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The Evolving Medical Management of Short Bowel Syndrome

Trevor A Winter* and Neha Shah

Division of Gastroenterology and Hepatology, Stanford School of Medicine, Stanford University, USA

Background

Management of patients with Short Bowel Syndrome (SBS) is complex, multidisciplinary and presents a significant clinical challenge. Physicians, specialized gastroenterologists, surgeons, dieticians, pharmacists, social workers and psychologists all play an important role in the treatment of these patients.

Short Bowel Syndrome (SBS) is generally considered to exist when there is less than 200 cm of small bowel remaining following trauma, vascular insufficiency, surgical resection or congenital defect. The presence of the colon plays an important role in SBS, providing an effective extra 50 cm of small bowel for optimization of SBS management.

Physiology of short bowel syndrome

Patients with SBS undergo significant metabolic alterations due to the anatomical loss of the small bowel. Malabsorption of nutrients arises due to reduction of the intestinal absorptive area, resulting in nutritional depletion of vital nutrients, weight loss, diarrhea and dehydration. Transient hypergastrinemia may occur, due to loss of the enteric hormonal feedback (protein PYY, glucagon-like peptide-1 (GLP-1), Cholecystokinin (CCK) and secretin) that helps to reduce gastric secretion. Altered motility is seen due to the loss of the 'ileal brake" that normally would serve to slow transit of nutrients, with reduction of the hormones glucagon-like peptide-2 (GLP-2), peptide YY, GLP-1, and neurotensin. Patients with significant distal ileal resection, >100 cm, are at risk for vitamin B12 deficiency, bile salt diarrhea and development of gallstones. This is due to the loss of the ileal area where vitamin B12 is absorbed and where bile salts are recycled back to the liver via enterohepatic circulation. This will result in increased stool output as bile salts enter the colon, and exert a cathartic action. Oxalate kidney stones may develop due to excessive absorption of oxalate in the colon. Bacterial overgrowth may arise as well. There is also a risk of D-lactic acidosis due to the colonic bacterial fermentation of simple Carbohydrates (CHO).

Nutritional management of SBS

Intestinal Rehabilitation is an important concept in the management of these complex patients with the aim of facilitating nutrient and fluid absorption and reduction of the need for parenteral support, in order to achieve the best possible quality of life.

Nutritional management of SBS includes various interventions, which includes the use of enteral nutrition, therapeutic manipulation of the diet and parenteral nutrition when required. Nutritional interventions for oral intake are individualized and designed to stimulate intestinal adaptation to maximize the function of existing small bowel. The gut has the ability to adapt over the course of 1 to 2 years, (intestinal adaptation), which includes the hypertrophy of the villi leading to a greater absorptive area to optimize nutritional capacity. The known length of the remaining small bowel and whether a colon is present or not determines the nutritional therapies utilized.

Enteral nutrition is the favored route. The use of gastrostomy or jejunostomy tubes to facilitate nocturnal feeding should also be considered. Parenteral nutrition (PN), along with intravenous fluids may be required initially until the patient stabilizes. Trophic enteral feeds can be used in conjunction of PN initially and with enteral feed advancement, can help to transition the SBS patient off PN. The use of an isotonic polymeric enteral formula is initially preferred to stimulate intestinal adaptation. If a patient does not adequately tolerate a polymeric enteral formula, then an isotonic elemental enteral formula can be attempted. A variety of polymeric and elemental enteral formulas are available. Patients with 100 cm small bowel or less without a colon or left with 50 cm small bowel with a colon inevitably stay TPN dependent. These patients are referred to as SBS-Intestinal Failure (IF) patients. Parenteral nutrition, however, carries a significant risk of line sepsis, vascular occlusion and liver dysfunction. Reduction and potential weaning of PN is the goal, and is done gradually and is initiated with a modest reduction in caloric provision. The weaning process is individualized, and is dependent on how well the patient progresses with increasing oral intake and/or enteral feeds while stabilizing nutritional parameters, such as weight status, hydration and stool output.

The macronutrient composition of the diet will differ between SBS patients that have a colon and those that do not and have end jejunostomies or ileostomies. Overall, a high caloric intake is needed to compensate for the malabsorption of nutrients that may occur initially with SBS.

Restriction of concentrated sweets such as fruit juices and sugary foods is indicated for all SBS patients as simple sugars have an osmotic effect on the intestinal tract, thus further contributing to fluid and nutritional losses. The presence of the colon is important, as salvage of energy in the form of short chain fatty acids from the bacterial fermentation of dietary carbohydrate may provide up to 1000 kCal/day (4.2 MJ/day) [1]. Patients with a colon are therefore encouraged to consume a high complex CHO diet (approximately 60% of calories). The use of soluble fiber (e.g. pectin and guar gum) in SBS patients with a colon may serve to slow gastric emptying and overall transit time, which may reduce stool output. Production of hydrogen and methane, however, may result in bloating and flatulence in some patients and may restrict the use of dietary fiber. In addition to the high CHO diet, a low fat diet (20-30% of total calories) is advised, as free fatty acids are cathartic due to the formation of hydroxy fatty acids by colonic bacteria. Medium Chain Triglycerides (MCT), which do not require pancreatic digestion for their absorption, have been shown to increase energy and fat absorption in patients with SBS with a colon, but not in those without. SBS patients with a colon are also at risk of developing oxalate renal stones, due to the effect of free fatty acids binding with calcium and releasing oxalate in the colon, where it is absorbed. A low

***Corresponding author:** Trevor A Winter MD, FACG, PhD, Associate Professor, Division of Gastroenterology and Hepatology, Stanford School of Medicine, Stanford University, USA, E-mail: tawinter@stanford.edu

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fat, low oxalate diet is recommended as well as optimizing hydration to reduce this risk.

Those without a colon may have increased stool output with increasing CHO intake, thus the recommendation is to consume a low-moderate CHO diet (40-50% of total calories). These SBS patients may consume a diet with higher amounts of fat (40% of total calories). Restriction in oxalate intake is not necessary.

SBS patients are at risk for dehydration with depletion of electrolytes in a setting of reduced absorptive area and increased stool output. This risk is especially evident in SBS patients with end jejunostomies and ileostomies. Drinking normal, hypotonic water is not recommended, as it carries the risk of further depletion of electrolytes. The goal of management is to enhance intestinal absorption of electrolytes by optimizing the use of the glucose-sodium coupled transport system. Isotonic Oral Rehydration Solutions (ORS) can serve to maintain hydration and prevent loss of electrolytes. ORS have defined ratios of water, sodium, potassium and glucose. ORS beverages are available readymade through various commercial settings or can be made using recipes that involve household ingredients of water, fruit juice and salt. The addition of zinc to ORS beverages has been explored as SBS patients are at risk for zinc deficiency in setting of increased stool output. Zinc supplementation in the form of ORS beverages needs further research to determine its full effectiveness.

From this author's experience, implementation of nutritional interventions for diet manipulation is a gradual step-by-step process as the patient learns to adopt and adjust to new ways of eating. Close guidance is essential to assist with successful nutritional management and treatment of these patients.

Pharmaceutical/Hormonal therapy of SBS

Management of patients with SBS generally involves the initial use of H2-Receptor Antagonists (H2RA) or Proton Pump Inhibitors (PPI's) to control hypergastrinemia. These agents have also been shown to increase water and sodium absorption [2].

Antidiarrheals (loperamide, codeine, tinct of opium) are cornerstone in-order to control diarrhea and increase intestinal "dwell time" [3].

Clonidine, which is an alpha-2-adenergic receptor agonist, may be useful to reduce diarrhea and sodium loss, particularly in patients with proximal jejunostomy [4].

Long acting somatostatin analogues such as octreotide, may increase absorption of sodium and water, and improve diarrhea, although a study indicated the effect was relatively small [5]. These agents are also associated with increased risk of cholelitiasis, and may compromise gut adaption and decrease luminal transport activity [6,7].

A number of pharmaceutical agents including glutamine, human growth hormone, and fiber have been also tried with the aim of promoting intestinal adaptation and reducing dependence of PN, with varied results.

Glutamine has been considered a preferential substrate for the small bowel. Parenteral glutamine has been shown to prevent gut mucosal atrophy and impaired gut permeability associated with the use of TPN [8]. However, oral glutamine has shown no effect on fluid or sodium absorption, or on small bowel morphology, transit time, D-Xylose absorption, or stool output [9].

Human Growth Hormone has anabolic activities, increasing amino acid transport, protein synthesis and Insulin-Like Growth Factor-1 (IGF-1) production. IGF-1 has been reported to stimulate intestinal adaption after resection [10].

Byrne et al. studied the effects of high dose GH (0.14 mg/kg/day), glutamine and high CHO diet on patients with SBS [11]. Patients were also provided rehydration solutions. Parenteral support was weaned from 40% of patients.

Ellegard reported the effects of low dose rhGH (0.024 mg/kg/day) or placebo in 10 patients with SBS, and demonstrated significant increases in IGF-1 with increased body weight. There was however no significant changes in absorptive capacity of water, energy or protein [12].

The role of rhGH, glutamine and a high fiber diet in the treatment of patients with SBS was reviewed by Scolapio et al. [13]. In a double-blind placebo-controlled crossover study, patients were randomized to receive rhGH 0.14 mg/kg/day, glutamine 0.63 g/kg/day and a high CHO diet, or placebo. The treatment arm resulted in transient weight gain, a modest increase in the absorption of sodium and potassium, and a delay in gastric emptying. There was however no improvements in small bowel morphology, stool losses or macronutrient absorption.

Szkudlarek et al. who also investigated the effect of high dose rhGH (0.12 mg/kg/day), oral glutamine (mean 28 g/day), and parenteral glutamine (mean 5.2 g/day, or placebo) [14]. In this study, treatment did not improve intestinal absorption of energy, CHO, fat, nitrogen, sodium, potassium, calcium or magnesium. A number of their patients experienced unpleasant side effects, including carpel tunnel syndrome, arthralgias, and peripheral edema.

In a further study of the response to rhGH, glutamine and a modified diet, Byrne et al. randomized patients with SBS to receive either rhGH 0.1mg/kg/day and glutamine 30g/day, or rhGH 0.1mg/kg/day and glutamine placebo, or glutamine 30g/day and hGH placebo [15]. All patients received what was considered an optimized oral diet, rich in protein (≅ 20%), low to moderate fat (≅ 30%), and high in CHO (≅ 50%). The glutamine, rhGH placebo arm was considered the control, as previous studies had indicated that glutamine alone did not affect nutrient absorption. Results indicated that the rhGH, glutamine and diet group had the greatest reduction in parenteral nutrition requirements (7.7 ± 3.2 L/week, 5751 ± 2082 calories/week, 4 ± 1 infusions/week), compared to 5.9 3.8 L/week, 4338 1858 calories/week, 3 2 infusions/week in the rhGH, glutamine placebo, diet group, and 3.8 ± 2.4 L/week, 2633 ± 1341, 2 ± 1 infusions/week, in the Glutamine and rhGH placebo group. Only the rhGH, glutamine, diet group maintained this for at last 3 months. Stool output, however, did not change significantly, and oral fluid intake increased similarly in all groups, probably as a consequence of the reduced PN requirement. Intestinal absorption studies were not performed.

The controversy surrounding the use of high dose rhGH, glutamine and high CHO diet in patients with SBS encouraged Seguy et al. to investigate the role of low dose rhGH alone for 3 weeks in patients who were PN dependent for the past 7 years [16]. Twelve patients with PN dependent SBS were randomized to receive low-dose rhGH 0.05 mg/kg/day. Patients were all on a hyperphagic diet providing 53 ± 6 kcal/kg/day. Treatment with rhGH increased intestinal absorption of energy (15 ± 5%, $p<0.002$), nitrogen (14 ± 6, $p<0.04$), and CHO (10 ± 4%, $p<0.04$). Absorption of fat was not significantly increased (12 ± 8%, P=NS). Xylose absorption increased with rhGH treatment (1.2 ± 0.2 vs. 0.8 ± 0.2 mmol/l), and body weight increased (57.2 ± 2.4 kg vs. 55.2 ± 2.2 kg, $p<0.003$). Treatment with rhGH also significantly increased

IGF-1 (p<0.002) and IGF-binding protein 3 (p<0.002). Citrulline levels were unchanged (20 ± 2 μmol vs. 17 ± 3). The authors concluded that the low dose rhGH significantly improved intestinal absorption in PN dependent SBS patients.

Small numbers and the probability that many of the patients recruited into the studies were rehabilitatable with attention to controlling diarrhea and providing adequate rehydration without the necessity for hormonal intervention with rhGH, compromise many of the studies. Although rhGH has been approved by the US Food and Drug Administration (FDA) for treatment of patients with SBS, a Cochrane Collaboration review concluded that although treatment of patients with SBS with rhGH with or without glutamine appeared to improve weight gain, energy absorption and nitrogen absorption, the effects were short-lived, raising the question of the clinical utility of this treatment. The evidence was therefore inconclusive to recommend this therapy.

Glucagon-Like Peptide 2 (GLP-2) is secreted by the L cells of the gut, following food ingestion. GLP-2 has been demonstrated to have intestinotrophic activities. Teduglutide is an analog of GLP-2. A recent phase 3 study comprised a 24-week trial of subcutaneous teduglutide 0.05 mg/kg, compared to placebo, in patients with SBS-IF [17]. Patients with SBS were required to have received at least 12 months of parenteral support, at least 3 times weekly. Patients with Crohn's disease had to be in clinical remission for at least 12 weeks prior to dosing. Exclusion criteria included cancer within 5 years, body mass index <15 kg/m^2, inflammatory bowel disease on immunosuppressives that had been introduced or changed within past 3 months or biologics within 6 months, previous use of native GLP-2 or human growth hormone within 6 months of screening and greater than four SBS-related hospital admissions within 12 months or within 30 days before screening.

Patients were placed on a parenteral support optimization schedule, with parenteral support adjusted according to 48 hour urine output, and then a time of parenteral support stabilization. Patients were randomized to teduglutide 0.05 mg/kg/day subcutaneously or placebo for a period of 24 weeks, with follow-up visits at weeks 1, 2, 4, 8, 12, 16, 20 and 24. Patients recorded 48 hour oral fluid intake and urinary volume. Parenteral support was reduced if 48 hour urine volumes exceeded baseline values by at least 10% on a weekly basis. The primary endpoint was the number of patients with >20% reduction of parenteral support volumes from baseline, at week 20, maintained to week 24 (responders).

The study reported that there were significantly more responders in the teduglutide group (27/43, 63%) compared to placebo (13/43, 30%), p=0.002. Parenteral support volume in the teduglutide group was reduced 4.4 ± 3.8 L/week at week 24, compared with 2.3 ± 2.7 L/week in the placebo group, p<0.01. More patients receiving teduglutide achieved a 1-day or greater reduction of weekly need for parenteral support (21/39, 54% vs. 9/36, 39%, p=0.005). At 24 weeks, plasma citrulline levels increased by 20.6 ± 17.5 μmol/l from baseline, in the teduglutide group, compared to 0.7 ± 6.3 μmol/l in the placebo treated group.

There was, however, a high placebo response rate of 30% in this study. This may be consequent to the residual small bowel length in many of the patients (mean of 122.8 cm and 137.7 cm) in patients with jejunostomy/ileostomy, where several of the patients may have been rehabilitatable without the requirement for teduglutide. The use of antidiarrheals, which is central to gut rehabilitation in the patients, was also remarkable low (37% and 51%). The mean time since bowel resection in this study was 7.9 and 6.9 years, whereas most "gut adaption" occurs in the first 2 years. It is likely that the response to teduglutide would be an even greater, if given earlier during the period of gut adaptation.

Teduglutide represents a significant advance in the management of patients with SBS-IF who are PN dependent. The agent was generally well tolerated and resulted in reduced volumes and numbers of days of parenteral support for patients with Short Bowel Syndrome with Intestinal Failure (SBS-IF). Its role in SBS where TPN is not required has not yet been evaluated, and this is an area that needs to be explored.

Conclusion

Short bowel syndrome remains a major clinical challenge. Much can be done to improve quality of life for these patients and avoid the complications of the condition and treatment options, particularly PN. Dedicated rehabilitation programs are important to optimize management strategies, and reduce or avoid dependence on PN and ultimately small bowel transplantation. Recent new developments, such as teduglutide, offer exciting new progress in the management of these patients.

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