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Medical management of pediatric intestinal failure

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The outcome for children with congenital enteropathies or massive surgical resections has improved significantly over the past two decades. Advances in understanding of the pathophysiology of intractable diarrhea and of the mutations causing many of the congenital enteropathies have enabled initiation of preventive measures for intractable diarrhea, and have enabled clinicians to provide focused treatment of immune-mediated congenital diarrheal illnesses. Children with surgical short bowel syndrome also face an improved outcome because of improvements in the composition of parenteral nutrition (TPN) and in enteral alimentation strategies. It is now recognized that, through adaptation, small intestinal surface area and absorptive function may improve over time to facilitate emancipation from parenteral nutrition. Beyond provision of enteral nutrition, ancillary therapies such as judicious use of acid suppression, antibiotics, prokinetic agents, and soluble fiber seem to accelerate the rate of adaptation in young children. In the future, trophic hormones such as epidermal growth factor (EGF) or glucagon-like peptide 2 (GLP-2) may become routine members of the therapeutic armamentarium for surgical short bowel syndrome, thus further improving outcomes.

With the dawn of the current millennium, the discipline of intestinal rehabilitation has taken flight.[1] Several reasons account for the new-found interest in this subspecialty. First, neonatology has evolved to the point that ultra-premature infants now have a reasonable likelihood of meaningful survival. Given that infants born at 26 weeks of gestational age or less can now be saved, necrotizing enterocolitis (NEC) commonly appears in most neonatal intensive care units. In the face of extensive NEC, pediatric surgeons and neonatologists seem more likely to use heroic measures to save these ultra-premature infants than they would in the past. Furthermore, because of improved delivery of parenteral nutrition, children with short bowel syndrome due to midgut volvulus, gastroschisis, extensive aganglionosis, and intestinal atresias are also more likely to survive the neonatal period than they were in the past. Finally, because the option of intestinal transplantation or bone marrow transplantation now exists, many children with congenital enteropathies are aggressively treated rather than being permitted to succumb.

The proliferation of centers of excellence specializing in intestinal rehabilitation now permits "crosstalk" among centers, and facilitates the development of protocol-driven care, clinical or research registries, and multicenter studies that will take clinicians dealing with intestinal failure to a higher level of understanding this disorder.

For centers to successfully communicate, uniform definitions of intestinal disabilities are essential. A nearly universally accepted operational definition of "intestinal failure" is as follows: it is a condition whereby either an extensive surgical bowel resection or a medical condition results in inadequate water or nutrient absorption to sustain life or (among children) growth unless parenteral nutrition (TPN) is provided. The term "short bowel syndrome" should be reserved for conditions in which extensive intestinal resection has resulted in intestinal failure. Adaptation

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is the process by which intestinal mass and intestinal surface area increase, and absorptive capacity of individual enterocytes improves, such that the residual intestine assumes functions essential to sustain life without the need for parenteral nutrition.

After surgical resections, adaptation begins almost immediately,[2] but bowel function generally cannot improve over time in patients afflicted with most congenital enteropathies. Because spontaneous bowel adaptation is unlikely, most patients with microvillus inclusion disease (MVID) (due to a mutation in MYO5B, a gene encoding for the myosin motor protein 5B),[3] tufting enteropathy (due to a splice site mutation in epithelial cell adhesion molecule),[4] and idiopathic intestinal pseudo-obstruction suffer an early death due to the complications of TPN unless they undergo successful intestinal transplantation. Among the autoimmune processes resulting in intestinal failure, the response to immunomodulatory therapy is variable, but selected patients receiving corticosteroids, calcineurin inhibitors, or target of rapamycin (TOR) inhibitors, may achieve intestinal autonomy.[5,6] While many of the nutritional management principles for congenital and autoimmune enteropathies are identical to those for surgical short bowel syndrome, it is beyond the scope of this article to discuss the treatment of those enteropathies in detail Instead, the focus will be upon the management of surgical short bowel syndrome.

General management principles

Three overriding principles govern the management of surgical short bowel syndrome. First, TPN must be provided in quantities and composition satisfactory to sustain growth in pediatric patients and to sustain life in fully grown patients while preventing metabolic complications. Second, the fecal loss of fluid, electrolytes, and nutrients must be minimized. Third, the natural process of intestinal adaptation must be enhanced.

Optimizing parenteral nutrition

A central venous line (CVC) is essential for children for whom long-term TPN is anticipated. While inpatients can be managed with percutaneously inserted central catheters (PICC lines), sending them home with such catheters is problematic. First, because they are uncuffed and non-tunneled, the risk of bloodstream infections increases in direct proportion with the duration of time for which they are within a specific site. Second, because the cuff of a tunneled catheter granulates into subcutaneous tissue, it is not as likely to be dislodged after it has "matured." Third, PICC lines have a tendency to migrate outward spontaneously, becoming peripheral in location. Unless the tip location is continually monitored, the risk of delivering a high-osmolality, central TPN solution peripherally is significant. Fourth, PICC lines are more likely, than tunneled central venous catheters, to migrate from the brachiocephalic vein or superior vena cava into the jugular venous system, permitting infusion of high-osmolality solutions into the veins draining the central nervous system. Thus, the use of a tunneled CVC seems prudent in children for whom home TPN is considered.

Strict protocols for line care, for accessing CVCs, and for dressing changes are customarily employed by both hospitals and home healthcare companies to decrease the frequency of line-associated complications.[7] One of the factors resulting in repeated line infections may be the propensity of bacteria to form biofilms, which are proteinacious films of bacterial colonies adherent to the walls of CVCs, that provide nutrients to viable, but aggregated bacteria as well as protection from systemic antibiotics. Bacteria are periodically shed from these films and produce systemic infections. A commonly accepted strategy to attack biofilms is the lock therapy in which an antibiotic or ethanol is instilled into a CVC and left in for 30–60 minutes daily to biochemically break down the film while exposing and killing bacteria. The propensity of developing antibiotic resistance when antibiotic locks are used suggests that ethanol locks are preferable to antibiotic locks. Studies on the use ethanol lock therapy for dissolution of established biofilms, and for prophylaxis, are ongoing.[8]

TPN should be designed to provide adequate calories, macronutrients, and micronutrients. When a surgical patient is in the perioperative period, some authors have advocated permissive undernutrition despite the increased energy requirements and the inflammatory conditions associated with surgery. The reason for this strategy being chosen is that calories (especially carbohydrate calories) might not be optimally used up by a patient experiencing an adrenal surge under stress. The risk of perioperative stress-induced hyperglycemia is a valid concern giving credence to the concept of permissive underfeeding. However, several days after a surgical insult, caloric intake may be increased. A group from Alder Hey Hospital in Liverpool, England has shown that following surgery the maximum glucose oxidative capacity is about 18 g/d or 12 mg/kg/min.[9]

Maintenance of proper electrolyte balance is of paramount importance as well. Often, clinicians erroneously attribute hypokalemia to excessive enteral potassium losses, whereas usually, pediatric patients with short bowel syndrome and an enterostomy or poor colonic function lose much more sodium than potassium in stool and may have prodigious parenteral sodium needs.[10] In the face of inadequate sodium replacement, serum sodium levels may be kept within the normal range by compensatory hyperaldosteronemia, reduced urinary sodium and vigorous kaliuresis. Therefore, urinary electrolytes should be monitored as carefully as serum electrolytes among pediatric patients with short bowel syndrome. Sodium should be administered in TPN in a quantity adequate to maintain urinary sodium >30 mEq/L and sodium to potassium ratios approximating 1:1. The pitfall of providing inadequate sodium is the development of salt-depletion syndrome which adversely affects both somatic growth and urinary calcium retention.[10]

Provision of enteral water-soluble vitamins is unnecessary while patients are on parenteral vitamin supplements, but if adaptation occurs and patients are weaned off TPN, enteral provision of most water-soluble vitamins is advisable. Vitamin B12 absorption may be impaired among patients who have undergone distal small bowel resections, and they may require provision of parenteral or intranasal B12. Serum levels of B12 are sometimes falsely elevated because of the production of biologically inactive B12 analogues among patients with bacterial overgrowth syndrome. B12 is a cofactor for the synthesis of succinyl-CoA and cysteine from methylmalonic acid and homocysteine, respectively. Therefore, elevated serum levels of methylmalonic acid and homocysteine are more sensitive markers of B12 deficiency than is the B12 level itself.[11]

Fat-soluble vitamin supplementation is delivered via parenteral vitamins and parenteral lipid generally preventing deficiency, but after weaning of TPN, enteral supplementation is advisable.

Iron deficiency can occur in patients with short bowel syndrome, but is frequently correctable with oral iron supplements because the efficiency of enteral iron absorption is maximal in the duodenum which is seldom lost in surgical resections. For patients who cannot tolerate enteral iron or who remain deficient despite enteral supplementation, parenteral iron may be given. Episodic parenteral administration is preferred to daily administration because high levels of iron in parenteral solutions foster the growth of "siderophagic" bacteria.[12]

Trace element depletion is also very common among patients with surgical short bowel syndrome if parenteral administration is inadequate. Adequate parenteral zinc supplementation is particularly important among patients who have undergone extensive intestinal resection because zinc losses can be as high as 17 mg/L in ileostomy fluid.[13] It is commonplace for pediatric patients with short bowel syndrome to require 300–500 μg/kg/d of zinc. Zinc functions as a cofactor in a variety of metabolic processes, and zinc deficiency can result in a myriad of abnormalities including bone marrow failure and reduced immunologic vigor. Classically, acrodermatitis enteropathica, characterized by a scaly exfoliative dermatitis, involving hands, feet, genitals, and face, appears among zinc-deficient patients. Serum zinc levels tend to be depressed when a patient is systemically zinc deficient, but, for a variety of reasons, these levels correlate relatively badly with deficiency. As zinc is a cofactor for alkaline phosphatase synthesis, an excellent surrogate marker for zinc deficiency is the serum alkaline phosphatase level, which is likely to be depressed in patients at risk for the clinical manifestations of zinc deficiency.

Copper deficiency is a trace element deficiency which is often iatrogenically created.[14] Common dogma holds that among infants or children with intestinal failure-associated liver disease (IFALD), hepatic copper retention places an excessive oxidative burden upon the liver. Whether or not this is true, common practice is to reduce or eliminate parenteral copper in patients with IFALD. This may result in clinically significant copper deficiency resulting in neutropenia, thrombocytopenia, or pancytopenia. If these findings are present in patients on copper-deficient TPN (whether they have presumed hypersplenism or not), copper and ceruloplasmin levels should be measured, and copper replaced, if evidence for copper deficiency exists.

Manganese is another trace element that has been implicated in IFALD. Its levels are significantly higher among cholestatic patients on TPN than among noncholestatic patients.[15] However, the exact effects of manganese overload upon hepatic function are unknown, and because manganese undergoes an enterohepatic circulation, elevated levels may be an epiphenomenon caused by liver dysfunction rather than producing liver dysfunction.

These examples of trace element excess or deficiency emphasize that pharmacies providing TPN better serve their patients by using automatic compounding devices that can deliver "designer, individualized" trace metals rather than "trace metal packages."

One of the most devastating disorders faced by patients on long-term TPN is IFALD. Patients on TPN are at risk for fatty liver, hepatic fibrosis, and cholestasis. The exact mechanisms are unknown, but a multifactorial etiology has been proposed implicating host factors such as a reduced bile acid pool or chronic endotoxemia, or toxic constituents of the TPN solution such as excessive protein, excessive glucose infusion rates, deficient choline, or deficient sulfated amino acids.[16] The observation that reduced quantities of parenteral soy-based lipid delays the onset of cholestasis among both pediatric and adult patients, has led to the development of liver-sparing TPN protocols. If parenteral soy-based lipid is limited to $<$0.5 g/kg/d, cholestasis may be reduced or even prevented.[17] Reduction in lipid calories must be compensated by a concomitant increase in glucose calories which can result in an excessive glucose infusion rate, hyperinsulinemia, hypertriglyceridemia, and increased septic risk.[18] Thus, a strategy of providing non-soy-based lipid has been proposed by a group at the Boston Children's Hospital.[19] Omegaven, a fish oil-based lipid investigational in North America, has been marketed in Europe for use in inflammatory conditions. It is intended as a supplementary rather than an exclusive source of lipid, but a relatively large cohort of infants with IFALD studied at Boston Children's Hospital seems to have tolerated it well and demonstrated improvement in very significant cholestasis. Whether this product or another (consisting of soy oil, medium chain triglyceride, olive oil, and fish oil [SMOF]) currently being studied in Europe, proves to replace soy-based parenteral lipid for children on TPN, remains to be seen.[20]

Improvement in fluid, electrolyte, and nutrient balance

The intestine undergoes many pathophysiologic changes after extensive resection (Table 1). These changes can sab-

Table 1 Metabolic derangements of short bowel syndrome and their consequences (Modified from Cohran V and Kocoshis S. Short Bowel, in Baker, SS, Baker RD, Davis AM, eds. Pediatric Nutrition Support. Sudbury, MA: Jones and Bartlet 2006:477-492)

Derangements	Consequences
Early	Early
Gastric hypersecretion	Peptic ulceration, inactivation of pancreatic enzymes, and bile acid precipitation
Dumping syndrome	Diarrhea, hyperglycemia, reactive hypoglycemia
Rapid intestinal transit	Nutrient malabsorption
High output from ileostomies	Electrolyte imbalance
Late	Late
Bile acid and fatty acid malabsorption	Gallstones, steatorrhea
Bowel dilation and stasis	Bacterial overgrowth, d-lactic acidosis
Saponification of malabsorbed fat with calcium	Oxaluria and renal stones
Anastomotic ulceration	Gastrointestinal bleeding

otage the advancement of enteral nutrition which is essential to further the process of adaptation.

Gastric hypersecretion is observed in up to 50% of patients who have undergone a major resection of the small intestine.[21] Because most gastrin catabolism takes place in the small intestine, these patients become hypergastrinemic and produce excessive gastric acid and gastric volume. The volume produced may contribute to fluid and electrolyte losses, and the hyperacidity may result in peptic ulceration. Furthermore, acid hypersecretion results in an acidic environment in the small intestine, resulting in bile acid precipitation with subsequent ineffective micelle formation, as well as inactivation of exocrine pancreatic enzymes whose maximal activity requires a luminal pH in the range of six to seven.

Bacterial overgrowth of the small intestine is also an extremely important pathophysiologic change in short bowel syndrome.[22] Adverse effects include deconjugation of bile acids, rendering them incapable of forming micelles, competitive metabolism and use of enteral nutrients and vitamins, synthesis of toxic metabolites such as d-lactate, and possibly, their translocation to produce bloodstream infections. Estimates that it occurs among 60%[22] of patients may be too low. It is virtually impossible to eradicate. Therefore, efforts should focus upon judicious reduction of overall bacterial load, and encouragement of flora that translocate poorly and provide metabolic byproducts useful to the host.

Customarily, nutrient malabsorption due to bacterial overgrowth occurs relatively late following resections in which compensatory bowel dilation has occurred, thus slowing transit and impairing effective intestinal "housekeeping." Malabsorption generally does not occur until counts of anaerobes have reached levels of $>10^5$ colony forming units per mL of luminal fluid. Hence, a rational antibacterial strategy is to give cycled 10- to 14-day courses of antibiotics highly specific for their anaerobic spectrum. These could be followed by 14- to 20-day rest periods. Antibiotics of choice include metronidazole, nitazoxanide, and rifaximin.

D-lactic acidosis occurs among patients whose gastrointestinal tract is colonized by d-lactate-synthesizing organisms.[23] Humans have the ability to rapidly catabolize l-lactate, which is a product of human anaerobic metabolism, but d-lactate can be catabolized and cleared very slowly and toxic blood levels can build up when the small intestine is overgrown with anaerobic bacteria. Signs and symptoms of d-lactic acidosis include confusion, somnolence, dementia, ataxia, or even seizures. This condition is characterized by acidosis associated with an anion gap but a normal blood l-lactate level. The antibacterial strategy employed for d-lactic acidosis is similar to that followed for malabsorption, but d-lactate levels can be followed to monitor success and duration of therapy. Because d-lactate is a product of carbohydrate metabolism, reduction in enteral carbohydrate can be achieved by giving a low carbohydrate diet to those patients who tolerate oral feedings and low carbohydrate formulas to those who are on tube feedings.

While translocation cannot be proven in humans, in animal models it is known that aerobic enteric flora translocate more readily than do anaerobic flora. Therefore, the preferred antibacterial strategy for reducing enteric bloodstream infections is selective decontamination aimed at reducing the load of aerobes and fostering anaerobic overgrowth.[24] While absorbable, broad-spectrum antibiotics can be used, an unabsorbable "cocktail" is theoretically less likely to adversely affect the bacterial microbiome in sites distant from the intestinal lumen. If the goal is to reduce the intraluminal bacterial load without selecting excessive quantities of resistant bacterial strains, the ideal strategy would be to alternate 7- to 14-day courses of antibiotics with 14- to 21-day rest periods.

The use of probiotics is intuitively attractive for patients colonized by excessive quantities of the "wrong type" of bacteria, and this strategy is probably harmless among those who no longer require TPN or fluids via a CVC. However, reports of bloodstream infections due to both anaerobic bacterial probiotics and probiotic yeasts have been reported among patients who have CVCs.[25] Therefore, circumspection is required before they may be used.

Fostering the adaptive process

The spontaneous recovery of intestinal function following massive surgical resection is termed "adaptation." As demonstrated in Figure 1, the process progresses in an orderly fashion, and can be influenced in two ways. First, the process can be accelerated by stimulating the intestine with intraluminal nutrients. Second, the process can reach a

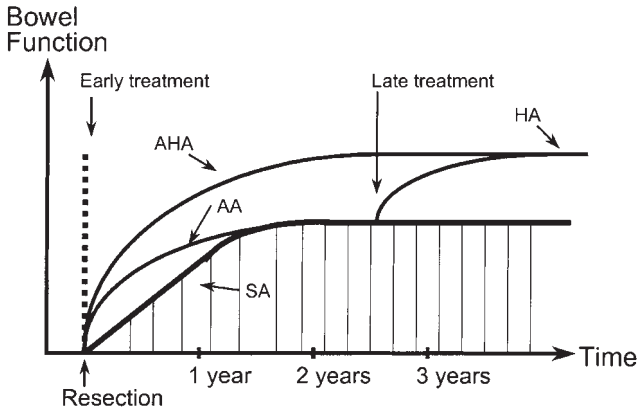

Figure 1 Depiction of the orderly progression of adaptation after an intestinal resection. The curve labeled "SA" represents spontaneous adaptation stimulated only by food. The curve labeled "AA" represents accelerated adaptation induced pharmacologically. An agent that typically accelerates the adaptive process is epidermal growth factor. The curve labeled "AHA" and "HA" indicates the changes of accelerated hyperadaptation with early pharmacologic treatment and hyperadaptation induced by late pharmacologic treatment. Glucagon-like peptide 2 (GLP-2) shows promise for inducing either early or late hyperadaptation. (Adapted from Jeppesen, PB. Clinical significance of GLP-2 in short bowel syndrome. J. Nutr. 2003;133:3721-3724).

higher level of function or "hyperadaptation" than expected. It is the search for hyperadaptation which has led to the search for an ideal "trophic" pharmacologic agent.

Maintenance of enteral nutrition despite all obstacles is a crucial step in guaranteeing that the maximal adaptive response will occur following a resection. There is little consensus as to the timing of initiation of feedings, but evidence suggests that following surgery for NEC, early feeding (on the fourth postoperative day) is associated with no greater recurrence rate but a shorter time to reach full feedings. Feedings can be initiated as bolus feedings or continuous feedings via a gastrostomy or nasogastric tube. Data from the pediatric and adult literature suggest that nutrient, fluid, and electrolyte absorption are all positively impacted by the use of continuous feedings to deliver at least some of the daily calorie requirements.[26,27] The relative value of providing a hypoallergenic formula to older children or adults remains unproven, but for infants with short bowel syndrome, maternal breast milk or a free amino acid formula has, in retrospective analysis, been proven superior to cow's milk formula, protein hydrolysates, or other nutritionally defined formulas.[28] In a small case series, a free amino acid formula was found to be superior to a protein hydrolysate.[29] Optimal caloric distribution of formulas for children remains unknown, but adult data from Europe suggest that among patients without a colon, there is little difference in the nutrient balance between patients on a high carbohydrate versus a high fat diet.[30] Among adults with a colon, energy conservation is marginally better if the diet is high in complex carbohydrates (60% carbohydrate vs 20% fat), possibly because of short chain fatty acid production due to fermentation.[30] Among children, who may have marginal colonic capacity, the trend has been to provide diets with at least 40% calories from fat to prevent fermentative diarrhea and d-lactic acidosis. A diet containing a combination of medium chain and long chain triglycerides in a ratio of 1:3 appears to be associated with optimal fat and energy balance in adult studies.[31] Data from adults with short bowel syndrome indicate that under most circumstances lactose need not be restricted.

No consensus occurs regarding the rate of advancement when continuous enteral feedings are chosen. In some programs, a slavish adherence to maintaining enteral output less than 50 mL/kg/d exists, but a small case series from Israel indicates that as long as infants maintain a positive fluid balance, adequate growth, and an absence of perineal disease, higher outputs can be tolerated.[32] Ultimately, the maximal allowable fecal output in pediatric patients is unknown and awaits more elegant nutrient balance studies.

Insoluble fiber, such as wheat bran or psyllium, may gelatinize stool, but it probably has no effect upon bowel adaptation. In contrast, soluble dietary fiber, such as pectin or guar gum, clearly impacts colonic adaptation positively.[33] It not only slows gastrointestinal transit, but both pectin and guar gum are fermented in the colon into short chain fatty acids of which butyrate seems to be the most important. Butyrate is an energy source for colonocytes and it regulates colonocyte proliferation. Among adults 500 to 1000 calories per day may be recovered from butyrate. Furthermore, butyrate upregulates one of the sodium-hydrogen exchangers (NH3) enhancing water and sodium absorption.[34] It is important to remember that the short chain fatty acids may exert an osmotic effect upon the bowel, and that the osmotic diarrhea effected by pectin itself in concentrations greater than 3% probably outweighs the salutary effect on NH3. It is also important to remember that there is a delay of NH3 upregulation by 58-72 hours after fiber is begun. Therefore, stool output may actually worsen before it improves following the ingestion of fiber. For patients without a colon, fiber is theoretically not helpful, but one animal study suggests that it may enhance small bowel adaptation.

For several decades, animal studies have demonstrated upregulation in certain hormones and other naturally occurring substances following extensive small bowel resection as well as hyperadaptation of the bowel following infusion of these "trophic" substances into experimental animals in pharmacologic doses.[35] The hormones best studied in animals include epidermal growth factor (EGF), growth hormone (GH), glucagon-like Peptide 2 (GLP-2), keratinocyte growth factor, and insulin-like growth factor 1 (IGF-1). EGF and IGF-1 have been investigated in humans for treatment of other disorders such as NEC, MVID, and primary IGF-1 deficiency, but not specifically for short bowel syndrome. On the other hand, GH and GLP-2 have been studied specifically for short bowel syndrome.

Trials of GH in combination with glucagon have shown inconsistent results. Studies by one group of scientists have shown that patients will demonstrate reduced parenteral needs and increased weight gain when treated with this combination, but others have shown contradictory results.[36,37] No large, randomized pediatric trials have been performed, and because of the expense of the therapy, the theoretic risk of mutagenesis, and the conflicting data, its use in pediatrics is relatively uncommon.

GLP-2 is a hormone whose synthesis is largely confined to the ileum and right colon. In animals, it inhibits apoptosis and stimulates proliferation of the entire small intestine, and it increases mucosal protein and DNA and upregulates a variety of transporters. Preliminary landmark studies were performed by Jeppesen and colleagues, and in open pilot human trials,[38] administration of a protease-resistant analogue of GLP-2 produced significantly improved water absorption but less impressive improvements in nutrient absorption and anthropometric measurements in patients who received it. A more recent, double blind, placebo-controlled study on 83 adults with short bowel syndrome showed that 25%–45% patients receiving the active GLP2 were able to reduce TPN requirements by >20% as opposed to only 6% on placebo.[39] Fluid and electrolyte conservation improved and serum citrulline, a marker of intestinal mass, increased. Pediatric trials are yet to be published. Disappointingly, the effects were only transient in these adults, persisting only while patients were using the drug. However, animal data suggest that if delivered to young infants early after a resection, the adaptive response may be "reset" to a hyperadaptive level.

Conclusion

Most large medical centers with pediatric intestinal rehabilitation programs now report survival of more than 80% pediatric patients with intestinal failure receiving medical management.[1,28] These data are encouraging, but the need for bowel preserving surgery or for intestinal transplantation persists. However, with improved infection-control methods, new methods of line care, new methods of preventing IFALD, more scientific feeding methods, and finally, the judicious use of trophic agents, the hope persists that even larger numbers of patients with short bowel syndrome will be saved. As controlled multicenter consortia mature, it is likely that within very few years the "art" of intestinal rehabilitation will finally become a science.

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