Enteral Nutrition in the Management of Pediatric Intestinal Failure

Kerri B. Gosselin, MD, MPH, and Christopher Duggan, MD, MPH

Intestinal failure (IF) is an uncommon but devastating condition whose natural history has dramatically improved over the past 2 decades.[1] Infants with IF because of severe short bowel syndrome (SBS) or other diagnoses previously considered incompatible with life are now routinely being saved and cared for in cutting edge, multidisciplinary programs. Enteral nutrition (EN) plays a central role in the management of children with IF. This review provides an overview of EN in pediatric IF, with specific emphasis on recent advances in clinical management, patient outcomes, and emerging therapies.

Definitions

IF occurs when there is a reduction of functional intestinal mass necessary for adequate digestion and absorption for nutrient, fluid, and growth requirements, resulting in the need for intensive nutritional support. The American Gastroenterological Association defines IF as the condition that results "from obstruction, dysmotility, surgical resection, congenital defect, or disease-associated loss of absorption and is characterized by the inability to maintain protein-energy, fluid, electrolyte, or micronutrient balance."[2] IF resulting from extensive intestinal resection is termed SBS (the common etiologies are listed in **Table I**), but other etiologies of IF are increasingly appreciated, including a wide range of gastrointestinal epithelial and motility disorders.

The goals of IF management are to support optimal nutritional status, promote quality of life, and limit morbidity and mortality by promoting enteral autonomy. Although life-saving, parenteral nutrition (PN) is associated with substantial morbidity, including IF-associated liver disease, catheter-related blood stream infections, and central line thrombus and malfunction. In addition, the social and financial burden for patients on prolonged PN is substantial, even with primarily outpatient management.[3] Limiting the duration of PN by promoting enteral autonomy has been shown to decrease complications[4] and improve survival for pediatric patients with IF.[5]

In order to successfully transition from PN to EN, the intestinal epithelium must adapt to optimize nutrient absorption. Depending on the severity of IF, full enteral autonomy may not always be possible. Fortunately, outcomes for pediatric patients with IF have been steadily improving, and prognostic biomarkers exist to aid in predicting clinical outcomes such as achievement of full EN. In addition, the introduction of novel therapies offer hope for enhancing the adaptive mechanisms of the small bowel and optimizing intestinal function.[6]

EN	Enteral nutrition
GLP-2	Glucagon-like peptide 2
IF	Intestinal failure
PN	Parenteral nutrition
SBS	Short bowel syndrome

Enteral Feeding in IF

Deprivation of enteral calories, often termed "gut rest" in the setting of surgical or other interventions, causes atrophy of the intestinal mucosa, even in the presence of adequate PN support.[7-9] Upon reintroduction of EN, the surgically or functionally shortened intestine must undergo structural and functional adaptations to best absorb luminal nutrients. The histologic hallmark of this compensatory response is intestinal epithelial cell hyperplasia, including increased villus height and crypt depth. Gross anatomic adaptations include bowel lengthening and dilatation. These processes, classically termed "intestinal adaptation"[5,6] are promoted by a combination of mechanical, humoral, and luminal factors,[10,11] and are likely driven by molecular signaling pathways. For example, increased expression of the Jagged-1 protein via the Notch-1 signaling pathway results in proliferation of small intestinal crypt epithelial cells.[12] In a study of greyhound dogs fed either intravenous or EN after jejunal resection, enteral feeding resulted in increased villus height and improved glucose absorption, demonstrating that the provision of luminal contents is essential to optimal postresection intestinal function.[7] In addition, numerous hormones including secretin, neurotensin, peptide YY, and glucagon-like peptide 2 (GLP-2) have been shown to be important mediators of intestinal adaptation.[13-15]

The degree of intestinal adaptation differs by anatomic location along the gastrointestinal tract, with the ileum having a greater ability to adapt compared with the more proximal small bowel.[16] Other factors that predispose to successful intestinal adaptation, as defined by successful weaning from PN support, include younger patient age,[17] longer residual bowel length,[18] intact ileocecal valve,[18] absence of gastrointestinal mucosal inflammation,[19] absence of cholestasis,[20] and normal gastrointestinal motility.[21]

From the Division of Gastroenterology, Hepatology, and Nutrition, Boston Children's Hospital, Boston, MA

Funded by the National Institutes of Health (K24 HD 058795 [to C.D.] and T32 DK 7477-30 [to K.G.]). C.D. is a site investigator for the NPS-sponsored trial of teduglutide (registered with ClinicalTrials.gov: NCT01952080). The authors declare no conflicts of interest.

http://dx.doi.org/10.1016/j.jpeds.2014.08.012

Table I. Etiologies of SBS in children in North America

Cause of SBS in children	Squires et al[44] n = 272	Quiros-Tejeira[63] n = 78	Wales et al[64] n = 40
Necrotizing enterocolitis	26%	22%	35%
Congenital intestinal atrestia (jejunal, ileal, apple peel)	10%	24%	10%
Abdominal wall defects (gastroschisis, omphalocele)	16%	24%	12.5%
Volvulus	9%	20%	10%
Hirschsprung disease	4%	NR	2.5%
Meconium ileus	NR	NR	20%
Other*	28%	10%	10%

*The category "other" in the study by Squires et al includes multiple single diagnoses, whereas "other" in the Quiros-Tejeira study refers to postsurgical intestinal obstruction, congenital SBS, abdominal trauma, and small bowel lymphoma.

The timing of advancement and composition of enteral feeds likely play an important roles in achieving enteral autonomy. The prompt initiation of enteral feeding after bowel resection has been shown to decrease the duration of hospitalization,[22] and increase the rate of achieving enteral autonomy[23] in neonates with SBS. Thus, feeds should be started as soon as postoperative ileus resolves. A guideline for enteral feeding advancement is provided in **Figure**. As with many aspects of medical care for infants with IF, this algorithm has not been rigorously tested, but provides a helpful approach.

Although data are few, the optimal choice for EN in infants with IF seems to be human milk, which contains growth factors and immunoglobulins that may promote intestinal adaptation.[24,25] Emerging evidence also suggests that human milk may help prevent IF-associated liver disease, although the exact mechanism is unknown.[26] If human milk is unavailable, amino acid-based formulas have been associated with improved outcomes.[20] Scarce human data exist with respect to whether various macronutrients (long vs medium vs short chain fats; intact vs hydrolyzed vs amino acid proteins) are associated with better short- or long-term outcomes. Animal data support the concept that intact macronutrients (eg, long chain fatty acids) stimulate better adaptation, but human data are limited.

Dietary fiber is metabolized by colonic bacteria into short-chain fatty acids, which provide an additional energy source and enhance the ability of the colon to absorb water. In select patients with IF with an intact colon and ileocecal valve, supplementation with dietary fiber may be helpful in reducing diarrhea. This was demonstrated in a case series of infants with SBS who experienced an improvement in diarrhea with the addition of 2 g/kg/d of dietary fiber.[27] Further study of dietary fiber supplementation in children with IF is needed.

Bolus enteral feeding produces cyclical changes in gastrointestinal hormones and is generally regarded as most closely mimicking true gastrointestinal physiology.[28] In patients with intestinal diseases including SBS, however, continuous EN has been shown to improve intestinal nutrient absorption and weight gain,[29,30] and may be better tolerated than bolus feeding.[31] We commonly employ an approach that uses both modalities (eg, continuous feeding at night and bolus feeding during the day). In addition, the introduction of complementary, age-appropriate foods between 4-6 months of age, as well as oral boluses of human milk/formula as soon as tolerated, is helpful to stimulate oral-motor development and prevent feeding aversion.[32] More studies are needed to identify prognostic factors in achieving enteral autonomy.

Micronutrient and Vitamin Deficiencies

Nutrients are differentially absorbed in various locations throughout the small intestine, and therefore, the type of bowel resected will predispose to specific micronutrient and vitamin deficiencies (**Table II**). For example, a patient with duodenal resection is at risk for iron and folate deficiency, whereas a patient with ileal resection is at risk for a deficiency of vitamin B12 and bile acid malabsorption. Bile acid deficiency may in turn predispose to deficiencies of the fat-soluble vitamins A, D, E, and K. Extensive small bowel resection predisposes to generalized carbohydrate fat, and protein malabsorption.[33]

Micronutrients play important roles in the maintenance of gastrointestinal structure and function, including mucosal immunity, and deficiencies of minerals or vitamins may inhibit intestinal adaptation. In a study of vitamin A deficient and sufficient rats with small bowel resection, vitamin A deficiency was associated with compromised intestinal adaptation including impaired crypt proliferation, decreased enterocyte migration, and increased crypt cell apoptosis.[34] Zinc deficiency has been shown to impede adaptive mucosal growth in response to extensive bowel resection in rats.[35]

Despite the use of PN and concomitant parenteral multivitamins, patients with IF remain at risk of micronutrient deficiencies, even or perhaps especially after achieving enteral autonomy. A longitudinal study of 30 children with IF by Yang et al found a high prevalence of micronutrient deficiencies in patients receiving partial PN support, including copper (56%), iron (46%), selenium (35%), and zinc (31%).[36] A similar study by Ubesie et al showed a significant reduction in the proportion of patients with iron deficiency after transition to EN, although the burden of iron deficiency remained high (61%).[37] Vitamin E status also improved.

The full discontinuation of PN also appears to worsen some micronutrient and vitamin deficiencies. For example, Yang et al found that the prevalence of vitamin D deficiency increased from 20% to 68% after transition to full EN, and the prevalence of zinc deficiency increased from 31% to 67%.[36] Several factors were associated with the development of vitamin and micronutrient deficiencies, including lower height-for-age *z*-score, lack of multivitamin supplementation, and absence of the ileocecal valve. These results support the conclusion that patients with IF remain at risk for nutrient deficiency even with full enteral feeding and emphasize the importance of supplementation with a multivitamin preparation containing water soluble forms of fat soluble vitamins, as