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Intestinal Rehabilitation and the Short Bowel Syndrome: Part 2

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The management of patients with intestinal failure due to short bowel syndrome is complex, requiring a comprehensive approach that frequently necessitates long-term, if not life-long, use of parenteral nutrition. Despite tremendous advances in the provision of parenteral nutrition over the past three decades, which have allowed significant improvements in the survival and quality of life of these patients, this mode of nutritional support carries with it significant risks to the patient, is very costly, and ultimately, does not attempt to improve the function of the remaining bowel. Intestinal rehabilitation refers to the process of restoring enteral autonomy, and thus, allowing freedom from parenteral nutrition, usually by means of dietary, medical, and occasionally, surgical strategies. While recent investigations have focused on the use of trophic substances to increase the absorptive function of the remaining gut, whether intestinal rehabilitation occurs as a consequence of enhanced bowel adaptation or is simply a result of an optimized, comprehensive approach to the care of these patients remains unclear. In Part 1 of this review, we provided an overview of short bowel syndrome and pathophysiological considerations related to the remaining bowel anatomy in these patients. We also reviewed intestinal adaptation and factors that may enhance the adaptive process, focusing on evidence derived from animal studies. In Part 2, relevant data on the development of intestinal adaptation in humans are reviewed as is the general management of short bowel syndrome. Lastly, the potential benefits of a multidisciplinary intestinal rehabilitation program in the care of these patients are also discussed.

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EVIDENCE OF INTESTINAL ADAPTATION IN HUMANS

Role of Luminal Nutrients and Diet

Three aspects of enteral nutrition may play a role in the process of intestinal adaptation: (1) the presence of food in the gut lumen; (2) the complexity of the diet; and (3) the presence of specific luminal nutrients (1).

Glutamine has been shown to prevent mucosal atrophy and deterioration in gut permeability in patients receiving only parenteral nutrition (PN) (2). Nonetheless, in a study in which glutamine was added to an oral rehydration solution provided to short bowel syndrome (SBS) patients with a jejunostomy, no benefit was seen in terms of fluid or sodium absorption (3). In a recent randomized, controlled, crossover study, the role of oral glutamine was evaluated in 8 patients with SBS. No difference in small bowel morphology, transit time, D-xylose absorption, or stool output was seen; however, interpretation of these findings may be limited due to differences in diet during the active and placebo treatment periods (4).

Fiber can be divided into soluble and insoluble forms. Insoluble fiber (*e.g.*, wheat bran) causes bulking of the stool and leads to a decrease in whole gut transit time, whereas soluble fiber (*e.g.*, pectin, guar gum) slows gastric emptying and overall gut transit resulting in a mild antidiarrheal effect. The energy derived from bacterial fermentation of soluble fiber yielding short-chain fatty acids may be substantial (5). While anecdotal reports of dietary supplementation with soluble fiber suggest improvement in nitrogen absorption (6), others have described an adverse effect of soluble fiber on fat and glucose absorption (7, 8).

Medium-chain triglycerides (MCT) do not require digestion by pancreatic enzymes for their absorption and are frequently used in SBS patients without clear evidence supporting their use. In a randomized, controlled, crossover study involving 19 patients (10 with colon, 9 without colon), patients were assigned to LCT and MCT + LCT groups (9). The diet enriched with MCT resulted in improved overall energy and fat absorption in the patients with a colon; however, in those without a colon, a slight increase in fat absorption was noted but no improvement in overall energy absorption was demonstrated due to a decrease in carbohydrate and protein absorption. Therefore, MCT supplementation may be of benefit in terms of providing additional calories only to those SBS patients with a colon.

Recently, the use of an emulsion containing the long-chain fatty acid, oleic acid, in patients with a variety of causes of chronic diarrhea including SBS was reported. Although uncontrolled, the findings suggested that, when ingested prior to a meal, a slowing of gastrointestinal transit and a reduction

in stool frequency and volume was possible (10). The mechanism of action presumably involves the stimulation of peptide YY release. A controlled study confirming these findings has yet to be completed.

Pancreatico-biliary secretions appear to be important factors involved in intestinal adaptation. Pancreatic function is reduced in patients on PN when no concomitant enteral diet is given (11). Nevertheless, there has been no consistent evidence showing a reduction in pancreatic secretions in patients with SBS who are given an oral diet and there is currently no evidence supporting the usefulness of pancreatic enzyme supplementation in humans with SBS. When more than 100 cm of distal ileum has been removed, the increased hepatic synthesis of bile salts cannot keep up with the stool losses ultimately resulting in fat malabsorption. The use of the synthetic, conjugated bile acid, cholylsarcosine, which does not undergo bacterial deconjugation, and therefore, does not cause colonic secretion and diarrhea has been studied in a few patients with SBS with or without a colon (12, 13). Variable improvements in fat and calcium absorption have been seen without an effect on overall stool output. Controlled trials are needed to confirm the efficacy of such agents.

Role of Hormones and Growth Factors

The administration of GH (growth hormone) has been shown to improve fluid and electrolyte absorption and nutrient transport in the human gastrointestinal tract. Recently, the effect of GH in patients with SBS was investigated. Ten patients were administered a relatively low dose of GH (0.024 mg/kg/day) daily for 8 wk while a number of nutritional parameters were monitored (14). GH resulted in an increase in body weight and lean body mass; however, no effect on absorptive capacity of energy, protein, or fluid was observed. In a more recent randomized, controlled, crossover study, 12 PN-dependent patients following a hyperphagic diet were treated with GH (0.05 mg/kg/day) or placebo (15). Treatment with GH increased energy absorption, macronutrient absorption, body weight, lean body mass, and D-xylose absorption. Plasma citrulline levels were not increased following this therapy suggesting that the improvements seen were not related to an increase in enterocyte mass. Rather, the authors speculated that the beneficial effects might be related to an enhanced functional adaptation at the enterocyte level instead.

The results from a small, open-label trial investigating the effects of GLP-2 in humans with SBS were recently published (16). Eight patients, 4 without a colon and receiving PN and 4 without a colon who did not require PN, received 400 μg GLP-2 twice daily for 35 days. Nutrient absorption studies, small bowel biopsies and measurements of body composition, and gastrointestinal transit time were performed. An increase in overall energy absorption, decrease in fecal wet weight, slowing of gastric emptying, and nonsignificant trend toward increased jejunal villus height and crypt depth were demonstrated.

On the basis of encouraging results from animal studies and disappointing results from the use of GH and glutamine as sole agents in humans, a pilot study investigated the effect of a combination of GH, oral glutamine, and an optimized diet on fluid and nutrient absorption in patients with SBS (7). Encouraging results led to a more extensive, open-label study of 47 adults with SBS (17). Patients were admitted to a clinical research center and treated for 3 wk with a GH (mean 0.11 mg/kg/day; range: 0.03–0.14), oral glutamine (30 g/day), and diet following a 1-wk stabilization/control period. This therapy resulted in an increase in water, electrolyte, and carbohydrate absorption while also causing a decrease in stool output. The effect on small bowel morphology was not studied. This group found that the most discriminating predictor of successful PN elimination was a bowel length-body weight ratio $\geq$0.5 cm/kg (18). A more recent uncontrolled study using similar methodology also demonstrated improvements in D-xylose absorption, stool nitrogen loss, and stool frequency (19). In contrast, two randomized, controlled, crossover studies did not confirm the benefits of this combination approach (20, 21) leading the authors to conclude that the beneficial effects demonstrated in the former studies may have been related to nonspecific luminal nutrients resulting from the dietary modification rather than from the addition of GH and glutamine (22, 23). Methodological differences among the studies limit definitive conclusions regarding the benefit of this therapy.

INTESTINAL REHABILITATION

The care of patients with SBS is complex, requiring a comprehensive approach and attention to detail. It is not the intent of this article to provide a comprehensive review of the general management of these patients. Instead, the discussion will focus on management relevant to the anatomical and physiological changes and the process of intestinal adaptation that occur following massive resection. In the process, an overview of the key aspects in the care of these patients, including potential complications, will be provided. For further details regarding the overall management of SBS, the readers are referred to several excellent recent reviews of the topic (24–26).

Although intestinal rehabilitation (IR) has been referred to by some authors as synonymous with the use of GH, glutamine, and a modified diet (19, 27), it is better thought of in broader terms as the clinical application of our understanding of the changes that occur in gastrointestinal physiology following massive bowel resection in an attempt to enhance the intestinal adaptive process and restore enteral autonomy.

Given the paucity of experimental evidence relevant to humans regarding the importance of luminal nutrients in the management of SBS, it is hardly surprising that there is limited consensus on the importance of the oral diet in the management of SBS. Few studies have investigated the effect of a diet program, as opposed to a specific nutrient, on the management of SBS. For reasons previously discussed, SBS patients would be expected to differ in their response to dietary manipulation depending upon their bowel anatomy; specifically, the presence or absence of a colon (28, 29). Norgaard and colleagues (29) demonstrated that for patients with a

colon, a high carbohydrate diet reduced fecal calorie loss and increased overall energy absorption compared to a diet high in fat. In contrast, for SBS patients without a colon, the high carbohydrate diet increased ostomy output. Clinical experience confirms the important role that diet plays in the successful management of these patients, particularly those with a colon, and in addition, suggests that with appropriate follow-up and compliance, this can result in the long-term reduction of PN needs while maintaining nutrition and hydration status (30, 31). While diet manipulation appears less useful in those patients without a colon, particularly in those with <50 cm of small bowel, an attempt to optimize the diet plan may still be of some benefit in terms of energy absorption and reducing stool output.

The long-term success of an optimized diet requires extensive education and monitoring to maintain compliance (32). In addition, the successful implementation of a diet program needs to be translated into foods and meal patterns that meet the individual's preferences, lifestyle, and in children, developmental age (33). The establishment of daily calorie and fluid intake goals for the patient followed by careful follow-up and adjustments based on tolerance as determined by the development of symptoms, stool output, micronutrient levels, weight, and hydration status is the cornerstone of intestinal rehabilitation. Individual calorie goals can generally be estimated using the calculated resting energy expenditure multiplied by activity and malabsorption factors. In general, most stable adult SBS patients absorb only about one-half to two-thirds as much energy as normal; thus, dietary intake must be increased by at least 50% (*i.e.*, hyperphagic diet). The increased quantity of food tends to be best tolerated when consumed throughout the day in 5–6 meals periods. When tolerated, tube feeding may be useful in selected patients of any age to meet their calorie needs, particularly when trying to wean PN. Nasoenteral and percutaneous enteral tubes/button devices can be utilized for delivery of enteral therapy. Enteral tube feeding with small quantities delivered over an extended period of time is better tolerated than bolus tube feeding due to greater absorption of nutrients and less osmotic diarrhea. In infants and children, small oral feedings should be used in conjunction with tube feeding as they are necessary at developmentally appropriate times to prevent eating disorders that may arise later.

The macronutrient and fluid components of the diet depend upon the remaining bowel anatomy (Table 1). Because of regional differences in water and sodium handling, those SBS patients without a colon generally require the use of such a glucose–electrolyte solution, whereas most of those patients with a colon can maintain adequate hydration without excessive fluid loss with hypotonic fluids. To optimize water and sodium absorption in the proximal jejunum and prevent secretion into the lumen, the ingestion of a glucose–electrolyte oral rehydration solution (ORS) with a sodium concentration of at least 90 mmol/L has been shown to be necessary (34–36). Two to three liters of such fluid daily, sipped throughout the day, may be needed to maintain adequate hydration. Several commercially available ORS formulas can be used; although, the least expensive one, recommended by the World Health Organization, can be easily prepared by the patient (37). While fluid composition is not as important in those with a colon, adequate dietary sodium should be provided. Measurement of urinary sodium or serum aldosterone levels may assist in the assessment of sodium balance in some patients. Regardless of bowel anatomy, hyper-osmolar fluids should be avoided, as they will aggravate stool losses. Those patients who tend to experience bowel movements shortly after eating (*i.e.*, dumping) may benefit from avoiding drinking fluids during meals. The addition of soluble fiber may be beneficial in those with large stool outputs despite dietary changes, use of oral rehydration solution, and adequate administration of antidiarrheal and antisecretory agents. Parenteral fluids will be necessary if the ostomy output continues to exceed fluid intake.

Table 1. Diet and Fluid Suggestions in Older Children and Adults with Short Bowel Syndrome (24, 32)

	Colon Present	Colon Absent
Carbohydrate	50–60% of caloric intake Complex carbohydrates	40–50% of caloric intake Complex carbohydrates
Fat	20–30% of caloric intake Ensure adequate essential fats MCT/LCT	30–40% of caloric intake Ensure adequate essential fats LCT
Protein	20–30% of caloric intake High biologic value	20–30% of caloric intake High biologic value
Fiber	Net secretors Soluble	Net secretors Soluble
Oxalate	Restrict	–
Fluids	ORS and/or hypotonic	ORS

MCT; medium-chain triglycerides, LCT; long-chain triglycerides, ORS; oral rehydration solution.

The provision of complex macronutrients in the diet of SBS patients is preferred. Complex carbohydrates reduce the osmotic load and potentially exert a positive effect on the adaptation process. Because the proximal jejunum is rarely resected in SBS patients, lactose is generally well tolerated (38) and should not be restricted unless the patient is clearly intolerant, as milk-based products provide an important source of calories and calcium. Concentrated sugars, fruit juices in particular, should be avoided as they generate a high osmotic load and potentiate stool output. With respect to protein, those with high biological value are preferred. The restriction of fat to 20–30% of the daily calories is recommended in only those adult SBS patients with a colon. This results in a reduction in steatorrhea, magnesium and calcium loss, and oxalate absorption. Oxalate restriction is important in those patients with a colon in order to decrease the risk of oxalate nephropathy that occurs in about 25% of patients with <200 cm of small bowel who have a colon (39). MCT may be useful in those patients with a colon, particularly in the presence of bile acid or pancreatic insufficiency (40); however, clinical experience suggests they are not well tolerated in the long term. They also have a slightly lower caloric density (8.3 *vs*

9 kcal/g), exert a greater osmotic load in the small bowel, and have less stimulatory effect on adaptation compared to LCT. The provision of essential fatty acids is important as deficiencies are common (41). Soluble fiber supplementation may also be useful given its potential effect on enhancing adaptation and slowing gastric emptying; although, it may result in increased gas and bloating for the patient.

In addition to changes in diet and fluids, the long-term use of antimotility and antisecretory agents may be necessary to control stool losses. These agents indirectly aid the process of functional adaptation by improving the absorptive efficiency of the bowel. Massive enterectomy is associated with a transient gastric hypergastrinemia and hypersecretion (42). H_2 receptor antagonists and proton pump inhibitors may be beneficial, particularly during the first year following resection, in reducing the volume of gastric secretions and, thus, stool losses, and decreasing acidity, which can lead to peptic complications and/or impairment in the function of certain digestive enzymes. Because absorption of oral medications may be impaired in patients with SBS, high doses may be needed; when <50 cm of jejunum is present, intravenous delivery or an oral solution/elixir may be needed. As gastric acid has a role in suppressing overgrowth of upper intestinal bacteria, acid-suppressing agents should be used sparingly in conditions of bacterial overgrowth (43). Uncommonly, certain patients, particularly the net secretors such as those with high output jejunostomies, may benefit from treatment with the somatostatin analogue, octreotide. Octreotide reduces a variety of gastrointestinal secretions and slows jejunal transit (44, 45). Open-label studies suggest clinical benefit of both short-acting and long-acting forms (46, 47); however, this beneficial effect is often short-lasting, and furthermore, the use of octreotide has not been shown to lead to the elimination of the need for PN. Due to an increased risk for cholelithiasis, expense, and studies in animal models suggesting that octreotide may inhibit bowel adaptation, the use of this agent should be reserved for patients with large volume stool losses in whom fluid and electrolyte management is problematic, and furthermore, should be avoided in the period soon after resection (48, 49).

Antidiarrheals work mainly to reduce intestinal motility but also cause a slight reduction in intestinal secretion. Commonly used agents include loperamide, diphenoxylate, codeine, and tincture of opium. The use of codeine and tincture of opium tends to be limited by their sedating effect, potential for addiction when used in the long term, and cost. Codeine has also been shown to increase stomal fat output in end-jejunostomy patients (50, 51). In adults, loperamide, 4 mg four times daily, has been shown to be more effective than codeine, 60 mg four times daily (51); however, there may be a synergistic effect when these agents are used together. The use of diphenoxylate has been largely replaced by loperamide due to a decreased incidence of central nervous system side effects with the latter agent. It should be remembered that loperamide enters the enterohepatic circulation, which is disrupted in SBS patients without an ileum; therefore, high doses are frequently needed. Indeed, doses as high as 16 mg four times daily have been used successfully. In the setting of SBS, these agents seem to be most effective when administered before meals and at bedtime. Clonidine may also be useful to treat high output stool losses *via* its effects on intestinal motility and secretion (52). Finally, it should be noted that while antimotility agents may be effective in reducing intestinal transit, in cases where bowel dilatation has occurred, they might actually worsen diarrhea by allowing bacterial proliferation. Clinical experience suggests that the reduction in stool losses by the appropriate use of these medications in addition to the diet and fluid changes described previously helps to reduce PN requirements (30, 53).

In adults, 3–5 g of bile salts circulates through the enterohepatic circulation. Loss of significant portions of the ileum (*i.e.*, >100 cm in adults) increases fluid loss and bile acid malabsorption may exceed maximal hepatic synthesis thereby decreasing the bile acid pool and resulting in impairment of luminal fat digestion. In an attempt to improve the bile salt pool without aggravating stool losses, several uncontrolled case studies using ox bile supplements (54) and the synthetic, conjugated bile acid, cholylsarcosine (55) have demonstrated improvements in fat absorption. While the initial reports are encouraging, these agents are not readily available at present. Finally, the use of bile acid sequestrants, such as cholestyramine, may actually worsen steatorrhea and fat soluble vitamin losses in those with >100 cm of distal ileum resected (56).

The development of small bowel bacterial overgrowth (SBBO) is common in SBS patients and may impact considerably on their ability to successfully wean PN because of difficulty tolerating an optimized diet as a consequence of precipitating symptoms and exacerbating malabsorption (57). The anatomical and physiological changes that occur in SBS, particularly the combination of bowel dilatation and slower transit, together with medications commonly used in these patients (*e.g.*, acid-suppressants, and antimotility agents) facilitate the development of SBBO. Although SBBO may have potential benefit (57), excess bacteria in the small bowel can induce inflammatory changes in the gut impairing absorption (58, 59), cause a number of gas-related symptoms, and aggravate stool losses. The diagnosis of SBBO is always difficult; this is particularly so in the SBS patient. While the identification of an excessive number of bacteria in small bowel fluid collected using a sterile tube passed through an endoscope is considered the gold standard, special measures are needed to obtain meaningful samples. Additionally, as $>50\%$ of the bacterial species in the gut are not culturable, the utility of this technique is further questioned. The primary noninvasive test is the hydrogen breath test, most commonly using glucose as the substrate. The utility of this test is limited when there is a predominance of nonhydrogen-producing bacteria in the gut. Furthermore, interpretation can sometimes be difficult due to rapid transit in the shortened bowel making it difficult to differentiate small bowel *versus* colonic hydrogen production. Other indicators suggestive of SBBO that are

occasionally useful include high serum D-lactate and folate levels, metabolic acidosis, and excess urine indicans (60). Once pathologic SBBO has been identified and the goals of treatment clearly identified, antimicrobial treatment is generally prescribed. A variety of antibiotics can be used with success being judged on improvement in symptoms, reduction in stool output, and/or weight gain. The continuous use of low-dose antibiotics in SBS may be necessary. To reduce the risk of antibiotic resistance, periodic rotation of the antibiotic used is advised. Although without evidence from controlled studies to support their utility, other strategies for controlling SBBO include limiting the use of antisecretory and antimotility agents, carbohydrate restriction, intermittent bowel flushing with polyethylene glycol, use of prokinetic agents, use of probiotic agents, and bowel-tapering operations (61–63).

Complications, Quality of Life, and Survival of SBS Patients

In addition to SBBO, a number of other complications have been described in SBS (Table 2). Chronic complications of PN also occur with some regularity and include hepatobiliary disease and a variety of central venous catheter-related problems including sepsis, catheter breakage or occlusion, and central venous thrombosis (Table 2). It is not the intent of this article to review these complications. For the interested reader, several excellent recent reviews of the topic are available (24, 25, 64, 65).

To our knowledge, there are no quality-of-life data for patients with SBS who do not require PN. Furthermore, much like problems related to SBS prevalence, quality-of-life information that is available includes all home PN patients without separate analysis of SBS patients. With respect to survival, studies from France and the United States have demonstrated 2-yr and 5-yr survival rates at over 80% and 70%, respectively (66, 67). Furthermore, the study from France reported PN-dependency at 2 yr of 49% and 45% at 5 yr (66). Survival rates were lowest in the jejunostomy and ultra-short small bowel groups. Other factors affecting survival include the patient's age, diagnosis, presence of chronic intestinal obstruction, and the experience of the team managing the patient (68).

Table 2. Complications in Short Bowel Syndrome Patients

Central venous catheter-related
Infection
Occlusion
Breakage
Central vein thrombosis
Parenteral nutrition-related
Hepatic
Biliary
Malnutrition
Fluid and electrolyte disturbances
Micronutrient deficiency/excess
Essential fatty acid deficiency
Small bowel bacterial overgrowth
D-lactic acidosis
Oxalate nephropathy
Renal dysfunction
Metabolic bone disease
Peptic ulcer disease

Weaning of Parenteral Nutrition

Implicit in the intent of intestinal rehabilitation is the goal of reducing or eliminating PN requirements by using dietary, medical, and sometimes, surgical means with the hope of improving patient morbidity and mortality while simultaneously reducing costs. By combining an understanding of the altered bowel anatomy and physiology with careful clinical assessment, attention to detail and a stepwise approach to care as outlined previously, many of these patients can be managed successfully. Clinical factors considered useful in predicting the success of eliminating the use of PN include the presence of residual disease in the remnant bowel, bowel length, presence of colon, presence of ileocecal valve, degree to which adaptation has occurred, and the duration of time on PN (69). Nevertheless, regardless of the bowel anatomy, we believe an aggressive attempt to wean PN should be undertaken in all SBS patients. Recently, Crenn and colleagues evaluated plasma citrulline, a nonprotein amino acid produced by the intestinal mucosa, as a potential biological marker of either permanent or transient intestinal failure in 57 patients with nonmalignant SBS with a clinical diagnosis of either permanent or transient intestinal failure who had been followed-up for at least 2 yr. A level <20 μmol/L classified SBS patients with permanent intestinal failure with high sensitivity, specificity, and positive and negative predictive values (95% and 86%, respectively), and was a more reliable indicator than anatomic variables to distinguish transient from permanent intestinal failure (70). Nevertheless, we have successfully eliminated PN in the long term in several patients with fasting plasma citrulline levels <20 μmol/L using techniques discussed in this review (71).

A critical component of the stepwise approach is to have certain goals in mind when deciding when and how much PN to wean. While nutritional balance studies might be considered the clinical ideal when weaning PN, these studies are not practical clinically in most circumstances. Alternatively, the frequent monitoring of food and fluid intake and stool and urine output provides clinically useful information without being too intrusive. In general, meeting the daily calorie and fluid intake goals established for the patient with careful and frequent follow-up and subsequent adjustments based on tolerance as determined by the development of symptoms, stool and urine output, micronutrient levels, weight, and hydration status is sufficient. The aggressive and appropriate prescription of enteral nutrition early after resection is central to successful weaning and avoidance of PN complication.

Micronutrient supplementation becomes necessary as PN is weaned and levels require periodic monitoring. Multivitamin and mineral preparations appropriate for age are commercially available and provide a complete balance of required micronutrients. Supplemental zinc may be required

in the presence excessive diarrheal stool losses. Zinc deficiency needs to be assessed in relation to alkaline phosphate levels as it is a zinc-containing enzyme. Iron supplementation is infrequently needed as it is absorbed in the upper gastrointestinal tract; an uncommon site of resection in SBS patients. Magnesium, fat-soluble vitamins, and essential fatty acid supplements are frequently needed. Excess administration of fat-soluble vitamins and some trace elements may cause toxicity and necessitate laboratory monitoring during parenteral therapy. Lifetime administration of supplemental vitamin B12 is needed in those with more than 50–60 cm of terminal ileum removed (72).

Investigational Pharmacological Options to Promote Intestinal Rehabilitation

The use of pharmacological agents to facilitate adaptation or enhance the tolerance of feedings in order to increase the absorptive function of the gut when attempts to wean PN are incomplete or unsuccessful despite an optimized diet and medical care has been poorly studied in man. To date, only uncontrolled trials of PN weaning using a combination of GH, glutamine, and an optimized diet have been published (17, 18, 73). Byrne *et al.* treated 47 patients, most of whom had a colon-in-continuity, with combination of GH, oral glutamine, and an optimized diet for 3 wk followed by continued use of the diet and glutamine. With follow-up for as long as 5 yr, they showed that 40% of patients could be weaned completely from PN while another 40% could make significant reductions in their PN use. This group has gone on to report similar results in over 200 patients. In a more recent uncontrolled, prospective case series, Zhu *et al.* used a similar treatment program and demonstrated very similar, long-lasting results; although, it is interesting to note that their patients were treated much sooner following their onset of SBS (mean 86 ± 105 days) (19). Nevertheless, due to conflicting findings on nutrient absorption reported in three subsequent randomized, controlled trials (15, 20, 21), the role of this combination of trophic factors and diet remains controversial. Indeed, it has been suggested that the weight gain in these patients likely reflects increased extracellular fluid related to GH, and the positive effects of this treatment are not sustained once discontinued (74). Byrne and colleagues have subsequently gone on to complete a randomized, controlled, prospective study of this treatment approach in 41 PN-dependent SBS patients (most with colon-in-continuity) in which PN reduction was the primary endpoint (75). The control group was treated with an optimized diet supplemented with glutamine. A recent report of the preliminary data demonstrated a significant reduction in PN requirements in all groups studied; however, the extent of reduction was greatest in the group in which GH was administered in addition to the diet and glutamine. The effect of this treatment on nutrient absorption and bowel morphology was not studied in this trial. While encouraging, further controlled studies investigating the optimal dose, duration, and timing of administration in relation to the onset of SBS are needed before this therapy can be routinely advocated for SBS patients.

Peptide YY may enhance functional adaptation by slowing transit and allowing more time for absorption to occur. Although a peptide YY analogue is available (76), it has yet to be studied in humans with SBS. Another potentially exciting trophic agent to aid in PN weaning is GLP-2. While a pilot trial has suggested a benefit in terms of enhancing energy and wet weight absorption (16), there are currently no data on its use in the setting of PN weaning. In this regard, a large, multinational, randomized, controlled trial to study this issue is soon to begin.

Surgical Options to Promote Intestinal Rehabilitation

Nearly half of patients with SBS will require reoperation at some point following their initial resection (77). An important consideration during these operations is to preserve as much of the existing intestine as possible. Several surgical techniques have been developed to preserve intestinal length and include stricturoplasty for strictures, serosal patches for strictures and perforations, and intestinal tapering and lengthening for dilated segments (78). In addition, nontransplant surgical therapeutic procedures have been devised with the goal of maximizing the function of the SBS patient's existing intestine by either improving absorption by the existing intestine or by increasing the area of absorption (79). These procedures are sometimes referred to as surgical intestinal rehabilitation or autologous gastrointestinal reconstruction. The choice of surgical therapy is influenced by the existing bowel length, function, and caliber and can be divided into procedures that optimize function (*e.g.*, restore continuity, lengthen, taper, relieve obstruction) or slow transit (*e.g.*, reversed segment). These procedures should only be considered after the initial adaptive period and with specific goals in mind. With the exception of intestinal tapering and lengthening operations, clinical experience has not demonstrated utility of these procedures in children as they may exacerbate SBBO. Despite encouraging results from case series, evidence of long-term efficacy with these procedures is lacking. Furthermore, only a small proportion of SBS patients are candidates for these procedures.

For most SBS patients, intestinal transplantation holds the greatest promise as a surgical intervention. Transplantation may be considered in cases of irreversible intestinal failure with life-long need for PN, when complications of PN occur (24, 80). Small bowel transplantation can be performed in isolation, in combination with liver transplantation, or in combination with transplantation of multiple organs (81). At the present time, there is more experience in small bowel transplantation in the pediatric population. The outcome following intestinal transplantation, with respect to improvements in survival and quality of life, has improved considerably with the development of improved immunosuppressants and other aspects of care following transplantation (82). While there are claims of better patient and graft survival in those transplanted over the last few years, published survival rates

from the 1997 report of the International Intestinal Transplant Registry (60–70% at 1 yr) do not yet approach those of other solid organ transplants such as liver and kidney (83). Furthermore, graft survival rates (50–60% at 1 yr) are significantly lower than patient survival rates and a considerable percentage of patients with a functioning graft may still require PN (83, 84). While transplantation remains a very promising and exciting therapeutic option, before it can be recommended to more patients with intestinal failure, improved patient and graft survival and an increased likelihood of graft function in order to ensure the discontinuation of PN is necessary.

Intestinal Rehabilitation Program—Putting it All Together

Despite tremendous advances in the provision of PN and intestinal transplantation over the last several decades, the risks, costs, and associated changes in quality of life associated with these therapeutic modalities remain significant obstacles to overcome. The relatively recent concept of intestinal rehabilitation (IR) emphasizes strategies to reduce or eliminate the need for PN and intestinal transplantation. The principles of IR can be applied both to adult and pediatric populations. Because a major component of intestinal rehabilitation consists of dietary manipulation, lifestyle changes are required on the part of the patient. In addition, the "trade-off" to the patient for not receiving PN is the need to take several medications orally (*e.g.*, micronutrient supplements and antidiarrheals) and increase the amount of food and fluid ingested daily. While these changes may be more difficult to maintain, particularly over the long-term, these patients are generally highly motivated.

The goal of an IR program is to provide a comprehensive range of services for patients with intestinal failure (Fig. 1). There are three interrelated therapeutic components to an IR program: (1) intestinal rehabilitation, (2) maintenance of long-term enteral or parenteral nutrition, and (3) transplantation. A multidisciplinary team including physicians, dietitians, nurses, psychologists, psychiatrists, and social workers is essential in the implementation of a successful program. Benefits of such an IR program include bringing people with special interest and expertise in the care of these patients together to optimize care, allowing patients to meet others with similar problems, and allowing sufficient numbers of patients with SBS to be available to conduct meaningful clinical research. On a larger scale, the establishment of a national registry of SBS patients and/or a national network of centers that specialize in the care of these patients may facilitate the study and care of all patients with SBS (85).

While the clinical effectiveness of an IR program has been demonstrated, its cost-effectiveness remains to be determined. The successful IR program requires the development of clinical care protocols and the flexibility to deviate from the protocols based upon the needs of the individual patient, close and careful patient follow-up, highly skilled multidisciplinary approach, and excellent communication with the patient and other members of the health care team. Consideration should be given to referral of patients to an IR program in the setting of (1) complications of PN such as recurrent, serious

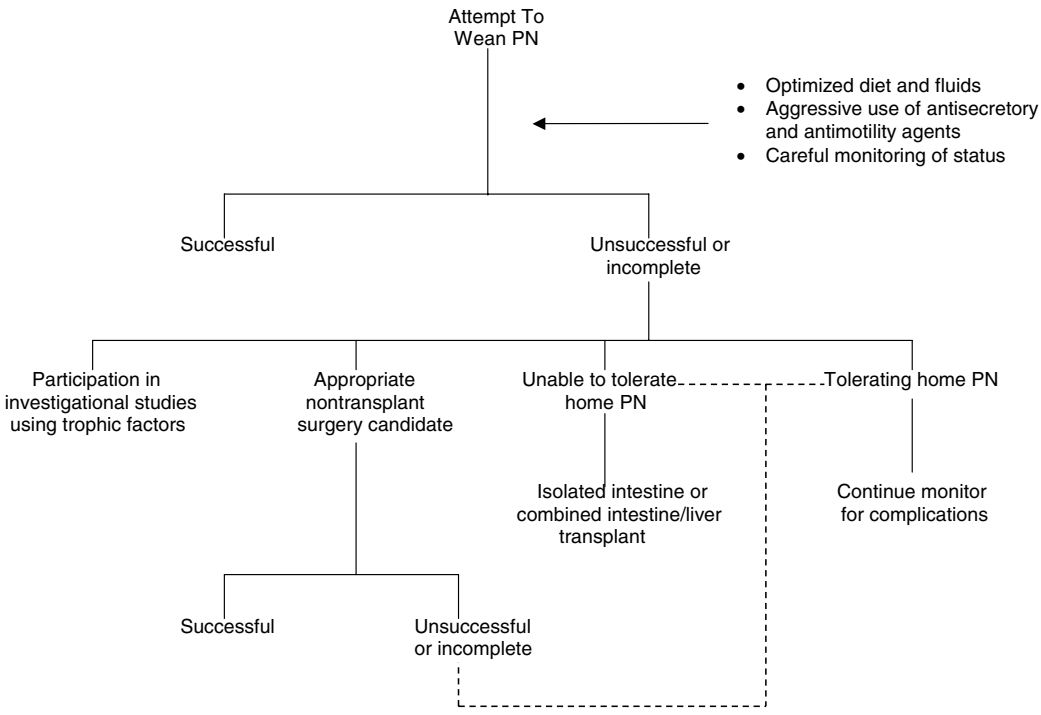

Figure 1. Diagrammatic illustration of the three interrelated therapeutic components of an intestinal rehabilitation program and a suggested approach to their use when attempting to wean parenteral nutrition. PN; parenteral nutrition.

catheter-related infections, liver disease, or compromised vascular access, (2) end-stage chronic intestinal pseudo-obstruction requiring frequent hospitalization, (3) complex surgical complications including fistulae and chronic bowel obstruction, (4) metabolic problems related to high-output stoma, and (5) PN weaning.

CONCLUSION

Intestinal adaptation following massive intestinal resection remains poorly understood. A number of structural and functional changes occur within the remaining bowel to help compensate for the malabsorption. It remains unclear whether the apparent improvements that are seen in fluid and nutrient absorption that occur following massive intestinal resection are related to permanent changes that have developed in the bowel or are simply the result of interventions employed by the clinician in the care of the SBS patient. The management of the SBS patient is complex and requires a comprehensive, multidisciplinary approach. Specific dietary intervention combined with careful medical management, and sometimes, surgical strategies offer the potential of PN reduction and improved clinical outcome. While the administration of trophic factors alone or combined with diet modification may allow for enhanced adaptation and PN reduction, there is currently insufficient evidence to support their routine clinical use. Intestinal transplantation remains a promising treatment for the appropriate candidate. Due to the complexities of managing these patients, particularly when attempting to wean PN, consideration should be given to referring these patients to centers experienced in the multidisciplinary management of SBS and able to offer a comprehensive range of services.

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