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What is This?
Increased Intestinal Absorption in the Era of Teduglutide and Its Impact on Management Strategies in Patients With Short Bowel Syndrome–Associated Intestinal Failure

Douglas L. Seidner, MD, AGAF, FACP, CNSC; Lauren K. Schwartz, MD; Marion F. Winkler, PhD, RD, LDN, CNSC, FASPEN; Khursheed Jeejeebhoy, MD, FRCP(C), PhD; Joseph I. Boullata, PharmD, RPh, BCNSP; and Kelly A. Tappenden, PhD, RD, FASPEN

Abstract

Short bowel syndrome–associated intestinal failure (SBS-IF) as a consequence of extensive surgical resection of the gastrointestinal (GI) tract results in a chronic reduction in intestinal absorption. The ensuing malabsorption of a conventional diet with associated diarrhea and weight loss results in a dependency on parenteral nutrition and/or intravenous fluids (PN/IV). A natural compensatory process of intestinal adaptation occurs in the years after bowel resection as the body responds to a lack of sufficient functional nutrient-processing intestinal surface area. The adaptive process improves bowel function but is a highly variable process, yielding different levels of symptom control and PN/IV independence among patients. Intestinal rehabilitation is the strategy of maximizing the absorptive capacity of the remnant GI tract. The approaches for achieving this goal have been limited to dietary intervention, antidiarrheal and antisecretory medications, and surgical bowel reconstruction. A targeted pharmacotherapy has now been developed that improves intestinal absorption. Teduglutide is a human recombinant analogue of glucagon-like peptide 2 that promotes the expansion of the intestinal surface area and increases the intestinal absorptive capacity. Enhanced absorption has been shown in clinical trials by a reduction in PN/IV requirements in patients with SBS-IF. This article details the clinical considerations and best-practice recommendations for intestinal rehabilitation, including optimization of fluids, electrolytes, and nutrients; the integration of teduglutide therapy; and approaches to PN/IV weaning. (JPEN J Parenter Enteral Nutr. 2013;37:201-211)

Keywords

intestinal failure; short bowel syndrome; malabsorption; multidisciplinary care; teduglutide; GLP-2, fluid balance; parenteral nutrition; treatment

Short bowel syndrome–associated intestinal failure (SBS-IF) is a chronic condition characterized by a clinically significant reduction in intestinal absorptive capacity after surgical bowel resection due to underlying disease, trauma, congenital defects, or complications of other surgery. Intestinal failure results when malabsorption prevents an individual’s fluid, electrolyte, and nutrient requirements from being achieved with a conventional oral diet, and the patient is dependent on parenteral nutrition and/or intravenous fluids (PN/IV) (Figure 1). Complications of SBS-IF include cholelithiasis, kidney stones, hypersecretion of gastric acid, D-lactic acidosis, metabolic bone disease, and a reduction in life expectancy. SBS-IF can also result in severe malabsorptive diarrhea with associated dehydration, electrolyte disturbances, weight loss, and malnutrition. The degree of malabsorption varies between individuals depending on the length and location of the resection and the degree of postsurgical intestinal adaptation. The management of fluid, electrolyte, and nutrient absorption is complex and should be highly individualized in patients with SBS-IF. PN/IV is necessary immediately after resection, but ideally patients will transition to enteral nutrients (preferably oral) for their long-term nutrition. Although complete nutrition autonomy may not be achieved by all patients, an improvement in lifestyle and minimization of the risk of long-term PN/IV complications are sought by reducing PN/IV requirements as much as possible.
The overall treatment goal for this population is intestinal rehabilitation, a process of maximizing the digestive and absorptive capacity of the remnant gastrointestinal (GI) tract to improve uptake of fluid, electrolytes, and nutrients. The individualized response may result in a reduced need for PN/IV. Currently, best-practice strategies for SBS-IF management have been limited to optimized dietary interventions, antisecretory medications, and antidiarrheal agents and, at times, surgical bowel reconstruction to achieve this end. A more recent addition to intestinal rehabilitation therapy is teduglutide (rDNA origin) (GATTEX; NPS Pharmaceuticals, Inc., Bedminster, NJ), a new targeted agent that was approved by the U.S. Food and Drug Administration (FDA) in December 2012 for the treatment of adult patients with short bowel syndrome who are dependent on parenteral support, which uniquely improves intestinal absorption. Teduglutide is a human recombinant enzyme degradation-resistant analogue of glucagon-like peptide 2 (GLP-2), a trophic hormone involved in the normal growth and maintenance of the intestinal epithelium. In a clinical study of patients with SBS-IF, the use of teduglutide promoted the expansion of normal intestinal epithelium and increased enterocyte mass, leading to increased villus height and crypt depth in the small bowel mucosa. In the largest placebo-controlled trial completed in patients with PN/IV-dependent SBS-IF, more than twice the number of patients who received teduglutide (0.05 mg/kg/d) had significant reductions in their PN/IV requirements compared with those who received placebo.

This report summarizes the discussion and consensus of clinical recommendations from a roundtable supported by NPS Pharmaceuticals, Inc., that focused on teduglutide and general strategies for the optimization of fluid, electrolyte, and nutrient status of patients with SBS-IF.

**Physiology of Absorption and Intestinal Adaptation**

The strategy for fluid and nutrition management of patients with SBS-IF is highly dependent on the remnant bowel anatomy (residual length, segment, and the presence or absence of colon), in addition to the adaptive potential that can occur after bowel resection.

**Absorption**

Under normal physiologic conditions, the daily fluid and nutrient input to the GI tract is 7 L from intestinal and accessory organ secretions and 2 L from dietary intake. Almost all of these fluids are absorbed by the small intestine (80%) and colon (18%), leading to minimal fecal output (100–300 g). In SBS-IF, the mechanisms that affect intestinal fluid and nutrient input (secretion, dietary intake) and output (absorptive capacity) are no longer in balance (Figure 2). Patients with SBS-IF experience gastric acid hypersecretion, rapid intestinal transit of food and fluid, loss of intestinal absorptive surface area, bile acid wasting (specifically with resection of the terminal ileum), and bacterial overgrowth. The resulting severe malabsorption and malnutrition lead to a substantially larger volume of intestinal losses.

Postresectional hyperphagia also contributes to fluid intake and losses. Hyperphagia is important to promote intake of sufficient nutrients to compensate for malabsorption; patients with SBS-IF greatly increase their dietary intake of fluids above the normal average of 2 L/d. Unfortunately, the shortened bowel cannot handle this increase, leading to elevated fluid excretion in the form of severe diarrhea or excessive stomal output. Fluid losses are compounded by the oral intake of hypertonic fluids, such as juices, or hypotonic fluids, such as water. A vicious cycle often develops in which the patient experiences thirst and by drinking water draws additional sodium and water out of the body, thereby increasing fecal losses and promoting additional fluid consumption. This cycle leads to and exacerbates dehydration and electrolyte derangements.

The remnant bowel anatomy is important but should be viewed functionally in terms of energy and fluid absorbed or lost rather than just overall length. Sections of the intestine are functionally responsible for the distinct absorption of macronutrients, micronutrients (vitamins and minerals), and fluids. The patients at greatest risk for dehydration and malnutrition are those with an end-jejunostomy and <115 cm, jejunocolostomy and <60 cm (absent ileocecal valve), and jejunocolonic anastomosis and <35 cm of residual small intestine (presence of ileocecal valve and colon). The compensatory absorption that can occur with time by the remaining intestinal sections is affected by their natural function. For example, segment-specific function, such as vitamin B₆ and bile absorption, cannot occur if the ileum is resected regardless of adaptation of the residual bowel. The ileum and colon are responsible for active...
absorption of salt and water from the diet, and loss of these segments prevents their conservation. The colon assumes an important role following the resection of the small bowel; the microbiota therein ferment various dietary fibers to produce short-chain fatty acids (SCFAs). However, when an extensive amount of small bowel is resected, the colon assumes a prominent role in fluid and energy balance by absorbing greater amounts of sodium, water, and SCFAs that result from the fermentation of malabsorbed carbohydrates. The colon is also able to absorb amino acids that can aid in the improvement of nitrogen balance in patients with SBS-IF.9 It is those patients without a colon in continuity who are at highest risk for malnutrition, nutrition deficiencies, dehydration, and diarrhea following extensive intestinal resection.

**Adaptation**

Intestinal adaptation is the natural compensatory process by which hypertrophy of the remnant bowel increases nutrient-processing surface area, thus exceeding the usual nutrient-absorptive capacity after extensive surgical resection.7,20 The process is highly variable, unique to every patient, and thought to take 2–3 years after resection to complete. Dynamic structural changes occur during intestinal adaptation that increase the digestive and absorptive surface area. These changes include remnant bowel dilation and elongation, epithelial cell proliferation, villus elongation, and increased enterocyte absorptive capacity. The effects of these structural alterations are further supported by functional adaptations, wherein intestinal transit time is slower, allowing for increased contact time of nutrients and fluids with the absorptive epithelium.7,20

Only a portion of patients with SBS-IF currently achieve sufficient intestinal adaptation to allow for full weaning of PN/IV. The remainder will require lifelong therapy. One factor that influences adaptation is the type of bowel in circuit. Because of the greater adaptive potential by the residual ileum, the increased macronutrient absorption necessary after a jejunal resection is often achieved.9,21 In contrast, the adaptive potential of the jejunum is limited, and compensation for the loss of specialized vitamin B₁₂−absorbing cells of the terminal ileum does not occur, therefore limiting the prognosis following ileal resection. Another factor affecting adaptation is the health of the remaining bowel; functional capacity of the residual bowel is often impaired in patients with mucosal disease (eg, Crohn’s disease, radiation enteritis).

The stimulation of intestinal adaptation by enteral nutrients cannot be overemphasized and must be maximized in intestinal rehabilitation strategies.21 It is well established using preclinical studies that oral feeding and luminal nutrition are essential for intestinal adaptation.21,23 In contrast, the absorptive surface area is decreased in exclusively PN/IV-fed animals.22,23 Preclinical results also suggest that specific enteral nutrients, including free fatty acids, high-protein diets, and disaccharides, enhance intestinal adaptation.21

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**Figure 2.** Daily intestinal fluid balance is altered in individuals with short bowel syndrome–associated intestinal failure (SBS-IF). Daily fluid and nutrient input to the gastrointestinal tract under normal physiologic conditions is absorbed by the small and large intestines, with resulting minimal fecal output (gray boxes). Patients with SBS-IF experience increased secretions and decreased absorption, leading to substantially larger volumes of intestinal losses (black text). d/t, due to.
Intestinal adaptation is mediated through the natural endogenous factors GLP-2, enteroglucagon, growth hormone (GH), epidermal growth factor, insulin-like growth factors, keratinocyte growth factor, cholecystokinin, gastrin, insulin, and neurotensin. Pharmacotherapy targeted to 2 of these intestinotrophic factors, GLP-2 and GH, triggered many clinical investigations and the development of replacement GLP-2 and human GH treatment options for an expanded strategy of intestinal rehabilitation.

**Intestinal Rehabilitation**

The goal of intestinal rehabilitation is to enhance nutrient processing and absorptive capacity of the remnant GI tract, allowing for maximal oral intake of nutrients and fluids. Introduction of PN/IV is appropriate when patients are unable to sustain adequate nutrient balance and hydration with diet modifications alone. PN/IV should provide the patient with adequate nutrition to prevent or address protein-energy malnutrition and also be sufficient to prevent or replenish micronutrient deficiencies and dehydration. Many patients are chronically dependent on PN/IV for nutrient and fluid support. Unfortunately, long-term PN/IV dependence can be associated with serious complications that often lead to frequent hospitalization and sometimes result in death. These complications include central line–associated bloodstream infections, venous occlusion due to thrombus or stenosis, advanced liver disease, metabolic bone disease, and renal failure. Importantly, the development of complications does not necessarily imply that PN/IV should be discontinued but rather that the formula composition might need to be adjusted and that efforts to prevent venous access–device complications need to be maximized. Consideration should be given to referring patients with frequent infections or major complications to a medical center specializing in the management of SBS-IF. The Oley Foundation is an excellent resource for connecting with experts and for patient-support activities (www.oley.org). Increasingly, a major objective in SBS-IF management is to optimize intestinal rehabilitation by combining fluid and nutrition interventions, adjunctive medications, and new targeted pharmacotherapy.

**Fluid and Nutrition Optimization**

The aims of nutrition optimization are to maintain lean body mass; to prevent and correct deficiencies in hydration, micro-nutrient (electrolytes, minerals, vitamins), and macronutrient (protein-energy) levels; to prevent or correct acid base disturbances; and to optimize absorption (medications, nutrients, fluids). Patients with SBS-IF are a heterogeneous population with complex fluid, electrolyte, and nutrient needs requiring individualized plans. Patients with SBS-IF should be managed as individuals because of the considerable differences in remnant bowel anatomy and function, psychosocial traits, and personal lifestyles and goals.

Dietary education and support should immediately follow an extensive bowel resection. Continued education of patients and caregivers is needed on the rationale and importance of the components of optimized fluid and nutrient interventions (ie, oral fluids, energy-rich nutrients, electrolytes, minerals, vitamins, salts). Equally important is that patients and caregivers be taught that as intestinal adaptation occurs, intake adjustments will be necessary.

Because fluid balance is integral to intestinal rehabilitation, patients can accomplish this, in part, by frequent sipping of oral rehydration solutions (ORS). These solutions have a balanced ratio of sodium and glucose (200–300 mOsm/L) that maximizes intestinal fluid absorption. Patients should be encouraged to drink 1–2 L/d of ORS while avoiding hypotonic fluids (eg, water) or sugary fluids (eg, juices and sodas) to maintain urinary sodium >20 mmol/L and urine output >1 L.

Patients should be encouraged to consume a daily hyperphagic diet of frequent, small, high-caloric meals, with the goal of consuming at least 50% more calories than a standard, non–short bowel diet. Dietary modification should be based on remnant bowel anatomy. The presence of a colon resulted in a larger absorption of calories in patients with SBS-IF on a high-carbohydrate, low-fat diet compared with those on a low-carbohydrate, high-fat diet. Patients without a colon have limited capacity to salvage energy from malabsorbed carbohydrates caused by the lack of colon-specific fermentation to SCFAs; in these patients, dietary fats are better tolerated. Complex carbohydrates are preferred over simple carbohydrates because of beneficial effects on luminal osmolarity and chyme viscosity affecting fluid and nutrient balance. Patients and caregivers also need to understand the benefit of dietary restrictions. Limitations of certain foods are critical in the prevention of some complications. For example, patients with a colon need to restrict oxalate-containing food because they are more susceptible to the formation of calcium oxalate renal stones. Dietary fats should be restricted when the colon is present because unabsorbed fatty acids can lead to secretion of colonic fluid, making diarrhea worse and increasing the risk for steatorrhea in these patients. Fat malabsorption is in part due to the reduced availability of bile salts, which can also contribute to the malabsorption of fat-soluble vitamins.

Deficiencies in vitamins and minerals commonly occur in patients with SBS-IF, and a supplementation regimen is necessary to prevent associated consequences. Optimization of minerals and vitamins may require regimens with doses vastly higher than normal daily recommendations; as patients receive less PN/IV, the amounts of minerals and vitamins, or oral supplements, may need to be increased. Supplementation of micronutrients should be tailored to the individual based on the site of the bowel resection and resultant laboratory values. Although most micronutrient supplements can be repleted orally, magnesium supplementation can be difficult, especially in individuals without a colon. Magnesium salts that readily dissociate at a neutral pH are often necessary to maximize absorption. However, intolerance to oral magnesium...
supplements or maximization of the stable magnesium quantity in PN means that some individuals will require intravenous magnesium to maintain normal blood levels. As noted earlier, vitamin B$_{12}$ deficiency needs to be addressed in patients with disease or resection of terminal ileum.

An important aspect of any individualized plan is the monitoring requirements that will assist the physician in assessing the progress of fluid and nutrition optimization. Patients with SBS-IF require extensive monitoring measures that encompass diet, hydration, body weight, stomal or stool output, blood chemistry profile, and performance status (Table 1). Patients and caregivers need to be encouraged to adhere to the monitoring schedule.

### Use of Adjunctive Medications

The option of adjunctive therapy with medications is an integral component of a rehabilitation program in achieving the goals of fluid and nutrient optimization. Pharmacologic interventions to reduce diarrheal losses to <2 L/d are a key component of SBS-IF management. Common anti-diarrheal medications include loperamide, diphenoxylate with atropine, and opioids. Dose requirements are often higher than normal prescriptions, and combination therapy is often necessary in patients with SBS-IF. Bile acid–binding resins, such as cholestyramine, may be beneficial for diarrheal control; however, their use can contribute to the malabsorption of fat-soluble vitamins. Consideration of whether pancreatic enzyme supplementation is necessary depends on the degree of uncontrolled gastric hypersecretion that inactivates pancreatic enzymes through disruption of the pH environment. Antisecretory agents, such as proton pump inhibitors and octreotide, are also useful in controlling hypersecretion, although the latter may limit adaptation and is associated with cholelithiasis. Antimicrobials are sometimes necessary because small intestine bacterial overgrowth can occur in patients with SBS-IF.

### Targeted Pharmacotherapy With Teduglutide

GLP-2 is a mediator of intestinal adaptation. It is a naturally occurring 33–amino acid intestinotrophic hormone secreted postprandially by the enteroendocrine L cells of the ileum and colon and is involved in the normal growth and maintenance of the intestinal epithelium. Preclinical data demonstrated that synthetic rat GLP-2 increased the proliferation of mucosal epithelium and inhibited enterocyte cell death, resulting in mucosal hypertrophy characterized by an increase in villus height and crypt depth. In addition, synthetic and recombinant human GLP-2 inhibited gastric acid secretion and motility in preclinical and phase I clinical studies. Teduglutide is a recombinant human GLP-2 analogue with a single amino acid substitution that substantially extends its half-life compared with native GLP-2, allowing it to be administered once daily by subcutaneous injection. A possible role for teduglutide in intestinal rehabilitation was demonstrated in a rat model of extensive intestinal resection. The rate and magnitude of the proximal intestinal adaptive response were augmented with teduglutide as assessed by increases in intestinal diameter, mucosal mass, crypt-villus height, and sucrase activity. The intestinal absorptive capacity, as assessed by the urinary appearance of orally dosed D-xylose, was restored with teduglutide treatment. Early human studies were conducted in patients with SBS-IF and no colon in continuity who received synthetic human GLP-2. These patients had improved intestinal absorption and nutrition status as assessed by increased energy absorption, weight, lean body mass, 24-hour urine creatinine excretion, and delayed gastric emptying. Increases in crypt depth and villus height were demonstrated in the majority of patients receiving synthetic GLP-2. Synthetic GLP-2 also augmented an increase in the postprandial mesenteric blood flow in healthy volunteers and SBS-IF patients with end-jejunostomy.

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BUN, blood urea nitrogen; GI, gastrointestinal; PN/IV, parenteral nutrition and/or intravenous fluid.

**Table 1. Monitoring on Long-Term PN/IV.**
Two phase III studies in patients with SBS-IF evaluated the effects of teduglutide on intestinal rehabilitation. These international, multicenter, double-blind, randomized, placebo-controlled, 24-week clinical trials studied the efficacy and safety of teduglutide in 170 patients with SBS-IF dependent on PN/IV. These studies represent the largest trials to date in this orphan disease (ClinicalTrials.gov identifiers: NCT00081458 and NCT00798967). Extension studies were planned for the 2 phase III studies that allowed for an assessment of the longer term effect of teduglutide (ClinicalTrials.gov identifiers: NCT00172185, NCT00930644, and NCT01560403).

As in earlier studies, dynamic structural changes of adaptation were observed in intestinal biopsy samples from patients with SBS-IF receiving teduglutide. Patients who received teduglutide had increased villus height and crypt depth compared with those who received placebo. There was no evidence of dysplasia in the intestinal samples. In addition, levels of plasma citrulline, the biomarker for enterocyte mass, increased in patients receiving teduglutide compared with patients receiving placebo.

As previously stated, the overall goal of intestinal rehabilitation is to enhance nutrient processing and maximize absorptive capacity of patients with SBS-IF. The larger phase III clinical trial, referred to hereafter as the registration study, had a primary efficacy end point of the percentage of responders who experienced a 20%–100% reduction in weekly PN/IV volume compared with baseline (ClinicalTrials.gov identifier: NCT00798967). Patients (n = 86) with SBS-IF and PN/IV dependency ≥1 year were enrolled, completed initial optimization (0–8 weeks) and stabilization (4–8 weeks) periods, and were randomized to receive placebo or teduglutide 0.05 mg/kg/d when urine volume was 1–2 L/d. A patient’s requirement for PN/IV was reduced through the study as measured by a reduction in his or her PN/IV volume and number of infusion days. Teduglutide or placebo was given to patients for a total of 24 weeks.

More than twice the number of patients receiving teduglutide 0.05 mg/kg/d significantly reduced their PN/IV volume requirements compared with those receiving placebo (63% vs 30% responders, respectively; \( P = .002 \)). Significant reductions in absolute volume were seen as early as week 8. By the end of treatment at week 24, teduglutide provided a 4.4-L/wk reduction from baseline, which was more than 2 L greater than placebo (Figure 3). The secondary outcome measure was reduction in number of PN/IV infusion days. After 24 weeks of treatment with teduglutide, 54% of patients receiving teduglutide reduced their number of infusion days per week by at least 1 day compared with 23% of those receiving placebo.

Complete independence from PN/IV occurred in 10 patients who received teduglutide 0.05 mg/kg/d. The patients had received teduglutide 0.05 mg/kg/d for 12–101 weeks at the time of PN/IV weaning. Although patients who achieved complete weaning off PN/IV with teduglutide had a wide range of baseline characteristics and demographics, an emerging pattern suggests that patients achieving PN/IV independence tend to have colon in continuity and lower baseline PN/IV needs. Long-term teduglutide treatment is associated with continued improvement in PN/IV weaning.

The PN/IV reduction algorithm in the larger 24-week registration study enabled an aggressive early approach to adjust PN/IV volumes during the study. Reductions in weekly PN/IV volume were permitted 2 weeks after initiating teduglutide (0.05 mg/kg/d) and could range from 10%–30% of the stabilized baseline PN/IV volume if the preceding 48-hour urine output increased at least 10% compared with baseline values.

GI-related adverse events were the most frequently reported in patients receiving teduglutide and were consistent with the known mechanism of action and the underlying disease condition. In the registration study, these events included abdominal pain, nausea, GI stoma changes, abdominal distention, and peripheral edema, which tended to develop soon after initiation and subsequently resolved as treatment continued.

Six patients from the teduglutide group and none from the placebo group developed antiseduglutide antibodies after the start of study drug; antibodies were nonneutralizing and without evidence of decreased effect on PN/IV volume reduction. Long-term data will be available in 2013 after the completion of the 2-year open-label extension study of patients who completed the registration study and the subsequent 1-year follow-on open-label study.

Clinical Considerations for Intestinal Rehabilitation in Patients Receiving Teduglutide

The approval of teduglutide by the FDA expands the options for clinicians treating patients with SBS-IF who are dependent on
The clinical utility of this agent for intestinal rehabilitation was evaluated in 2 large well-controlled, multicenter, clinical trial settings. Consequently, translating the specifics of the clinical trial protocol (eg, optimal monitoring capabilities) into everyday practice can be a challenge. The experience of all the authors in the treatment of adults with SBS-IF and the subset of authors involved in the clinical studies of teduglutide allows for some best-practice recommendations for clinicians considering the use of teduglutide.

**Before Teduglutide**

The individual needs of each patient should be taken into account as well as adherence to the criteria of the prescribing information when considering the initiation of therapy with teduglutide. It is vital that fluids, electrolytes, nutrients, and adjunctive medications are optimized before teduglutide is initiated. The strategies described earlier for fluid and nutrition interventions should be attempted first because some patients may respond by improving their absorption. In addition, nocturnal enteral feedings should be considered to increase daytime ambulation and daytime appetite stimulation, as well as to improve nutrient absorption that may allow for a reduction in PN/IV.

No step-up in monitoring frequency is needed before initiation of therapy, but establishment and recording of baseline parameters should be completed. Patients who require long-term home PN/IV need regular monitoring to assess nutrient balance and liver function; parameters should minimally include body weight, urine output (24- to 48-hour measure, if possible), or surrogate markers of hydration status (including urine-specific gravity and/or urine sodium) for patients in whom a 24- to 48-hour urine output measure may be difficult (eg, working patients, women, concurrent diarrhea); serum creatinine/serum urea nitrogen; and basic metabolic panel plus phosphorus and magnesium (see Table 1 for complete list).

The typical patient with SBS-IF will likely receive care from a multidisciplinary team of specialized care providers that includes a surgeon, gastroenterologist, registered dietitian, clinical pharmacist, and nurse. These healthcare practitioners frequently work in several distinct settings, including hospitals, home infusion companies, home care agencies, and long-term care facilities. In some situations, a hospital-based nutrition support service may manage care. Preplanning and communication between the various healthcare providers and the patient are strongly recommended to allow for a well-coordinated care plan. Ideally, the prescriber of teduglutide and PN/IV will be the same individual. If the prescriber of teduglutide and prescriber of PN/IV are different, close coordination is necessary to ensure appropriate oversight and monitoring of laboratory values, PN/IV constituents and volume, and initiation and timing of subsequent PN/IV weaning. It is recommended that patients be referred to major centers with experience in intestinal rehabilitation at least during the initiation and stabilization phase of treatment. If it is unrealistic or unreasonable for a patient to travel to a major center, the treating clinician should have access to timely communication with experts in the field of intestinal rehabilitation. Experts can offer guidance when questions arise regarding the initiation of teduglutide and management of patient expectations regarding their diet, the drug, and adjustments to PN/IV.

**Treatment With Teduglutide**

The criteria for patient selection in the clinical trial setting do not apply to all patients with SBS-IF who may be under consideration for teduglutide treatment. Therefore, some clinical guidance is needed for physicians to establish patient suitability for treatment with teduglutide. In the largest completed trial with teduglutide, the patients with SBS-IF were PN/IV dependent for at least 12 continuous months, required PN/IV for ≥3 times/wk, and had a body mass index >15 kg/m². Table 2 lists considerations for appropriate patient suitability for treatment with teduglutide, including that the patient (1) be clinically stable, with nonobstructive and nonmalignant disease; (2) have persistent need for PN/IV despite optimized therapy, including dietary modifications and pharmacologic

| Table 2. Considerations for Patient Suitability for Treatment With Teduglutide. |
|---------------------------------|-----------------|-----------------|
| **Clinical Status**            | **PN/IV Requirem ents** | **Nutrients and Fluids** |
| Stable                          | Dependent on PN/IV despite • Optimized dietary modifications • Adjunctive medications | Nutritionally optimized and in fluid balance as assessed by • Realistic target body weight that permits optimal functioning • Serum albumin status • BUN/creatinine ratio • Vitamin status • Mineral status |
| Nonobstructive disease          | Prior unsuccessful attempts to wean from PN/IV | BUN, blood urea nitrogen; PN/IV, parenteral nutrition and/or intravenous fluid. |
| Nonmalignant disease            | Patient has desire to reduce or discontinue PN/IV | |

PN/IV, parenteral nutrition and/or intravenous fluid.
interventions; (3) be nutritionally optimized and in fluid balance; and (4) must desire to reduce or discontinue PN/IV. Patients with a range of bowel anatomies can be considered for treatment with teduglutide because efficacy was not affected by the presence or absence of colon in continuity, nor was the bowel length a predictor of response.\textsuperscript{13}

The efficacy of teduglutide was established in patients who underwent a multiweek optimization and stabilization period of PN/IV and oral fluid intake with a stable target urine output of 1–2 L/d.\textsuperscript{13} This element of the study design was to ensure that before treatment, patients were receiving a stable level of PN/IV with adequate hydration while avoiding excessive hydration. The approved dose and formulation is 0.05 mg/kg/d administered by subcutaneous injection into the abdomen, thigh, or upper arm once daily at approximately the same time each day.

Teduglutide prescribers should adhere to the overall precautions and to the requirements for the specific population of patients described in the label. For patients with compromised renal function, label guidance for dosing adjustments should be followed. Teduglutide is contraindicated in patients with suspected or active malignancy and in patients with a history of malignancies (excluding basal cell carcinoma); patients with a history of cancer within the past 5 years were excluded from the clinical trial.\textsuperscript{11,13} Because of increased intestinal absorption, a potential risk may exist for interactions with concomitant oral drugs that have a narrow therapeutic index or are titrated to effect. Consideration should be given to whether dose adjustments for concurrent medications are required. Because of the exclusion criteria of the clinical trials, there are no data on the use of teduglutide in the presence of octreotide or biologic or immunosuppressant therapies.

The clinical trials were not designed to determine the optimal timing of teduglutide treatment after the onset of SBS-IF. Similarly, because the completed clinical trials did not collect follow-up information, additional data are needed to assess the effects on patients after teduglutide is discontinued. Jeppesen et al\textsuperscript{13} discussed the fact that the duration of effect of teduglutide following discontinuation was highly variable, with some patients maintaining reductions up to 1 year later, whereas others needed immediate increases in their PN/IV volumes.

Monitoring of the parameters recorded before starting teduglutide should continue through each phase of the treatment period: initiation, adjustments, weaning, and maintenance (Tables 1 and 3). In the clinical trial setting, scheduled office visits occurred at weeks 2 and 4 followed by every 4 weeks for the duration of treatment.\textsuperscript{13} Recommendations outside of that setting are for collection of laboratory results every week, with an office visit every 4 weeks (Table 3) until supplemental PN/IV requirements are stable, at which time the frequency of visits can be reduced.

Strategies for PN/IV Weaning

The intended approach to PN/IV reductions should clearly be determined in the planning stages ahead of teduglutide initiation and should address the patient and their caregiver preferences for a weaning strategy. Although PN/IV can be lifesaving, the associated complications make reduction a goal of intestinal rehabilitation. Despite the widespread use of PN/IV after resection and that some patients initially requiring PN/IV can be weaned off,\textsuperscript{2} there is a paucity of detailed information in the literature on weaning strategy recommendations. There are currently no published guidelines regarding the recommended approach for weaning a patient off PN/IV.\textsuperscript{48} This may partially be accounted for by the wide range of individualized management strategies required for the complex control of fluid, electrolytes, and nutrition requirements.

As the bowel adapts and absorbs more fluid and nutrients, PN/IV requirements are likely to decrease. This is reflected in gradual weight gain despite stable PN-calorie content and increased urine output despite stable PN/IV volumes. If these parameters are met and the goal weight is achieved, PN/IV weaning should be considered with the patient and his or her team of healthcare providers (Table 3). The PN/IV reduction algorithm used during the 24-week registration study was that reductions in weekly PN/IV volume were permitted 2 weeks after initiating teduglutide and could range from 10%–30% of the stabilized baseline PN/IV volume if the preceding 48-hour urine output increased at least 10% over baseline values.\textsuperscript{13} In that clinical trial, the choice of whether to remove 1 day in the PN/IV cycle or to reduce the percentage of PN/IV volume on all days in the cycle was the combined decision based on the patient’s preference and the clinical investigator’s judgment. In the clinical practice setting, clinicians may use this algorithm as a guide when adjusting PN/IV volume, while simultaneously applying best clinical judgment with respect to individual patient variability of response onset and intensity, possible delays in PN/IV delivery, and the timing of implementation of PN/IV prescription changes. It may be prudent for the treating clinician to establish access to experts in the field of intestinal rehabilitation, ahead of initiating teduglutide, for guidance regarding the adjustments to PN/IV leading to weaning.

Throughout the weaning process, with or without teduglutide, continued monitoring of body weight, sufficient urine output, fluid balance, and micronutrient status should be tracked closely to ensure safe withdrawal of PN/IV (Tables 1 and 3). In the largest completed trial with teduglutide, adjustments to PN/IV were made at scheduled office visits that assessed 48-hour oral fluid intake and urinary output measurements.\textsuperscript{13} We strongly recommend that patients keep a diary to record oral food and fluid intake, urine output, and stool/stoma characteristics (see Table 1) and that this record be forwarded or brought to the prescribing physician’s office for review and discussion.

Because of the proabsorptive and intestinotrophic effects of teduglutide, patients should be educated on signs of fluid overload that could arise during the weaning process, especially if insufficient PN/IV reductions occur. Patients should be advised to report rapid changes in weight and urine output to their prescribing physician. As the patient becomes more
Table 3. Summary of Clinical Recommendations for Managing Patients on Teduglutide Therapy.

<table>
<thead>
<tr>
<th>Initiation Period</th>
<th>Maintenance Phase</th>
<th>Nutrients and Fluids</th>
<th>PN/IV Requirements</th>
<th>Additional</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong communicative network established</td>
<td>Continue monitoring of body weight and urine output</td>
<td>Parameters to consider in PN/IV weaning decision</td>
<td>Attempt at PN/IV weaning should be based on weekly volume and total urine output</td>
<td>Counsel patients to report changes during weaning attempts</td>
</tr>
<tr>
<td>• Teduglutide prescriber</td>
<td></td>
<td>• Gradual weight gain with stable PN/IV calorie content</td>
<td></td>
<td>• Risk of sudden fluid balance interruptions</td>
</tr>
<tr>
<td>• PN/IV prescriber</td>
<td></td>
<td>• Increased urine output despite stable PN/IV volumes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Home infusion company</td>
<td></td>
<td>• Achieving target body weight that permits optimal functioning</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>• Electrolytes</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>• Micronutrient needs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monitor body weight</td>
<td>Office visit every 4 weeks</td>
<td>Consider patient preference for PN/IV volume changes</td>
<td>Provide straightforward and clear communication on PN/IV volume changes, Calorie reductions, Electrolyte compositions</td>
<td></td>
</tr>
<tr>
<td>Monitor urine output</td>
<td>Clinical exam at office or home nursing visit when</td>
<td>Adjust PN/IV constituents, as needed</td>
<td>Office visits can be reduced when PN/IV stabilized</td>
<td></td>
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<tr>
<td>• Shortness of breath</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>• Signs of fluid overload</td>
<td></td>
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<tr>
<td>Obtain lab results every week</td>
<td>Telephone consults when</td>
<td>Add oral vitamins and micronutrients when PN/IV days are reduced</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Weight changes</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>• Increases in stool and/or ostomy output</td>
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<tr>
<td>Reassessment of dosage for concurrent medications</td>
<td></td>
<td>If PN/IV is &lt;3 d/wk</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Suggest a trial of PN/IV discontinuation</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PN/IV, parenteral nutrition and/or intravenous fluid.
independent of PN/IV, special attention should be given to monitoring the levels of vitamins and minerals. Oral supplementation of micronutrients, particularly potassium and magnesium, is often necessary.

Conclusion
The optimization and management of fluid, electrolyte, and nutrient absorption are complex and should be carefully individualized in patients with SBS-IF. The management strategy is highly dependent on the remnant bowel anatomy as well as the degree of intestinal adaptation that occurs after bowel resection. The goal of intestinal rehabilitation is to maximize nutrient processing and absorptive capacity in patients with SBS-IF. Enteral nutrition is a stimulator of intestinal adaptation and should be central to any plan for intestinal rehabilitation. Because the natural endogenous factor GLP-2 is a mediator of intestinal adaptation, it was targeted for development as a pharmacotherapy. Teduglutide, a GLP-2 analogue, achieves intestinal adaptation as evidenced by reductions in PN/IV requirements in patients with SBS-IF. Reductions in the volume of PN/IV infused per day or the number of PN/IV days can be as beneficial as complete weaning for some patients. Because the typical patient with SBS-IF receives care from several physician specialists and clinicians from 1 or more home healthcare agencies in the outpatient setting, it is important that a strong cross-communication network is established before initiating teduglutide for the treatment of SBS-IF. Thus, a coordinated approach to PN/IV weaning using teduglutide may result in more successful outcomes.

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References


