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Enteral Nutrition Formula Selection: Current Evidence and Implications for Practice

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Abstract

Many new enteral nutrition (EN) formulas have been created over the past several decades with a variety of intended uses. Although each is intended to promote improved outcomes, research is often unclear and, in many cases, conflicting. It is important to note that EN products are considered medical foods by the U.S. Food and Drug Administration and therefore do not have to complete premarket review or approval and are not regulated to the same extent as pharmaceuticals. While standard EN formulas are designed to meet the basic macro- and micronutrient requirements of individuals who cannot meet nutrition needs orally, specialty EN products have been developed to exhibit pharmacologic properties, such as immune-enhancing formulas containing arginine, glutamine, nucleotides, and ω-3 fatty acids. With the vast number of products available, rising costs of healthcare, and the drive toward evidence-based practice, it is imperative that clinicians carefully consider research regarding use of specialty formulas, paying close attention to the quality, patient population, clinical end points, and cost to patient and/or facility. (*Nutr Clin Pract*. 2015;30:72-85)

Keywords

enteral formula; medical food; pharmaconutrition; nutritional support; formulated food; nutrition therapy; enteral nutrition; tube feeding

Administration of enteral nutrition (EN) has long been considered the standard of care for nutrition support among patients unable to meet energy and protein requirements orally in efforts to prevent undesirable outcomes associated with malnutrition. EN formulas are considered medical foods by the U.S. Food and Drug Administration (FDA) and are not regulated to the same extent as pharmaceuticals.[1] Unlike medications, EN products are not required to complete premarket review or approval.[1] The FDA defines a medical food as "a food which is formulated to be consumed or administered enterally under the supervision of a physician, and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation."[1] Furthermore, EN formulas are consistent with the definition of medical foods as these products "are specially formulated and processed (as opposed to a naturally occurring foodstuff used in a natural state) for a patient who is critically ill or who requires use of the product as a major component of a disease or condition's specific dietary management."[1]

Before commercial tube feeding products were available, most patients were fed by blending hospital food thin enough to be put through a feeding tube. However, microbial concerns and ease of preparation led to the development of commercially prepared formulas. The first formulas were elemental and introduced in the late 1960s; the first nutrient-intact formula came on the market in 1973.[2] Most early formulas did not contain fiber due to difficulty with flow and clumping issues. The first fiber-containing formula came out in 1987, using soy protein.[2]

Today, EN products vary greatly with respect to intended use. Standard EN products are designed to meet the basic macro- and micronutrient needs of patients who cannot meet nutrition needs orally. In contrast, specialty EN products have been developed to exhibit pharmacologic properties, such as immune-moderating formulas containing arginine, glutamine, dietary nucleotides, and ω-3 fatty acids, intended to enhance the immune response.[3,4]

Review of EN Formulations

The following sections review categories of EN products, clinical indications, and potential benefits associated with product use. A summary of findings is included in (Table 1).

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Table 1. Summary of Characteristics of Enteral Formulations and Recommendations for Use.

Formula Type	Summary of Characteristics	Recommendations for Use
Polymeric	• Contain macronutrients as nonhydrolyzed protein, fat, and carbohydrate • Range in concentration from 1–2 kcal/mL • 1–1.5 liters usually meets RDA for vitamins and minerals • May be disease specific and/or contain pre- and probiotics	• Intended for use among patients without severe malabsorptive disorders
Fiber containing[5–16]	• Fiber content intended to improve the health of the GI tracts regulating frequency and/or consistency of stool by maintaining healthy GI flora • Fiber content is typically well below total daily fiber recommendations • May contain prebiotics in the form of fructooligosaccharides, oligofructose, or inulin • May also contain probiotics	• Recommended for use among patients with diarrhea and/or to promote/maintain gut microbiota
Whole food/blenderized[17]	• Blenderized whole foods designed to allow patients to receive qualities of food not found in standard enteral formulas, such as phytochemicals	• Only considered for use in medically stable patients with a healed feeding tube site and no signs of infection • Best suited for patients with safe food practices and tube maintenance techniques • Should be provided as bolus feeds to maintain safe food practices (hang time ≤2 hours) • RD should be involved in development of feeding composition to ensure adequate nutrient delivery
Diabetes/glucose intolerance[18–25]	• Intended to reduce hyperglycemia with macronutrient composition of 40% carbohydrate, 40% fat, and 20% protein • Fat and soluble fiber content may slow gastric emptying and prevent elevated blood glucose	• Use of DM-specific enteral formulas is not currently supported by strong research; instead, efforts should be made to prevent overfeeding
Renal[9,26–32]	• Fluid restricted	• Standard enteral formula should be the first line for patients with renal insufficiency
	• Contain lower amounts of electrolytes, specifically potassium and phosphorous to prevent excessive delivery to patients with renal insufficiency	• If significant electrolyte abnormalities exist or develop, a renal formula should be considered until electrolytes stabilize
	• Protein content varies	• Standard, high-protein formulas without fluid restriction should be used among critically ill patients receiving dialysis; if electrolyte abnormalities exist without dialysis, renal formulas should be considered
Hepatic[9,33–39]	• Contain lower protein content with higher percentage of branched-chain amino acids, lower aromatic amino acids to prevent hepatic encephalopathy	• Standard EN formula should be administered as first line among patients with hepatic encephalopathy
	• Low protein content may result in inadequate protein delivery • Fluid and sodium restricted to attenuate effects of ascites	• Reserve only for use among encephalopathic patients in whom standard therapy with luminal acting antibiotics and lactulose does not improve encephalopathy
Bariatric[9,40–49]	• Contain approximately 37% kcal from protein in efforts to maintain positive nitrogen balance, modest carbohydrate content for glucose control, and EPA/DHA in efforts to modulate inflammatory response	• Intended for patients with BMI >30 kg/m^2

(continued)

Table 1. (continued)

Formula Type	Summary of Characteristics	Recommendations for Use
		• Goal enteral delivery should not exceed 60%–70% of target energy requirements, but provide adequate protein
Elemental/semi-elemental[52–55]	• Macronutrients are hydrolyzed to maximize absorption	• Intended for use among patients with malabsorptive disorders; not intended for routine use
Pulmonary/fish oil[56–73]	• In efforts to reduce carbon dioxide production, these formulas are contain >50% total calories from fat, with lower carbohydrate (<30%) and similar protein content (16%–18%)	• Efforts to prevent excessive EN delivery should be employed to reduce complications associated with overfeeding
	• Typically also contain ω-3 fatty acids derived from fish oil to increase delivery of anti-inflammatory properties of EPA/DHA	• Pulmonary formulas should be used with caution among septic, critically ill patients
Immunonutrition/ immune modulating[66–67,70–71,73–88]	• Contain pharmacologically active substances, such as arginine, glutamine, ω-3 fatty acids, γ-linolenic acid, nucleotides, and/or antioxidants in efforts to modulate immune function	• Administration of immune-modulating substances as components of EN are potentially beneficial when used for patients undergoing elective surgery; however, research is not sufficient to recommend immune-modulating formulas for routine use among critically ill patients

BMI, body mass index; DHA, docosahexaenoic acid; DM, diabetes mellitus; EN, enteral nutrition; EPA, eicosapentaenoic acid; GI, gastrointestinal; RD, registered dietitian; RDA, recommended dietary allowances.

Standard Polymeric Formulas

Standard polymeric formulas are most commonly used for patients requiring EN support. These formulas are designed to mimic a general diet by providing carbohydrate, protein, and fat in nonhydrolyzed forms. Common sources of carbohydrate in enteral formulas include corn maltodextrin and corn syrup solids. Common sources of protein include sodium and calcium caseinates and soy protein isolates. Lipid sources are usually canola, soybean, and/or safflower oil. Normal digestion function is typically required for polymeric formulas. These formulas meet basic nutrition needs for most non–critically ill patients. Typically 1–1.5 liters of formula provide 100% of the Recommended Dietary Allowances (RDA) for most vitamins and minerals. Standard formulas are generally lactose and gluten free as well as kosher.

Polymeric formulas differ based on concentration, ranging from 1–2 kcal/mL. Highly concentrated formulas (2 kcal/mL) may be useful for patients requiring fluid restriction, such as patients with renal or heart failure or those with syndrome of inappropriate antidiuretic hormone (SIADH), ascites, or fluid overload. Concentrated formulas may also be useful in providing adequate calories with a lower volume for patients with high calorie requirements. It is important to note that concentrated formulas may require additional free water flushes to maintain adequate hydration when fluid restriction is not warranted.

Polymeric formulas also differ based on protein concentration. High-protein formulas may be beneficial for those with higher protein requirements, such as patients with protein-energy malnutrition, muscle wasting, or wounds. Clinicians must take care to ensure adequate hydration with provision of high-protein formulas, especially above 1.5 g protein/kg body weight; monitor serum urea nitrogen levels; and adjust feedings accordingly. High-protein formulas may or may not be appropriate for those with chronic renal failure who are not receiving dialysis, as excessive protein delivery may result in azotemia.

Fiber-Containing Formulas

Many fiber-containing enteral formulas are on the market. Fiber-containing EN formulas may improve digestive health and normal bowel function. It is important to consider the amount, type (soluble vs insoluble), and potential prebiotic properties. Common sources of fiber used for enteral formulas include soy fiber and guar gum. Although fiber containing, many formulas provide well below the recommended 25–38 g fiber/d[5] when administered within reasonable caloric goals, therefore possibly necessitating supplementation with modular fiber product to meet the RDA, which may be administered separately from the EN formula.

Fiber formulas are often selected to promote gastrointestinal (GI) health and maintain GI motility and regularly occurring bowel movements. Diarrhea associated with enteral feeds is common in the acute setting,[6] whereas constipation may be of more concern among patients requiring long-term EN support.[7] Results of a meta-analysis indicate a significant reduction in the incidence of diarrhea with use of fiber-containing

enteral feeds (odds ratio [OR], 0.68; 95% confidence interval [CI], 0.48–0.96; $P = .03$).[8] However, when intensive care unit (ICU) and non-ICU patients were analyzed separately, there were no differences in the incidence of diarrhea among ICU patients (OR, 0.98; 95% CI, 0.62–1.56; $P = .93$), although a reduction was still noted among non–critically ill patients (OR, 0.42; 95% CI, 0.25–0.72; $P = .001$).[8] Of note, fiber was determined to be most beneficial in reducing diarrhea among patients with the highest occurrence of loose stools. Little research has been conducted to evaluate the use of fiber-containing formulas in the prevention or reduction of constipation; elimination or reduction in the use of laxatives has been found among studies examining the use of fiber-containing EN formulas in the long-term care setting.[9] The American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) suggests grade E evidence exists for the following statement: "If there is evidence of diarrhea, soluble fiber-containing or small peptide formulations may be utilized."[9(p300)]

Another potential benefit of fiber-containing enteral formulas is the inclusion of prebiotic fibers. Prebiotics are "nondigestible food ingredients that beneficially affect the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon, and thus improves host health."[10] The most commonly researched prebiotic fibers include fructooligosaccharide (FOS), oligofructose, and inulin. Prebiotics may help improve immunity by affecting the gut-associated lymphoid tissue (GALT), as well as improve bowel function. Although modulation of the gut microbiota with prebiotic-supplemented enteral formula has been established with notable increases in host bifidobacteria,[11,12] limited research has evaluated clinical outcomes associated with the use of prebiotic enteral formulas. The most notable trial was conducted in 155 older adults in which those receiving a fiber/prebiotic enteral formula had significantly less bowel movements per week (4.1 vs 6.3, $P = .008$), as well as more formed stools (31% vs 21%, $P = .001$) compared with those who had a fiber-free feeding.[13] However, significantly more patients in the fiber-free group were receiving laxatives as part of traditional care, which may have contributed to the increase in diarrhea. Given insufficient research examining clinical outcomes associated with prebiotic-containing formulas, no direct conclusions can be made.

In addition, fiber-containing formulas have been touted to improve glycemic control among glucose-intolerant patients. Visek and colleagues[14] found no differences in either postprandial glycemia or insulinemia between patients receiving fiber-containing vs non-fiber-containing formulas. Overall, limited evidence exists to support the use of fiber-containing formulas exclusively to improve glycemic control, especially among healthy nondiabetic patients. Further discussion of diabetic formulas will be reviewed in upcoming sections.

While fiber-containing formulas may be beneficial in decreasing GI transit time, thereby reducing frequency of diarrhea, use of fiber among critically ill patients requiring multiple vasopressors to maintain adequate mean arterial pressure may not be advised. Decreased GI transit time as result of using fiber-containing formulas theoretically may increase the risk of bowel obstruction[15] and increase the risk for bowel ischemia among hypotensive patients.[16] However, there is little evidence to support these hypotheses.

Blenderized Formulas

Use of blenderized tube feeding (BTF) formulas is on the rise, with a consumer push toward more "natural" products. BTF formula is typically made at home by blending food or meals into a liquid thin enough to be administered via a feeding tube. BTF may be completely made of food or a combination of food and standard formula. Additionally, preprepared real-food EN products are available for patients receiving long-term nutrition support desiring real-food EN without having to prepare homemade formula.

Potential benefits of BTF include decreased cost and possible improvement in constipation or diarrhea,[17] although these claims have not been well researched. BTF offers patients and family members the opportunity to choose "real" food and to maintain some sense of control over the nutrition provided. Use of BTF allows the feeding tube to be viewed as a "second mouth" instead of a medical necessity. In addition, use of BTF may allow for more variety in nutrients and may be more likely to include a greater variety of phytochemicals not present in standard polymeric formulas. Also, BTF may be viewed as a more "natural" option compared with preprepared products and may make the transition to long-term EN easier.

Several factors need to be considered prior to initiating use of BTF. Use of BTF may not be appropriate among medically unstable patients or those with nonhealed tube sites given the potential for infection associated with food-borne illness. Preparation of BTF requires time and commitment of the patient or, more commonly, the caregiver. In addition to time spent blending food, it is important to ensure BTF is adequate in protein, energy, vitamins, minerals, and fluid. Registered dietitians/registered dietitians nutritionists (RDs/RDNs) should determine nutrition requirements and adequacy of BTF delivery in the home environment, specifically discussing proper food-handling techniques and delivery of adequate nutrition and hydration via the feeding tube. As mentioned previously, food safety is a concern for BTF; care must be taken to ensure all foods are cooked thoroughly, kept at appropriate temperatures, and prepared with safe handling techniques to prevent cross-contamination. For this reason, BTF should be administered as a bolus infusion rather than continuously since BTF must not be left at room temperature for more than 2 hours.[17] There may also be an increased risk of tube occlusion with BTF if not pureed appropriately and flushed with adequate fluid; therefore, BTF may not be suitable for patients with less than a 14 French feeding tube.[17]

Diabetes Mellitus/Glucose Intolerance Formulas

Diabetes-specific EN formulas are designed to reduce the likelihood of hyperglycemia, based on the premise that standard EN formulas hinder glycemic control secondary to rapid gastric emptying and nutrient absorption, largely due to higher carbohydrate concentration, much of which is corn syrup.[18] Diabetes mellitus (DM) EN formulas have a different macronutrient breakdown compared with standard formulas, intended to aid in improved glycemic control: approximately 40% kcal from carbohydrate, 20% from protein, and 40% from fat.[18,19] In addition, these products typically contain a blend of dietary fiber, including FOS, soy fiber, and pureed fruit and vegetable fiber.[18,19] Manufacturers of DM products suggest that the higher fat and soluble fiber content slow gastric emptying, thereby preventing fluctuations in blood glucose.[2,19] In addition, these products may contain higher amounts of monounsaturated fatty acids (MUFAs), antioxidants, and chromium picolinate intended to promote cardiovascular health and carbohydrate metabolism.[18–20] The macro- and micronutrient composition of DM EN formulas is not consistent with current major guidelines for secondary prevention to manage DM.[21] These guidelines advocate consuming a variety of carbohydrate sources, limiting saturated fat to <7% daily calorie intake, and consuming 15%–20% of daily calories from protein.[21] With regard to fiber content improving glycemic control, these guidelines cite insufficient evidence to advocate that individuals with DM consume a higher fiber intake than the general population or consume additional antioxidants or chromium.[21]

Results of a meta-analysis including 23 studies (16 studies using oral nutrition supplement, 7 using EN), published in 2005, suggested use of DM-specific EN formulas was associated with reduced postprandial rise in blood glucose, peak blood glucose concentration, and glucose area under the curve, with no significant effects on lipid profile compared with standard EN.[18] However, this analysis included studies that scored low in methodologic quality, lacked adequate power to detect clinical differences in morbidity and mortality, and did not include studies examining the use of these EN formulas in critical illness.[18]

In 2012, A.S.P.E.N. released clinical guidelines for nutrition support of adult patients with hyperglycemia,[22] posing the question, "Should diabetes-specific enteral formulations be used for adult hospitalized patients with hyperglycemia?" The authors of these guidelines were not able to make a recommendation on this question, citing the need for further research. Only 2 studies examining the use of DM-specific EN formulas in the hospital setting were identified. One study compared 2 different DM-specific EN formulas among patients with type 2 DM hospitalized with either head/neck cancer or neurologic disorders.[23] No control (standard EN formula) was used in this study, and most patients met energy goals via EN (compared with usual, unintentional underfeeding in the hospitalized setting).[23] No significant differences in glucose, triglycerides, or insulin requirements were found.[23] A second study compared high-protein/high-MUFA + fiber EN formula (DM-specific) with a standard EN formula among ICU patients with either type 1 or 2 DM, or stress hyperglycemia.[24] Researchers reported significant improvement in glycemic control ($P = .001$) with a median insulin requirement of 14 days ($P = .001$).[24]

The Academy of Nutrition and Dietetics' Evidence Analysis Library (EAL) explored whether the nutrient composition of EN affects the cost of medical care, mortality, hospital length of stay, and infectious complications of critically ill patients with DM.[25] A "not assignable" recommendation was released based on the paucity of research available.[25] At this time, it does not appear the routine use of DM-specific EN formulas is indicated. If clinicians choose to use a DM-specific EN formula, it is important to use caution among individuals with or at risk for gastroparesis. The higher fat and fiber content of these formulas may result in poor GI tolerance.

Renal Formulas

EN formulas designed for patients with renal dysfunction are typically fluid restricted and contain lower amounts of electrolytes, specifically potassium and phosphorous.[26–28] However, sometimes these formulas are so low in potassium and phosphorous that serum levels of these nutrients can drop below reference laboratory ranges. The protein content of these formulas varies based on intended renal population; formulas designed for patients with chronic kidney disease (CKD) who are not receiving dialysis are protein restricted,[27] while other formulas have higher protein content and are designed to meet the catabolic needs associated with dialysis.[26,28] In 2005, Stratton and colleagues[29] conducted a systematic review and meta-analysis, including 18 studies, evaluating the use of oral nutrition supplements (ONS) and EN among patients receiving chronic dialysis. These authors concluded that the use of renal-specific ONS and EN products may increase serum albumin and total nutrient intake; however, they reported insufficient data to determine whether the use of ONS or EN improved clinical outcomes.[29] In addition, there was a lack of data comparing disease-specific EN products and standard formulas, no meaningful comparisons could be made.[29] One small study (n = 10) included in the Stratton et al meta-analysis noted that hypophosphatemia was a common occurrence, suggesting that nonrenal EN formulas may be appropriate in some situations.[30]

The Society of Critical Care Medicine (SCCM)/A.S.P.E.N. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient include a grade E (level of evidence: nonrandomized historical controls, case series, uncontrolled studies, expert opinion) recommendation for critically ill patients with acute kidney injury (AKI) and CKD who require EN.[9] These guidelines state that those with kidney injury "should be placed on standard enteral

formulations, and standard ICU recommendations for protein and calorie provision should be followed. If significant electrolyte abnormalities exist or develop, a specialty formulation designed for renal failure (with appropriate electrolyte profile) may be considered."[9(p306)] A.S.P.E.N. also published separate clinical guidelines for nutrition support in adult acute and chronic renal failure in 2010,[31] addressing the overall use of EN if intestinal function permits, energy and protein goals, and need for adjustments in electrolyte intake based on serum concentrations (grades D, E). These guidelines did not include specific recommendations on the ideal composition of EN formulas for patients with AKI or CKD.

The European Society for Parenteral and Enteral Nutrition (ESPEN) has also issued clinical practice guidelines for the use of EN in the setting of renal failure.[32] For patients with CKD not receiving dialysis, ESPEN issued a grade C recommendation (level IV evidence: expert opinions and/or clinical experience of respected authorities), stating "standard formulae can be used for short-term EN in undernourished CRF patients, but for EN for more than 5 days, special or disease-specific formulae (protein-restricted formulae with reduced electrolyte content) should be used."[32(p304)] For those on maintenance dialysis, ESPEN also issued a grade C recommendation advocating the use of hemodialysis-specific EN formulas as the preferred choice but noting that phosphorous and potassium content of the formula should be assessed and considered with regard to clinical picture prior to initiation of feeds. Further research is needed to determine if these products are beneficial.

At this time, there are no specialty EN products marketed for critically ill patients with AKI requiring continuous renal replacement therapy (CRRT). Current recommendations are for critically ill patients receiving CRRT to receive a high-protein standard EN formula without fluid or electrolyte restrictions.[9,32] However, close electrolyte monitoring and individualization of the nutrition care plan are indicated. In certain situations, patients with AKI who are not receiving dialysis may benefit from a renal EN formula.[32]

Hepatic Formulas

Hepatic EN formulas are designed based on the rationale that providing a lower protein content with a higher amount of branched-chain amino acids (BCAAs) and lower amount of aromatic amino acids (AAAs) may improve symptoms of hepatic encephalopathy (HE) and restore muscle mass.[33,34] The proposed mechanism of BCAA EN formulas is that BCAAs do not compete with AAAs for transport across the blood-brain barrier, thus reducing the signs and symptoms of HE.[33] Hepatic EN products are also fluid restricted and low in sodium to attenuate effects of ascites, which is commonly observed among patients with liver failure.[33] The SCCM/A.S.P.E.N. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient include a grade C (supported by level II investigations: small, randomized trials with uncertain results; moderate to high risk of false-positive or false-negative errors) recommendation that standard enteral formulations should be used in ICU patients with acute and chronic liver disease, reserving use of BCAA formulations for "the rare encephalopathic patient who is refractory to standard treatment with luminal acting antibiotics and lactulose."[9]

The ESPEN guidelines on EN for liver disease include grade C (expert opinions and/or clinical experience of respected authorities) recommendations for the use of whole-protein EN formulas and the use of concentrated, high-energy EN formulas for patients with ascites.[35] However, a grade A (meta-analysis of randomized controlled trials or at least 1 randomized controlled trial) recommendation was issued for the use of BCAA-enriched formula among patients with hepatic encephalopathy that arises during EN therapy, including those with alcoholic steatohepatitis, liver cirrhosis, and transplantation and surgery.[35]

In 2012, Koretz and colleagues[36] published a Cochrane review on nutrition support for liver disease. The only significant finding with respect to EN was that use of EN support may be associated with improved nitrogen balance in medical patients and reduced postoperative complications in surgical patients. Although 37 studies were identified, the authors concluded that current research does not support the routine use of parenteral, enteral, or oral nutrition supplements among patients with liver disease.[36] This recommendation is based on criticisms of the state of the literature, including low sample sizes, design, and risk of bias. In addition, the authors advocated for the need for well-designed, randomized trials with sufficient power to observe clinically significant improvements.[36]

At this time, there appears to be some agreement that until more research is available, patients with liver disease should receive a standard protein EN formula, reserving hepatic EN formulas for those who do not respond to medical treatment of HE and/or if HE develops after initiation of EN support. Recently, there has been an emphasis on determining appropriate protein goals for this population. It was previously thought that protein restrictions would be helpful in the setting of HE; however, more recent research suggests that patients receiving up to 1.5 g protein/kg/d experience improved clinical outcomes (decreased protein catabolism, improvements in HE symptoms).[37,38] The American College of Gastroenterology practice guidelines for HE suggest a progressive increase in protein provision until the target of 1–1.5 g protein/kg/d is achieved.[39] Based on these higher protein recommendations, it is unlikely that most patients' protein needs can be met with a BCAA EN formula without overfeeding total kcal.

Bariatric Formulas

Bariatric EN formulas were developed based on the findings of several small studies with overweight and obese patients receiving either EN or parenteral nutrition (PN) support.[40–47]

The results of these studies indicate patients who received hypocaloric (50%–70% estimated energy requirements or <14 kcal/kg actual body weight) and high-protein feedings (2–2.5 g protein/kg ideal body weight [IBW], adjusted as needed based on results of nitrogen balance studies) had at least equivalent clinical outcomes compared with those who received high-protein, eucaloric feeding.[45] One bariatric EN formula available in the United States contains 1 kcal/mL and 93 g protein/L (37% kcal from protein),[48] modest amounts of carbohydrate intended to improve blood glucose control, and eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) with intent to reduce the inflammatory response associated with stress and critical illness.[48]

The SCCM/A.S.P.E.N. practice guidelines include a grade D recommendation (supported by at least 2 level III investigations: nonrandomized, contemporaneous controls) for the use of hypocaloric, high-protein feeding regimens for critically ill obese patients.[9] Specifically, the recommendation is for obese patients (body mass index [BMI] >30 kg/m^2) to receive an EN regimen that does not exceed 60%–70% of target energy requirements, 11–14 kcal/kg actual weight, or 22–25 kcal/kg ideal body weight and delivers ≥2.0 g protein/kg IBW (BMI 30–40 kg/m^2) and ≥2.5 g protein/kg IBW (BMI ≥40 kg/m^2).[9]

In 2013, A.S.P.E.N. issued a separate clinical guideline for nutrition support of hospitalized adult patients with obesity.[47] Previously published guidelines recommended hypocaloric, high-protein diets (defined as 50%–70% estimated energy needs, or <14 kcal/kg actual weight, and protein of 1.2 g/kg actual weight, increasing to 2–2.5 g/kg IBW, making adjustments based on results of nitrogen balance studies).[9] In the updated guidelines, A.S.P.E.N. issued a weak recommendation for this practice, citing low-grade evidence. Furthermore, the authors identified the need for a large, randomized controlled trial to determine if this feeding practice offers a therapeutic advantage compared with eucaloric feeding with respect to clinical outcomes, including the avoidance of complications associated with overfeeding.[47] Future research is also needed to address whether bariatric formulas are effective among individuals requiring long-term EN support. To date, data only exist for using these formulas in the intensive care and acute care settings.

The American Academy of Nutrition and Dietetics' EAL also addresses questions whether hypocaloric, high-protein feeding (defined as <20 kcal/kg actual weight and 2 g protein/kg IBW) is associated with improved clinical outcomes.[49] When examining this feeding practice with respect to mortality, infectious complications, and number of days of mechanical ventilation, grade III (limited) evidence was cited, based on "unclear" effects.[49] The authors cite grade III evidence indicating shorter ICU stays for obese patients who received a hypocaloric, high-protein feeding regimen; however, the total length of stay did not differ.[49] Last, the EAL explored whether hypocaloric feeding practices affect cost of care, but there was insufficient research to assign a grade.[49] At this time, there are no guidelines from ESPEN or the Cochrane Collaboration addressing the use of hyocaloric, high-protein enteral formulas. As stated previously, this EN formula may be widely used in critical care, but additional research is warranted.

Elemental/Semi-Elemental Formulas

Elemental and semi-elemental formulas are often used among patients with malabsorptive disorders and/or those having a difficulties absorbing and digesting standard polymeric formulas. Macronutrients are hydrolyzed to improve absorption. Carbohydrate may be included from sources such as hydrolyzed cornstarch, maltodextrin, or fructose; protein from free amino acids and dipeptides or tripeptides (hydrolyzed casein, whey, or soy protein isolate); and lipid from fatty acid esters or medium-chain triglycerides.

There is limited research comparing outcomes associated with the use of polymeric vs elemental formulas. Tiengou and colleagues[50] reported similar tolerance between semi-elemental and polymeric formulas in a group of patients with pancreatitis, although they did note significantly reduced hospital length of stay among those receiving semi-elemental EN. Conversely, Taylor and colleagues[51] found no difference in outcomes or remission rates in a group of pediatric patients with Crohn's disease receiving a semi-elemental formula compared with those receiving a polymeric formula. In contrast, an earlier study, published in 1990, randomized patients (n = 30) with Crohn's disease to receive either an elemental formula or a polymeric formula for 4 weeks.[52] During assessment on days 10 and 28, the investigators observed that clinical remission occurred in 5 (36%) of the 14 patients receiving the polymeric formula compared with 12 (75%) of the 16 patients assigned to the elemental formula. The difference in remission rate was significant ($P < .03$).[52]

ESPEN does not recommend the routine use of elemental formulas in the use of Crohn's disease, ulcerative colitis, or short bowel syndrome.[53] A Cochrane Review published in 2007 reviewed data on the use of EN for the induction of remission and Crohn's disease.[54] In the subgroup analysis, the authors found no statistically significant differences between elemental, semi-elemental, and polymeric diets.[54] The authors advocate caution in the interpretation of these findings due to the included studies' heterogeneity and small sample sizes.[54]

In 2014, the British Dietetic Association (BDA) published evidence-based guidelines for the dietary management of Crohn's disease in adults.[55] The authors of this guideline reviewed 15 studies that evaluated the roles of EN to induce remission, food reintroduction diets to structure food reintroduction and maintain remission, and dietary management of structuring disease, as well as whether probiotics or prebiotics induce or maintain remission.[55] The BDA found evidence supporting the use of EN (elemental or nonelemental) as an alternative to corticosteroids to induce remission of Crohn's disease.[55] Due to the lack of larger, randomized controlled

trials comparing elemental and nonelemental formulas, some clinicians have concluded that elemental formulas should be used only when standard formulas are poorly tolerated due to decreased digestive enzyme production. At this time, there remains conflicting data on whether elemental or nonelemental formulas are superior in the management of Crohn's disease, and further study is warranted.

Fish Oil/Pulmonary Formulas

Specialized pulmonary enteral formulas were initially designed for patients with chronic pulmonary diseases with the intent to aid weaning from mechanical ventilation and were later used among those with acute lung injury (ALI) and acute respiratory distress syndrome (ARDS). In efforts to reduce carbon dioxide production, these formulas are high in fat (>50% total kcal), lower in carbohydrate (<30% total kcal), and similar in protein content (16%–18% total kcal) to standard polymeric formulas.[56] Pulmonary formulas differ from standard formulas with regard to fatty acid composition as well, incorporating immune-modulating substrates, specifically fish oil–derived ω-3 fatty acids and γ-linolenic acid (GLA), and have been developed to offer anti-inflammatory benefits over the ω-6 fat-rich standard formulas for patients with ALI and ARDS. The proposed benefit between fish oil–derived ω-3 fatty acids and reduced inflammation is that eicosanoids, such as proastaglandins, thromboxanes, and leukotrienes, contain a high proportion of ω-6 fatty acids, specifically arachidonic acid, which can be influenced by dietary intake and have been found to result in an increase in proinflammatory marker production.[57] Increased intake of long-chain ω-3 fats, EPA and DHA, results in higher proportions of ω-3 fats into the phospholipids of inflammatory cells, displacing ω-6 arachidonic acid in these cells. The anti-inflammatory effects of EPA and DHA are thought to be multifactorial, including decreased leukocyte chemotaxis, decreased production of reactive oxygen species and proinflammatory cytokines, and decreased adhesion molecule expression. This has been researched among free-living individuals with chronic obstructive pulmonary disease, in whom diets rich in fish oil–derived ω-3 fatty acids were found to reduce systemic and pulmonary markers of inflammation, specifically a reduction in both serum and sputum leukotriene B4, tumor necrosis factor–α (TNF-α), and interleukin-8 levels in the sputum.[58]

Conflicting results have been reported on whether use of low-carbohydrate, high-fat "pulmonary" formulas has improved measures of volume oxygen consumption (VO_2), carbon dioxide produced (VCO_2), and the respiratory quotient (RQ). Outcomes of early research comparing use of pulmonary vs standard formulas and pulmonary function provided mixed results, including no differences in VO_2 or VCO_2 measurements[59]; improvements in RQ, VCO_2, minute ventilation, or end-tidal CO_2[60–63]; and improved $PaCO_2$ (P = .003) and mechanical ventilation (P = .006).[64] However, more recent research concluded that differences in VO_2, VCO_2, RQ, and specifically hypercapnia may be better explained by overfeeding, rather than lower delivery of carbohydrate.[65]

Although some researchers have reported that use of immune-enhanced pulmonary formulas, compared with standard controls, resulted in decreased inflammation, improved oxygenation, and reduced ventilator days, ICU length of stay (LOS), and incidence of new organ failure,[66–68] others conclude that use of EPA/GLA-enriched formulas does not improve ICU LOS or time on mechanical ventilation.[69] These patients, however, received approximately 1000–1200 kcal/d from the enteral formula, in addition to approximately 1000 kcal/d from propofol infusion, possibly leading to overfeeding, specifically from an ω-6–rich source (propofol). Initial studies reporting benefits of use of formulas high in ω-3 fish oil have been criticized for use of the standard EN formula with high proinflammatory ω-6 fatty acid content as a control, potentially leading to increased inflammatory response and confounding the outcomes in favor of the fish oil–containing formulas by way of administering a proinflammatory substrate that may have exacerbated the inflammatory response.

The ARDS Network Omega Trial[70] was a double-blind, controlled trial, in which patients were randomized to receive an enteral supplement containing ω-3, GLA, and antioxidants, administered twice daily, or an isocaloric, isovolumic control, also administered twice daily. The trial was terminated early for futility after failing to achieve fewer ventilator-free days (14.0 vs 17.2; P = .02) (difference, –3.2 days; 95% CI, –5.8 to –0.7) or ICU-free days (14.0 vs 16.7; P = .04) among those receiving the supplement, despite an 8-fold increase in plasma EPA concentration. Those receiving the supplement had fewer nonpulmonary organ failure–free days (12.3 vs 15.5; P = .02) and a marginally significant higher 60-day hospital mortality (26.6% vs 16.3%; P = .054), although this became nonsignificant after adjusting for potential confounders (25.1% vs 17.6%; P = .11). Interestingly, those receiving the ω-3 supplement experienced more days with diarrhea (29% vs 21%; P = .001). Study design and low mortality among control patients, bolus administration of the immune-modulating nutrients, and uncertainty of mechanism of ω-3 incorporation into the plasma membrane may have affected outcomes.[71]

A recent systematic review concluded that use of continuously administered fish oil/antioxidant enteral formulas (but not bolus dosing of immune-modulating substances) was associated with a reduction in ICU LOS (weighted mean difference, –3.67 days; 95% CI, –6.01 to –1.33; P = .002) with significant heterogeneity (I^2 = 78%) and a reduction in ventilator days (weighted mean difference, –4.83; 95% CI, –7.96 to –1.70; P = .002) with significant heterogeneity (I^2 = 88%)[72]; more research is needed to confirm these findings. Although initial research seemed promising for the use of enteral formulas designed to improve outcomes associated with pulmonary dysfunction, research remains inconclusive. Use of high-fat enteral formulas alone or in combination with ω-3 fish oil has not been found to be beneficial as previously thought. When

administered as a component of EN, these substances may be beneficial in reducing mortality among those with ALI/ARDS, although they are not recommended among critically ill patients with sepsis.[73] Instead, efforts to prevent excessive EN delivery should be employed to reduce complications associated with overfeeding.

Immunonutrition and Immune-Modulating Formulas

As discussed, a wide variety of EN formulations exist, each with the potential benefit of improved clinical outcomes among specific patient populations; however, the arena of clinical care is outcome driven, and attributing improvements in outcomes related to use of specialized nutrition formulations proves challenging. Historically, the primary focus of clinical nutrition has been delivery of adequate energy and nitrogen to meet requirements and prevent degradation of lean body mass for gluconeogensis. Over the past two decades, the focus has shifted to immunonutrition—the administration of pharmacologically active substances, such as arginine, glutamine, selenium, ω-3 fatty acids such as EPA and DHA, GLA, nucleotides, and/or antioxidants in efforts to modulate the metabolic response to surgery or stress by enhancing immune function. These potentially immune-modulating substances have been administered as components of both EN and PN support, as well as individual substances. Many of the immune-modulating enteral formulas contain ω-3 fatty acids in efforts to produce an anti-inflammatory response as discussed in the previous section.

Research of specialty formulations with regard to improved patient outcomes is limited, with the exception in the area of immunonutrition. Most of the literature in the area of immunonutrition has been conducted among patients undergoing elective GI surgeries in the pre- and perioperative states. The impact of immunonutrition has been demonstrated to favorably affect outcomes, including reduced LOS in various clinical settings, particularly patients undergoing elective GI surgeries.[74] In addition, it has been suggested that immune-modulating enteral formulas may also be cost-effective when used in specific healthcare settings.[75,76]

Immune-modulating nutrition has been explored in a variety of settings, including but not limited to pre- and postsurgical, pulmonary, trauma, critical care, neurology, and oncology patients. A recent systematic review and meta-analysis conducted to assess the impact of arginine-enriched enteral formulas among patients undergoing surgery for head and neck cancers found that use of arginine-containing formulas was associated with a reduction in fistulas (OR, 0.36; 95% CI, 0.14 to 0.95; $P = .039$) and LOS (mean difference, −6.8 days; 95% CI, −12.6 to −0.9; $P = .023$) but no reduction in wound infections (OR, 1.04; 95% CI, 0.49 to 2.17; $P = .925$), other infections (OR, 0.79; 95% CI, 0.48 to 1.31; $P = .369$), or occurrence of diarrhea (OR, 1.80; 95% CI, 0.50 to 6.52; $P = .375$).[77] Among a group patients with esophageal squamous cell carcinoma receiving concurrent chemotherapy and radiation requiring EN support, those who received a standard formula were found to have higher increases in C-reactive protein (CRP) ($P = .001$) and TNF-α ($P = .014$) during treatment compared with those who received an immune-modulating enteral formula with a combination of ω-3 fatty acids, glutamine, and arginine,[78] leading the authors to the conclusion that enteral immunotherapy during concurrent chemotherapy and radiation therapy reduced the rise in inflammatory cytokines.

While administration of an arginine, fish oil–based ω-3–containing EN formula was found to reduce infection and hospital LOS among patients undergoing elective surgery,[74] use among critically ill patients remains unclear.[71] Reduced incidence of cardiovascular and pulmonary organ failure has been reported with randomization to feeding of a commercially available enteral formula containing ω-3, GLA, and antioxidants,[79] although study design and definitions were brought into question.[80,81] Early randomized controlled trials (RCTs) among critically ill patients found improved oxygenation, shorter ventilator duration, reduced rates of organ failure, shorter ICU LOS, and lower mortality compared with standard enteral formulas.[66–68,82] Several meta-analyses have been conducted over the past 15 years, each finding no difference in mortality in either surgical or medical patients.[83–86] However, more recent literature has begun to examine implications for those in the intensive care setting, resulting in a lack of consensus among guidelines for the use of immune-modulating formulas. The SCCM/A.S.P.E.N. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient provide grade A recommendations for use of immune-modulating components among surgical patients and grade B recommendations for medical ICU patients.[9] In addition, these guidelines suggest that immune-modulating nutrients should be used among appropriate critically ill patients requiring mechanical ventilator support, using caution with those with severe sepsis.[9] The ESPEN guidelines cite no general indication for use of immune-modulating nutrients in EN among those with severe illness or sepsis with an Acute Physiology and Chronic Health Evaluation II (APACHE II) score >15.[87] The most recent Surviving Sepsis Campaign guidelines recommend against the use of immunonutrition among patients with severe sepsis.[73] These recommendations likely stem from the findings of the highly publicized ARDS Network Omega Trial[70] and Canadian Reducing Deaths Due to Oxidative Stress (REDOX)[88] trial.

While the ARDS Network Omega Trial,[70] in which patients were randomly assigned to receive enteral ω-3, GLA, and antioxidant-supplements twice daily, failed to achieve fewer ventilator-free days, despite significant increases in plasma EPA concentrations, another large, multicenter, placebo-controlled, double-blind trial (REDOX) compared the effects of glutamine and/or selenium among critically ill patients with multiple organ dysfunction.[88] Immune-modulating components (glutamine and antioxidants including selenium, both, or placebo)

were provided as intravenous and enteral boluses within 24 hours of ICU admission. Those receiving glutamine had a longer time to discharge from the ICU and hospital. Furthermore, in-hospital and 6-month mortality was higher among those who received glutamine supplementation compared with those who had not, although no effect on organ failure or infectious complications was noted. Antioxidants alone had no effect on 28-day mortality. Post hoc analysis by the authors confirmed these findings, concluding that early provision of high-dose glutamine or antioxidants administered separately from nutrition support may be associated with increased mortality, particularly critically ill patients with multiorgan failure, including renal dysfunction.[88]

More recently, researchers of the MetaPlus study, a randomized, multicenter trial, compared morbidity and mortality outcomes between patients randomized to administration of a high-protein, immune-modulating formula containing glutamine, ω-3 fatty acids, and antioxidants with a standard, isocaloric, high-protein formula among ICU patients requiring mechanical ventilation.[89] These researchers report no statistically or clinically significant differences in the incidence of new infections; however, after adjusting for age and APACHE II scores, 6-month mortality among medical patients receiving the high-protein, immune-modulating formula was significantly higher than for those receiving the standard, high-protein formula (52% [95% CI, 40%–67%] vs 35% [95% CI, 22%–49%], respectively), with a hazard ratio of 1.57 (95% CI, 1.03–2.39; $P = .04$).

The immune-modulating effects of nutrients, particularly glutamine and selenium, have also been studied among those receiving EN and/or PN support, generally finding reductions in nosocomial infections among critically ill patients. In 2011, the Scottish Intensive care Glutamine or selenium Evaluative Trial (SIGNET) Trials Group examined the incidence of new infections and mortality among critically ill patients receiving PN supplemented with glutamine, selenium, or both as a component of PN.[90] No effect was seen on the incidence of new infections or morality when PN was supplemented with either component, except among those receiving ≥5 days of selenium supplementation, where a reduction in new infections was noted. A 2014 systematic review conducted by Wischmeyer et al[91] examined RCTs of parenterally administered glutamine among critically ill patients, concluding that as a component of PN, glutamine supplementation is associated with a significant reduction in hospital mortality and LOS. Although a significant reduction in hospital mortality (relative risk [RR], 0.68; 95% CI, 0.51 to 0.90; $P = .008$) and hospital LOS (weighted mean difference [WMD], –5.26; 95% CI, –4.71 to –0.42; $P = .02$) was noted, there were only *trends* toward reduction of overall mortality (RR, 0.88; 95% CI, 0.75 to 1.02; $P = .09$), infectious complications (RR, 0.86; 95% CI, 0.73 to 1.05; $P = .09$), and ICU LOS (WMD, –1.91; 95% CI, –4.10 to 0.28; $P = .09$).

Another meta-analysis of RCTs published in 2014 by Chen et al[92] examined the effects of glutamine supplementation via enteral, parenteral, or both routes, concluding that glutamine supplementation posed no benefit in overall mortality or hospital LOS but resulted in lower incidence of nosocomial infections among critically ill patients (RR, 0.85; 95% CI, 0.74–0.97; $P = .02$), surgical ICU patients (RR, 0.70; 95% CI, 0.52–0.94; $P = .04$), and PN subgroups (RR, 0.83; 95% CI, 0.80–0.98; $P = .03$). This group also reported that high-dose glutamine supplementation (>0.5 g/kg/d) significantly increased mortality among critically ill patients (RR, 1.18; 95% CI, 1.02–1.38; $P = .03$). A separate group of researchers recently conducted a randomized, multicenter trial to evaluate to effect of 5-day intravenous (IV) glutamine supplementation on trauma ICU patients, finding that 60% of patients had low-plasma glutamine levels, which persisted in 39% of the treated group following randomization to receive 0.5 g/kg/weight IV glutamine.[93] Low-plasma glutamine was also associated with higher rates of infection (59% vs 81%; $P = .032$), longer ICU (9 vs 20 days; $P = .01$), and hospital LOS (24 vs 41 days; $P = .01$) compared with those who received placebo. This is concerning because not only did high-dose supplementation fail to achieve normal plasma glutamine levels, but the dose used was that in which researchers in the previously discussed meta-analysis described a risk factor for increased mortality among critically ill patients. Large, well-designed RCTs have failed to demonstrate mortality benefits with administration of immune-modulating substances separate from or in addition to a standard nutrition support regimen, particularly among the critically ill. Administration of immune-modulating substances as components of EN is potentially beneficial when used for patients undergoing elective surgery; however, research is not sufficient to recommend for routine use among critically ill patients at this time.

Implications for Practice

Ochoa and colleagues[94] have reviewed the industry processes uses when developing new EN formulation. As stated previously, EN products do not have to undergo the 4-phase process for gaining FDA approval, as required for pharmaceutical agents.[94] One reason cited for this difference is that medical foods are reimbursed at a much lower rate compared with pharmaceutical agents; therefore, EN developers are limited in the initial financial investment for product developmen.[94] Although there is a less rigorous process for FDA approval, EN formulas intended to exhibit pharmacologic properties have been studied for efficacy and impact on clinical outcomes. Standard formulas, however, are rarely studied, except when being compared with specialty formulas. As specialty EN products are designed and marketed to exert therapeutic effects, clinicians must be knowledgeable of the quality, design, and outcomes associated with the research, as well as potential conflicts of interest associated with funding sources that may influence reported outcomes and health claims of these medical foods.

Table 2. Resources for Enteral Nutrition Support.

Organization or Product	Website/Resource
Professional organizations	
American Society for Parenteral and Enteral Nutrition	http://www.nutritioncare.org
European Society for Parenteral and Enteral Nutrition	http://www.ESPEN.org
Support and living with enteral nutrition	
Tube Feeding Awareness	http://www.feedingtubeawareness.com
Oley Foundation	http://www.oley.org
Hand to Hold	http://handtohold.org
Oral Cancer Foundation	http://www.oralcancerfoundation.org/nutrition
Mobile device applications[a]	
A.S.P.E.N. eBooks	Available from American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.)
Journal of Parenteral and Enteral Nutrition[b]	http://www.pen.sagepub.com
Nutrition in Clinical Practice[b]	http://www.ncp.sagepub.com
ESPEN	B-com Event Technologies
Tube Feeding Calculator	Tube Feeding Calculator + by Christopher Ciaio

[a]Applications available in both Apple App Store and Google Play Store.
[b]Applications available in the Apple App Store only.

At this time, there are over 100 EN formulas and modular products (ie, protein supplements) available for pediatric (non-infant) and adult patients in the United States.[95] To make the most informed EN selection, Cresci and colleagues[33] recommend evaluating whether the research used to market an EN formula is in vitro vs in vivo (animal vs human). In addition, Cresci et al advocate careful evaluation of the quality and type of the study design, including prospective RCT (gold standard), retrospective review, case reports, patient population studied (homogeneity, clinical environment), and generalized results.[33] Given the rising costs of healthcare and the move toward evidence-based practice, it is imperative that clinicians carefully evaluate studies used to support specific EN formulas, paying close attention to the quality, patient population (ie, ambulatory, critical care, long-term care, etc), clinical end points, and cost to patient and/or facility. Table 2 provides EN resources for clinicians and individuals receiving this therapy.

When selecting an appropriate EN formula, it is essential that clinicians employ clinical judgment with regard to efficacy, tolerance, and, in many cases, cost. Healthcare facilities must complete a cost-benefit analysis when developing an EN formulary and choose products appropriately to reduce expenditure. EN products may or may not be eligible for reimbursement during an acute care admission since many facilities consider EN a "food," including it as part of the daily charge. For example, under Medicare Part A guidelines, EN therapy is typically considered part of a diagnosis-related group (DRG), therefore, and is not separately reimbursable.[96] Among patients expected to receive home EN, the formula and associated supplies are reimbursed through a government program such as Medicaid or Medicare, commercial health insurance, or private pay. For Medicare beneficiaries, coverage is available through the Part B prosthetic device benefit[96] for which patients must have documentation in their medical record indicating they meet the following criteria: there must be permanent functional impairment of the GI tract (ie, permanent nonfunction or disease of the structures that normally permit food to reach or be absorbed from the small bowel), and EN is deemed to be beneficial and necessary for the beneficiary (patient), as well as deemed necessary to maintain weight and strength commensurate with health status.[96] To receive reimbursement for "specialty" EN formulas, proper documentation and justification must be submitted to the Centers for Medicare & Medicaid Services (CMS).[96] Many insurers follow reimbursement guidelines similar to those used by CMS; however, it is always recommended that health insurance providers are contacted to determine coverage for EN therapy prior to initiation. EN products can be costly and, in some cases, may not be feasible for patients to administer at home due to out-of-pocket costs.

Conclusion

A wide variety of EN formulas exist and with continuous development of new products marketed to nutrition support clinicians. Standard polymeric formulas are indicated for most patients requiring EN support. EN formula characteristics and research used to support each formula type must be carefully evaluated. Clinicians should monitor the content of EN products due to frequency of manufacturing changes that may affect efficacy and applicability. EN support clinicians must carefully evaluate studies used to support the use of specific EN formulas, paying close attention to the quality, the patient population, clinical end points, and cost to patient and/or facility when selecting EN products.

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