertheless, the results should not be ignored. Analysis of the sparse clinical data provides some insight into who might be included in the susceptible patient population. Fifteen of the 21 TPN patients and 15 of the 18 enteral patients with severe sepsis or septic shock randomized were nonsurgical patients, with the majority (15 in each of the groups) septic from pneumonia. Taken in the context of the Mendez et al. (33) and Dent et al. (12) trials and with the currently available data, pneumonia may be the risk factor for increased mortality with these specialty diets.

There is no evidence to suggest that increased risk of mortality exists in other critically ill populations. Clinical data do not suggest deleterious effects in trauma patients or other critically ill patients with head injuries or burns. This conclusion is at odds with the recently published Canadian Practice Guidelines (20) for nutrition support in mechanically ventilated, critically ill adult patients, which recommended that the diets not be used for nutrition support in these patients. In these meta-analysis-driven guidelines, 14 trials (5 were trauma) were used to assess mortality, and 10 trials (4 trauma) were used to assess infectious complications. Overall, the meta-analysis showed a significant reduction in length of stay ($p = 0.05$) and a trend toward a reduction in ICU stay ($p = 0.08$) and decreased ventilator days ($p = 0.07$) with immunonutrition (arginine and other specialty nutrient-containing diets). There was, however, significant heterogeneity in the patient populations, which is expected when studies of patients with burns and closed-head injury, medical ICU patients, trauma patients, and patients undergoing major surgery are combined. The rationale for rejecting the diets was intriguing. The document (20) states that "Given the potential harm (increased mortality) associated with the use of diets supplemented with arginine and other nutrients in septic patients and the increased costs, the committee decided to recommend against their use in critically ill patients." Since the context was for all mechanically ventilated, critically ill adult patients, it remains unclear how the Dent et al. (12), Bower et al. (3), and Bertolini et al. (2) trials could be generalized to all patient populations including trauma (in whom the diets have been demonstrated to be beneficial), general surgical patients (in whom diets have been shown to be beneficial when given pre- and postoperatively), or closed-head injury or burn patients (in whom data is inadequate to assess their usefulness). At this point, the data show that severely septic patients (who usually do not tolerate enteral feeding), particularly if they are septic with pneumonia, should not receive these diets. There is no evidence of increased mortality in mechanically ventilated general surgical patients or in trauma patients either with or without sepsis. In fact, when these diets are withheld from nutritionally at-risk patients undergoing major general surgical operations or from trauma patients with ATI >24 or ISS ≥ 20, the result is poorer outcome.

CONSENSUS PANEL RESULTS

A consensus panel convened to discuss indications and contraindications for immunonutrition use (9). The group concluded that immunonutrition was not indicated in (*a*) patients who expected to resume an oral diet within five days, (*b*) patients admitted for ICU monitoring only, (*c*) patients with a distal bowel obstruction, (*d*) patients with incomplete resuscitation, and (*e*) patients with an upper GI hemorrhage.

Data suggest immunonutrition not be administered postoperatively to well-nourished patients who are unlikely to develop complications. The benefit of pre-operative treatment in this population, however, holds promise.

Clear indications for immunonutrition existed for the following populations:

1. Trauma patients with blunt or penetrating injuries with an ISS >18 (i.e., patients with two or more body systems injured, with at least one severely injured) or with an ATI >20, particularly those with severe colon, pancreas, duodenal, or gastric injuries or combinations of severe and nonsevere injuries.
2. General surgery patients undergoing elective esophageal, gastric, or pancreatic surgery who have moderate to severe malnutrition. With no evidence of inflammation to depress albumin levels (e.g., normal C-reactive protein levels), specialty diets should be used in esophagectomy patients with an albumin <3.7 g/dL or in patients undergoing gastric or elective pancreatic surgery if the albumin is <3.25 g/dL. For lower GI resection, only patients with an albumin <2.8 g/dL are likely to benefit.
3. General surgery patients who receive at least one liter for five to seven days preoperatively may also benefit.

There is inconclusive evidence of immunonutrition effectiveness in patients with severe head injuries, in patients with burns over >30% of body surface area, or in ventilator-dependent, nonseptic medial patients. Clinical judgment is warranted in these patients.

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