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Enteral nutrition in the management of pediatric intestinal failure

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

Definitions

Intestinal failure (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).” Intestinal failure resulting from extensive intestinal resection is termed short bowel syndrome (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 intestinal failure 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 (IFALD), catheter-related blood stream infections (CRBSI), and central line thrombus and malfunction. Additionally, the social and financial burden for patients on prolonged PN is substantial, even with primarily outpatient management (3).

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Limiting the duration of PN by promoting enteral autonomy has been shown to decrease complications (4) and improve survival for pediatric IF patients (5).

In order to successfully transition from parenteral to enteral nutrition (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 enteral nutrition. Additionally, the introduction of novel therapies offer hope for enhancing the adaptive mechanisms of the small bowel and optimizing intestinal function (6).

Enteral Feeding in Intestinal Failure

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 parenteral nutrition support (7-9). Upon reintroduction of EN, the surgically or functionally shortened intestine must undergo structural and functional adaptations in order 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 enteral nutrition 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 post-resection intestinal function (7). Additionally, numerous hormones including secretin, neurotensin, peptide YY, and glucagon-like peptide 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).

The timing of advancement and composition of enteral feeds all likely play an important role 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 post-operative ileus resolves. A guideline for enteral feeding advancement is provided in **Table II**. As with many aspect 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 enteral nutrition in infants with IF seems to be human milk, which contains growth factors and immunoglobulins which may promote intestinal adaptation (24, 25). Emerging evidence also suggests that human milk may help prevent IFALD, 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 IF patients 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/day 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 (e.g., 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 III**). 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 and protein malabsorption (33).

Micronutrients play important roles in the maintenance of GI 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 intestinal failure 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 enteral nutrition, and the prevalence of zinc deficiency increased from 31% to 67% (36). Several risk 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 well as zinc. Furthermore, adequate somatic growth does not preclude the presence of micronutrient deficiencies, emphasizing the importance of routine biochemical monitoring and comprehensive follow-up in these patients during transitions in feeding (33). After achieving enteral autonomy, careful monitoring of growth variables should continue. Appropriate interval growth signals adequate intestinal adaptation and sufficient absorptive capacity, and impaired growth may signal the need to resume specialized nutrition (38).

An emerging challenge in caring for patients with IF is frequent shortages of intravenous micronutrient and electrolyte preparations. During critical micronutrient shortages, patients who are unable to tolerate enteral supplementation may experience adverse outcomes. In 2012, the US Centers for Disease Control and Prevention issued a report of seven infants receiving PN lacking zinc, six of whom developed symptoms consistent with zinc deficiency dermatitis which resolved with zinc administration (39). In 2013, a shortage of parenteral selenium led to biochemical selenium deficiency in five infants with IF receiving exclusive PN (40). During a national shortage of parenteral copper in 2012, several cases of acquired copper deficiency, manifesting as bone disease, were reported (41, 42). During a recent shortage of parenteral phosphorus, providers utilized the absorptive capacity of the rectum and repleted phosphorus via administration of hypertonic sodium-phosphate enema (43). Advocacy and regulatory steps are needed to prevent substantial morbidity from nutrient shortages in this susceptible population.

Outcomes of Intestinal Failure

Another important challenge in the care of patients with IF is the limited longitudinal data available to guide clinical decisions. The Pediatric Intestinal Failure Consortium (PIFCon) is a group of 14 pediatric centers with multidisciplinary intestinal rehabilitation programs. A study of 272 infants with IF reported that the cumulative incidence of infants with sustained enteral autonomy at 3 years was 44%, and 26% had died and 23% underwent intestinal

transplantation (44). Notably, 30% of patients who achieved enteral autonomy took longer than 12 months to do so, often requiring 36-48 months of parenteral nutrition and transitional periods before tolerating a full enteral diet. In a study of 80 pediatric patients with SBS, Spencer et al showed that 64% (51 patients) had successfully weaned off PN during a mean follow-up period of 5.1 years (18). The strongest reported clinical predictors of enteral autonomy included a residual bowel length greater than 10% of expected and the presence of the ileocecal valve. Underlying diagnosis, receiving care at a specialized rehabilitation center, and the provision of human milk have also been identified as predictors of enteral autonomy (45).

In addition to clinical factors which may predict the ability to wean from PN, plasma citrulline has emerged as a promising biomarker. Citrulline is a non-essential amino acid produced by the enterocytes of the small bowel, and plasma citrulline concentration has been shown to reflect intestinal mass in various gastrointestinal diseases including enteropathies such as celiac disease, HIV-enteropathy, and IF (46). In a study of 24 children with SBS, a citrulline concentration of 19 micromol/L had a 94% sensitivity and 64% specificity for the prediction of enteral autonomy (47). In a study of 27 pediatric patients with SBS, citrulline concentrations >15 micromol/L predicted the attainment of enteral autonomy (48). Larger, prospective studies of this potential biomarker are needed.

Emerging therapies

Two recent medical therapies have recently emerged for the treatment of IF: glucagon-like peptide 2 (GLP-2) and somatropin (human growth hormone). The endogenous peptide GLP-2 is secreted by intestinal L cells and enhances nutrient absorption and increases mucosal surface area, but has a short half-life due to degradation by the enzyme dipeptidyl peptase IV (49). Teduglutide is a human recombinant GLP-2 analogue engineered with a single amino acid substitution, resulting in a longer half-life, allowing daily subcutaneous dosing (50). Several studies have shown promising results with teduglutide therapy in adults with SBS (51). In a randomized, double-blind, placebo-controlled trial of 83 adult patients with SBS, teduglutide resulted in lower PN volume requirement and improved lean body mass; three patients were able to achieve enteral autonomy (52). Safety concerns include the risk for fluid overload due to increased absorption, intestinal obstruction due to mucosal hypertrophy and a risk of acceleration of neoplastic growth (53, 54). The FDA approved teduglutide (Gattex; NPS Pharmaceuticals, Inc., Bedminster, NJ) for adults with SBS in 2012. A multicenter pediatric trial (registered with ClinicalTrials.gov: NCT01952080) is currently underway.

Unlike GLP-2, somatropin is not intestine-specific, and likely exerts its intestinal tropic effects via insulin-like growth factor 1 (55). In a study of 8 pediatric patients with SBS, daily subcutaneous somatropin therapy led to increased enteral intake, and 2 patients achieved enteral autonomy during the follow-up period of 12 months (56). In a separate study of 14 pediatric patients with SBS, therapy with somatropin for 4 months did not improve the ability to wean from PN at 6 months follow-up (57). No adverse events were reported in these pediatric trials, although short and long term adverse events in children treated with somatropin have been reported elsewhere (58). These include increased

incidence of type 2 diabetes, pseudotumor cerebri, and concern about the effects of somatropin on tumorigenesis. Currently, somatropin (Zorbtive, EMD Serono Inc., Rockland, MA) is approved for the short-term treatment of SBS in adults.

Discussion

The outlook for children with intestinal failure has improved dramatically, with survival improving from 54% in one of the earliest published series (59) to 73-100% more recently (44, 60-64). Multidisciplinary programs now provide comprehensive and longitudinal IF care and improve survival for pediatric IF patients (65). Current therapeutic goals in these patients include promotion of intestinal adaptation, optimization of quality of life, limiting of PN-associated morbidity and eventual transition to EN. During and after transition to EN, monitoring of growth and treatment with multiple micronutrients is critical. Although neonatal medical and surgical care continues to improve, emerging therapies, based on insights from work in organoid models (66) and/or intestinal stem cell lines (67), have the potential to promote intestinal adaptation and improve enteral tolerance in refractory pediatric intestinal failure patients.

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List of abbreviations

IF	intestinal failure
EN	enteral nutrition
PN	parenteral nutrition
IFALD	intestinal failure-associated liver disease
CRBSI	catheter-related blood stream infection
SBS	short bowel syndrome

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Table 1

Etiologies of short bowel syndrome 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 atresia (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 post-surgical intestinal obstruction, congenital SBS, abdominal trauma, and small bowel lymphoma.

Table 2**Suggested Guidelines for Enteral Feeding Advancement in the Infant with Intestinal Failure**Feeding Advancement Principles

- Quantify feeding intolerance primarily by stool or ostomy output.
- Assess tolerance no more than twice per 24 hours. Advance no more than once per 24-hour period.
- Ultimate goals: 150 to 200 mL/kg/d
100 to 140 kcal/kg/d
- If ostomy/stool output precludes volume advancement at 20 cal/oz for 7 days, then increasing caloric density of the formula can be performed.
- As feedings are advanced, PN should be reduced such that weight gain velocity is maintained.

Guidelines for feeding advancement

Stool output:

If < 10 mL/kg/d or < 10 stools/d -----> advance rate by 10 to 20 mL/kg/d

If 10 to 20 mL/kg/d or 10 to 12 stools/d ----> no change

If > 20 mL/kg/d or > 12 stools/d -----> reduce rate or hold feeds *

Ostomy output:

If < 2 mL/kg/h -----> advance rate by 10 to 20 mL/kg/d

If 2 to 3 mL/kg/h -----> no change

If > 3 mL/kg/h -----> reduce rate or hold feeds *

Stool reducing substances:

If < 1% -----> advance feeds per stool or ostomy output

If 1% -----> no change

If > 1% -----> reduce rate or hold feeds *

Signs of dehydration:

If absent -----> advance feeds per stool or ostomy output

If present -----> reduce rate or hold feeds *

Gastric aspirates:

< four times previous hour's infusion -----> advance feeds

> four times previous hour's infusion -----> reduce rate or hold feeds *

NB: Oral feeds may be offered as follows:

1. Infant is developmentally able to feed by mouth (PO).
2. One hour's worth of continuous feeds may be offered PO BID-TID after 5 days of continuous feeds. During this time, tube feeds should be held.
3. More than 1 hour's worth of continuous feeds may be offered PO once the infant has reached full volume of feeds by continuous route and is demonstrating weight gain at least 7 days have passed on the feeding advancement protocol.

Supplemental IV fluids may be needed.

Adapted from Brenn M, Gura KM, Duggan C. Intestinal failure. In: Sonnevile K, Duggan C, editors. Manual of Pediatric Nutrition; People's Medical Publishing House, 5th edition, 2014.

* Feeds should generally be held for 8 hours, then restarted at 75% of the previous rate.

Table 3

Anatomic resection and risk of deficiencies in short bowel syndrome.

<u>Site of resection</u>	<u>Risk of nutrient deficiency</u>
Duodenum	iron, folate
Jejunum	calcium, zinc
Ileum	vitamin B12, bile acids, fat-soluble vitamins (A,D,E,K)
Ileocecal valve	Macronutrient malabsorption (due to faster intestinal transit)