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Immunonutrition in 2016: Benefit, Harm or Neither?

Kelly Roehl

Over the past two decades, there have been numerous clinical trials, meta-analyses, and systematic reviews on the use of immunonutrition (IN) in a variety of populations. Although clinicians remain intrigued by the potential to alter the immune response through nutrition, there remains much debate on what is considered appropriate and efficacious use of IN, including lack of consensus from critical care guidelines and the international nutrition support community. Clinicians practicing in nutrition support must first evaluate outcome benefit, as well as consider the patient population and cost when determining whether IN is appropriate. While administration of IN prior to or following elective GI surgery, may be beneficial in preventing post-op infectious complications and reduce hospital length of stay (LOS), there is inadequate evidence to support the routine use of IN among the critically ill population as a whole.

INTRODUCTION

Infection is the most common cause of morbidity and mortality following surgery[1] and during critical illness,[2] potentially resulting in prolonged length of stay and increased hospital costs.[3,4] Enteral nutrition (EN) support is currently provided as the standard of care in an effort to prevent degradation of lean body mass (LBM) for gluconeogenesis and prevent malnutrition, a risk factor for infectious complications. Over the past two decades, interest has moved to not only prevention of malnutrition, but also modulating the immune response through nutrition, often referred to as immunonutrition (IN). The potential for altering the immune system and associated clinical outcomes is exciting, but current research and practical implications are not robust enough to drive practice. The aim of this article is to review evidence to date on the safety, efficacy and recommendations for use of IN.

Kelly Roehl, MS, RDN, LDN, CNSC, Advanced Level Dietitian, Rush University Medical Center, Chicago, IL

Overview of immunonutrition (IN)

Specific nutrients and dietary components, including arginine, glutamine, selenium, omega-3 (n-3) fatty acids, (eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]), the omega-6 gamma-linolenic acid [GLA], nucleotides and/or antioxidants have been implicated for their potential to modulate the metabolic response to surgery or stress by enhancing immune function. Specialty enteral products have been developed to include nutrients that are believed to enhance or modulate the immune response (Table 1). Many of the IN enteral formulations currently available were designed for use among those undergoing gastrointestinal (GI) surgery, and are therefore elemental or semi-elemental as a presumed necessary criteria.

Table 1. Comparison of Standard, Semi- Or Complete-Elemental and Immune-Enhancing Products

Product & Manufacturer	kcal/ml	Semi-elemental (yes/no)	Fiber (g/L)	EPA/DHA (g/L)
Non-immune-enhancing, standard formulas				
Nutren 1.0*	1.0	No	0	0
Osmolite 1.0**	1.06	No	0	0
Non-immune-enhancing, semi-elemental or elemental formulas				
Peptamen*	1.0	Yes	0	0
Vital 1.0**	1.0	Yes	4.2	0
Immune-enhancing formulas				
Impact Advanced Recovery (drink)*	1.4	No	15.2	4.6
Impact – Nestlé	1.0	No	0	1.7
Impact Peptide 1.5*	1.5	Yes	0	4.9
Oxepa**	1.5	No	0	4.6
Peptamen AF*	1.2	Yes	5.2	2.4
Perative**	1.3	Yes	6.5	0
Pivot 1.5**	1.5	Yes	7.5	3.7
Tolerex *	1.0	Yes	0	0
Vital AF 1.2**	1.2	Yes	5.1	3.8
Vivonex Plus*	1.0	Yes	0	0
Vivonex RTF*	1.0	Yes	0	0
Vivonex TEN*	1.0	Yes	0	0

*Nestlé Health Science (800-422-2752; www.nestlehealthscience.us); **Abbott Nutrition 00-227-5765; www.abbottnutrition.com)

The composition of the IN enteral and oral products available varies greatly, not only in nutrients, but also the concentration of each specific component. Unfortunately, clinical trials of the individual potentially immune-modulating nutrients have either not been conducted, or have failed to demonstrate benefit.[5,6] It has yet to be established which, how much (if any), when, and for whom IN may provide benefit.

Meet the "Immune-Modulating" Nutrients

Glutamine, most notably known as the primary fuel for enterocytes, lymphocytes and macrophages,[5] is also a conditionally essential amino acid during metabolic stress. It serves as a substrate for gluconeogenesis, and may be oxidized for fuel for rapidly proliferating cells.[8] Additionally, it is a precursor for renal ammoniagenesis, the process by which ammonia is excreted from the body.[8]

Arginine is a conditionally essential amino acid during metabolic stress as it is a precursor for many compounds within the human body. It is required for normal T- and B-lymphocyte and macrophage functions, and can be metabolized and utilized in collagen production by way of proline synthesis.[9]

Available for Use In the United States

Nucleotides (g/L)	Arginine (g/L)	Glutamine (g/L)	Other	Cost per 1000 kcal ($)*	Number of Studies**
0	0	0	--	8.50	--
0	0	0	--	6.33	--
0	0	0	--	28.33	14
0	0	0	--	22.59	0
1.8	17.7	11.8	--	12.45	28
1.2	12.5	0	--	40.00	***
1.8	18.7	8.1	--	25.55	***
0	0	0	4 g GLA, elevated vitamin C, E, beta-carotene	n/a	4
0	0	0	Elevated vitamin C, E, selenium	27.22	1
0	8	0	--	10.44	2
	13	7.6	Elevated vitamin C, E, beta-carotene	24.75	5
0	3.5	2.4	--	27.61	0
0	0	0	Elevated vitamin C, D, E	25.27	7
0	6.3	9.5	30% BCAAs	21.11	0
0	5.9	0	29% BCAAs	31.89	0
0	3.9	4.8	--	27.78	0

Arginine stimulates secretion of growth hormone, insulin, and glucagon,[10] and can be metabolized to nitric oxide, thereby altering blood flow, angiogenesis, epithelialization, and tissue granulation.[11]

Omega-3 fatty acids, specifically EPA and DHA, are believed to be immunosupressive by reducing the production of the pro-inflammatory omega-6 fatty acid, arachanonic acid, whose production results in higher levels of the pro-inflammatory eicosanoids, prostaglandins, leukotrienes, and thromboxanes.[12] Furthermore, EPA and DHA are postulated to reduce macrophage adhesion, alter T-cell proliferation, and stabilize the cytokine response.[13] Some have suggested that arginine and n-3 fatty acids may synergistically improve immune function with:

1. arginine delivery improving cytokine and nitric oxide production,
2. n-3 fatty acids reducing pro-inflammatory eicosanoid production, and
3. increasing arginine availability by decreasing expression of arginase I, an

enzyme responsible for degradation of arginine.[14,15]

Given the role of *nucleotides* in structural integrity of DNA and RNA, and involvement in the transfer of energy and coordination of hormonal signals, they are often added to IN formulas intended for use during times of stress and/or rapid tissue proliferation.[7] Interestingly, the processing techniques utilized in the production of commercial EN formula results in the removal of nucleotides;therefore, some have suggested that standard EN products do not provide adequate nucleotide content for those experiencing metabolic stress.[13]

Antioxidants, including vitamins C and E, beta-carotene, and selenium are often added in an effort to reduce oxidative stress among patients with acute metabolic stress.

A number of formulas with varying IN compositions are available in the United States (Table 1). Some of these products have been used in research in attempts to demonstrate efficacy for their use, but many of the products have never been tested for efficacy or safety in the populations for which they are marketed or in a clinical trial of any kind.

Reviewing the Evidence

Although immune-enhancing nutrition has been explored in a variety of settings, including pulmonary, trauma, neurology, oncology, and critical care, much of the research has been conducted among patients with GI disorders, specifically elective surgeries for cancers of the GI tract. Those undergoing elective surgery are an attractive and easy group to study because enteral and/or oral nutrition support is often utilized to prevent unintended complications related to malnutrition as many patients struggle to meet nutrition requirements orally during the pre- and post-operative periods.

Over the past two decades, there have been at least 16 meta-analyses and systematic reviews to evaluate the efficacy of IN among patients undergoing elective surgery (Table 2) and the critically ill (Table 3), yet use of IN remains controversial, particularly among the critically ill. In fact, the most recent Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient, jointly published by the American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) and Society of Critical Care Medicine (SCCM), recommends that immune-modulating EN formulations not be used routinely among medical ICU patients, reserving it for those with traumatic brain injuries and perioperatively in the surgical ICU populations.[31] Additionally, they do not recommend routine use of fish-oil and antioxidant-containing EN among patients with ARDS or ALI, citing insufficient evidence and conflicting data. Much of the backing behind these recommendations stems from research with wide heterogeneity and inconsistency in outcomes, as well as meta-analyses. Since methodologic and funding concerns blanket much of the IN research, it is an important point to consider that the strength of any meta-analysis or systemic review is only as strong as the studies that they are comprised of.

Review of Efficacy for Use of IN Among Elective Surgical Populations

Among those undergoing elective surgery, most commonly for GI malignancy, improvements in post-operative infectious complications and LOS may result in reduction in cost of care. Additionally, pre-operative nutrition status, a topic that itself has a murky array of definitions, may explain the differences found in pre-op versus post-op IN outcomes.[32]

Despite at least 10 meta-analyses and systematic reviews (Table 2), it remains unclear which nutrients, how much, timing, length of treatment, and specific surgical populations may benefit from IN. Researchers generally conclude that provision of IN among patients undergoing elective surgery may reduce incidence of infection and decrease hospital LOS, but find no reduction in mortality. A more critical evaluation of the meta-analyses reveals wide heterogeneity with regards to population and volumes of feeding delivered, therefore potential differences in amount of IN components delivered. According to one group, perioperative administration of 500-1000 mL/day of an IN formula for 5-7 days prior to surgery, with continuation into the post-op period reduces infection, other complications and hospital LOS, regardless of preexisting nutrition status.[33] Although they conclude that single-substrate administration does not impact clinical outcome, and describe a potential synergistic effect between arginine and fish oils, recommending that these nutrients be used together, this has yet to be proven. Given the variation in formula composition and actual amounts delivered in various studies, it is impossible to determine which specific nutrient is

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Table 2. Summary Of Meta-Analyses and Systematic Reviews Comparing Use of Immunonutrition (IN) Via Oral or Enteral

Reference	Population & Timing	N =	Nutrients Studied
Heyland et al. 2001[16]	• Critical illness and surgical; subgroup analyses • During but not before critical illness; pre-operative, perioperative, post-operative for surgical	2419	• Enteral IN support with any combination of arginine, glutamine, n-3 fatty acids, or nucleotides vs. standard EN
Waitzburg et al. 2006[17]	• Elective surgical only • Pre-operative, perioperative, post-operative, during critical illness	2305	• Enteral IN or oral IN containing any combination of nutrients vs standard enteral or oral supplements
Zheng et al. 2007[18]	• Elective mixed GI surgical • Pre-operative, perioperative, post-operative	1269	• Enteral IN or oral IN containing any combination of nutrients vs. standard diet
Marik and Zaloga 2010[19]	• Elective surgical only (GI, head/neck cancers, general abdominal surgery, cardiac surgery) • Pre-operative, perioperative, post-operative	1918	• Enteral IN with arginine alone, fish oil alone or combination vs. standard EN
Cerantola et al. 2010[20]	• Elective GI surgical only • Pre-operative, perioperative, post-operative	2730	• Enteral IN with any combination of IN nutrients vs. standard EN
Zhang et al. 2012[21]	• Elective surgical for GI cancer only • Perioperative	2331	• Enteral IN or oral IN containing any combination of nutrients vs. standard diet
Marimuthu et al. 2012[22]	• Open GI surgical only • Perioperative	2496	• Enteral IN versus standard diet
Drover et al. 2012[23]	• Elective surgical only • Pre-operative, perioperative, post-operative	Unspecified	• Enteral IN with arginine alone, fish oil alone or combination vs. standard EN
Vidal-Casariego et al. 2014[24]	• Elective surgical head/neck cancer only • Pre-operative, perioperative, post-operative	397	• Enteral IN with arginine alone, fish oil alone or combination vs. standard EN
Hegazi et al. 2014[25]	• Elective surgical patients • Preoperative only	561	• Oral IN with arginine alone, fish oil alone or combination vs. standard oral supplement or standard oral diet

IN, immunonutrition; n-3, omega-3; EN, enteral nutrition; RR, relative risk; OR, odds ratio; CI, confidence interval; LOS, length of stay

Nutrition Support Versus Standard Diet or Standard Enteral Nutrition Support Among Elective Surgical Populations

Outcomes	Author Affiliations
• Overall significant reduction in infectious complications and hospital LOS • High-arginine IN resulted in significantly lower incidence of infection, shorter hospital LOS compared to low-arginine IN • Surgical patients had significantly fewer infectious complications than the critically ill • No effect on mortality	• Heyland was a paid site investigator on the Ross (now Nestle) product (Impact)
• Decreased hospital LOS (3.1 days) and infectious complications • No effect on mortality	• Hypothesis conceived at workshop sponsored by Novartis Medical Nutrition
• Reduced infectious complications, hospital LOS (weighted mean difference • No effect on mortality	• None disclosed
• Post-operative and perioperative IN with both arginine and fish oil reduced risk of acquired infection , wound, and LOS	• Zaloga was a paid employee of Baxter Healthcare, Inc. – though Baxter Healthcare did not manufacture any of the enteral immune-modulating diets mentioned in the article
• Reduction in overall complications • No effect on mortality	• None disclosed
• Reduction in hospital LOS, infectious complications, and non-infectious complications • No mortality analysis	• None disclosed
• Deceased infectious complications, non-infectious complications, and hospital LOS • No effect on morality	• Ljungqvist and Lobo had received research funding from Nutricia Clinical Care • Varadhan was supported by research fellowships from the Nottingham Digestive Diseases Centre National Institute for Health Research Biomedical Research Unit, and the Enhanced Recovery After Surgery Society.
• Reduced infectious complications; with the greatest effect with pre and post-operative administration • No effect on mortality	• Heyland received a research grant as the principal investigator and a speaker honorarium from Nestle. • Ochoa was a paid consultant for Nestle until July 2010, and received a salary as Medical • Scientific Director for Nestle for 2 years leading up to publication
• Reduced incidence of fistula • No reductions in diarrhea, wound infections or other infections were noted • No mortality analysis	• None disclosed
• Oral IN vs. standard oral supplement: no difference in wound infection, all infectious complications, non-infectious complications, or LOS • Oral IN vs standard oral diet: decreased infectious complications	• Evans was the recipient of educational grants from Nestle Nutrition and Abbott Laboratories, as well as speaker honoraria from Abbott Laboratories • Hegazi and Hustead were full-time employees of Abbott Laboratories

potentially improving outcomes, if any.

To offer fair comparisons between groups where nutrition is provided to both, allowing IN to be the intervention or treatment, nearly all of the randomized controlled trials (RCTs) that provide the basis for the meta-analyses and systematic reviews described in Table 2 compare administration of IN to standard EN. Similar reductions in LOS have been reported when IN was utilized in the pre- versus post-operative periods.[34] Hegazi, et al. reported that pre-op oral IN only provided benefit when compared to those that received non-supplemented oral diets,[25] suggesting that adequate delivery of basic nutrients results in prevention of post-op complications. However, given that the standard of care (control) is no nutrition intervention, perhaps the benefits of preoperative nutrition can be attributed to carbohydrate loading to maximize glycogen stores as recommended for Enhanced Recovery After Surgery (ERAS), which has been shown to significantly reduce complications and hospital LOS.[35,36] Though some researchers have reported that pre-op carbohydrate loading may prevent loss of LBM,[37-39] reduce insulin resistance, tissue glycosylation in the operative period, and optimize glycemic control post-op,[40-42] direct comparisons have not yet been made. Is it simply the provision of extra (or adequate) calories above the 'standard' intake the patient would be able to consume usually in the pre-op period that is resulting in benefits? More research is needed.

Review of Efficacy for Use of IN Among Critically Ill Populations

Given the role infectious complications play in the critically ill population, any intervention that might decrease that risk is worthy of investigation. Generally, the outcomes of meta-analyses examining efficacy of IN among the critically ill (Table 3) are similar to those for the elective surgical population with regards to reduced incidence of infection and decreased hospital LOS, with no difference in mortality; however, some researchers[16] suggest that provision of IN among the critically ill may result in adverse outcomes, and therefore, be a safety concern. Like that in the elective surgical population, the research for use of IN in the critical care arena is full of methodologic and heterogeneity concerns.

Much of the debate regarding efficacy of IN among critically ill patients surrounds the safety of its use – specifically relating to arginine. In a 2001 meta-analysis, Heyland et al.,[16] concluded that arginine-supplemented IN provided no benefit among the critically ill, and may potentially result in adverse outcomes, a conclusion made due to a trend toward increased mortality among those receiving IN; however, these results were not statistically significant. Since this time, concerns regarding the safety of IN, specifically arginine supplementation, among septic patients has been hotly debated; however, research remains limited, and the debate has mainly surrounded three *theories* (though none confirmed):

1. Sepsis results in arginine deficiency and supplementation may improve septic state.[43]

2. Sepsis is caused by excess nitric oxide (NO) production. Since NO is the end-product of arginine metabolism that causes vasodilation, arginine supplementation may exacerbate the septic syndrome.[43]

3. Arginine infusion among septic medical and surgical patients does not cause hemodynamic instability.[44]

As many of the IN products available contain a number of potentially immune-modulating components, and it remains unclear which (if any) nutrient may be providing the most benefit, researchers have attempted to scrutinize immune-modulating nutrients independent from nutrition delivery.

IN, Individual Delivery, Biomarkers and Outcomes Among the Critically Ill

As the goal of IN is to enhance the immune response, researchers have examined inflammatory biomarkers concurrently with *clinical outcomes* in attempts to demonstrate potential changes in outcomes. However, it is imperative to remember that changes in surrogate markers do not necessarily translate to differences in clinical outcomes, a point that is often missed in interpretation. One group concluded that delivery of IN EN containing n-3 fatty acids, glutamine and arginine among those with esophageal cancer undergoing concurrent chemotherapy and radiation resulted in a reduced rise in the inflammatory cytokines C-reactive protein (CRP) (p=0.001) and tumor-necrosis

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Table 3. Summary of Meta-Analyses and Systematic Reviews Comparing Use of Immunonutrition (IN) Via Enteral

Reference	Population & Timing	N =	Nutrients Studied
Heys et al. 1999[26]	• Mixed critical illness (surgery, trauma, burns, cancer, sepsis) • Post-operative only	1009	• Enteral IN support with any combination of arginine, glutamine, BCAAs, n-3 fatty acids, RNA vs standard EN
Beale et al. 1999[27]	• Mixed critical illness (medical, surgical, trauma) • During, but not prior to critical illness	1482	• Enteral IN support with arginine alone or arginine in combination with glutamine, nucleotides, n-3 fatty acids vs. standard EN
Heyland et al. 2001[16]	• Critical illness and surgical; subgroup analyses • During critical illness and pre-operative, perioperative, post-operative for surgical	2914	• Enteral IN support with any combination of arginine, glutamine, n-3 fatty acids, or nucleotides vs standard EN
Montejo et al. 2003[28]	• Mixed critical illness (surgical, trauma, burn, mixed) • Post-operative, during critical illness	Unspecified	• Enteral IN vs standard EN; any combination of IN
Marik and Zaloga 2008[29]	• 9Mixed critical illness (mixed, burn, trauma) • During, but not prior to critical illness	3013	• Enteral IN support with fish oil alone OR arginine alone or arginine in combination with glutamine, nucleotides, n-3 fatty acids vs. standard EN
Glenn et al. 2014[30]	• Mixed critical illness	Unspecified	• Enteral IN with fish oil vs. standard EN

IN, immunonutrition; BCAAs, branched chain amino acids; n-3, omega-3; RNA, ribonucleic acid; EN, enteral nutrition;

factor-alpha (TNF-α) (p=0.014) compared to those receiving standard EN support.[45] It is important to note that although statistically significant change in markers of inflammation were found, these authors failed to connect their results to clinical outcomes, which is necessary to drive change in practice.

To further illustrate this point, researchers of the highly publicized ARDS Network Omega Trial (n= 272), administered n-3, GLA, and antioxidants separate from the enteral formulas twice daily.[5] Although delivery of n-3 fatty acid increased plasma EPA concentration 8-fold, there were no differences in ventilator-free or

Nutrition Support Versus Standard Enteral Nutrition Support Among Critically Ill Populations

Outcomes	Author Affiliations
• Significant reduction in infectious complications and hospital LOS (2.5 days) • No mortality analysis	• None disclosed
• Significant reductions in ventilator days, infection rate, and hospital LOS • No effect on mortality	• Partially sponsored by Novartis Nutrition
• Overall significant reduction in infectious complications and hospital LOS • High-arginine IN resulted in significantly lower incidence of infection, shorter hospital LOS compared to low-arginine IN • Surgical patients had significantly fewer infectious complications than the critically ill • No effect on mortality	• Heyland was a paid site investigator on the Ross (now Nestle) product (Impact)
• Lower incidence of abdominal abscesses, nosocomnial pneumonia, bacteremia • Reduced mechanical ventilation in trauma patients only • Reduced ICU LOS (mean reduction 1.6 days; and hospital LOS (mean reduction 3.4 days; in trauma and surgical patients only • No effect on mortality	• Partially sponsored by Novartis Consumer Health
• No effect on LOS or mortality with arginine, with or without glutamine of n-3 fatty acids • Significant reduction in mortality, secondary infections, and LOS with fish oil-only IN	• Zaloga was a paid employee of Baxter Healthcare, Inc., which does not manufacture any of the enteral immune modulating formulas mentioned in the manuscript, does market a glutamine enteral supplement, but did not sponsor any of the trials included in this review
• Reduction in ICU LOS, and reduction in ventilator days when EN with fish oil was administered, but not with bolus dosing of IN substance separate from EN • No mortality analysis	• Wischmeyer served as a consultant for Abbott Inc. on the use of fish oil containing enteral formulas in the critical care setting

OR, odds ratio; CI, confidence interval; LOS, length of stay

ICU-free days among those receiving the supplemental immune-enhancing nutrients.

In the Reducing Deaths Due to Oxidative Stress (REDOX) trial comparing the effects of glutamine and/or selenium administered separate from the EN formula, unexpectedly, researchers reported longer time to ICU and hospital discharge.[6] Interestingly, post hoc analysis revealed that high dose glutamine and/or antioxidants may be associated with increased mortality, especially in those with multiorgan failure. Furthermore, Van Zanten et al.[46] found that after adjusting for Acute Physiology and Chronic Health Evaluation II (APACHE II) scores,

patients requiring mechanical ventilation that received an IN formula containing glutamine, n-3 fatty acids and antioxidants were found to have significantly higher 6-month mortality than those receiving an isocaloric, high protein formula (54% vs 35% in the control EN group, p=0.04). Conversely, a systematic review concluded that use of fish oil/antioxidant containing enteral formulas or supplements were associated with a reduction in ICU LOS and ventilator days; However, after excluding the Omega trials[5] where fish oil was administered as a twice daily bolus outside of the EN, use of continuously administered EN containing fish oil was associated with a significant reduction in mortality (P=0.004).[30]

The influence of IN nutrients glutamine and selenium among patients requiring both enteral and parenteral support remains inconclusive. Although most have concluded that glutamine and selenium supplementation may result in reduction of nosocomial infections among the critically ill, researchers of one meta-analysis concluded that glutamine supplementation via enteral, parenteral, or a combination of these routes posed no benefit in overall mortality or hospital LOS, but did result in lower incidence of noscocomial infections among the critically ill.[47] Furthermore, these researchers, as well as a separate group[48] concluded that high-dose supplementation (>0.5 g/kg/day) significantly increased mortality among the critically ill, resulting in higher rates of infection, and longer ICU and hospital LOS. Appropriately, the A.S.P.E.N./SCCM 2016 guidelines suggest that supplemental enteral glutamine (above what is standard in EN formulas) NOT be supplemented in critically ill adults.[31]

Cost

The potential ability to reduce the cost of medical care was one of the driving forces behind initial efforts to study the impact effect(s) of IN on post-op morbidity, and continues to influence the decision to use IN. Researchers have suggested that IN enteral formulas may be cost-effective when used in specific populations and healthcare settings;[49,50] However, this is only if they work, which remains unclear. Products with IN properties are significantly more expensive than standard preparations (Table 1) with some IN EN formulations costing up to 6 times that of a standard formula. Although nutrition support is widely accepted as a life-sustaining therapy, insurance coverage differs among payers and administration settings, making cost-benefit analyses complicated. Differences in coverage may depend on route of administration (oral, enteral or parenteral).[51] Therefore, clinicians must be cognizant of coverage to prevent a cost burden not only to the patient, but also the healthcare system as a whole.

CONCLUSION

Despite the large volume of research conducted on efficacy of IN products over the past three decades, there is still no consensus on whether or not they provide benefit. More concerning, some suggest potential risk to the critically ill. Researchers have attempted to find a pattern of potential benefit by conducting meta-analyses and systematic reviews. However, overall, these have revealed no difference in the ultimate outcome of mortality in a variety of populations with enteral IN was compared to standard EN support, in either the surgical and critically ill populations. The literature is riddled with limitations, including research design, heterogeneity, and possible bias from conflicts of interest, thereby preventing the ability to draw solid conclusions and make specific recommendations for clinical practice.

Guidelines and recommendations for use are derived from research conducted by a relatively small group of individuals, many of which receive financial gain/funding from the makers of IN formulas. Given the lack of consensus and exorbitant cost associated with IN, clinicians must demand a well constructed, multi-center, non-biased robust study that addresses the limitations of previous research, and is designed to test the true efficacy of these formulas among critically ill patients. ■

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