CME

Short Bowel Syndrome: Navigating Treatment Decisions in a Complex Clinical Picture to Improve Patient Outcomes and Quality of Life

PeerView inBrief

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Activity Information

Activity Description and Educational Objectives
In this activity, an expert in intestinal rehabilitation and transplantation explores the optimal management of short bowel syndrome (SBS) in the context of current evidence and therapeutic modalities.

Upon completion of this activity, participants should be better able to:
- Recognize the pathophysiology, anatomy, and prognosis of short bowel syndrome (SBS)
- Identify benefits and limitations associated with nutritional and pharmacologic treatment modalities for SBS
- Employ individualized and comprehensive approaches in the management of SBS to improve intestinal absorption, reduce the need for parenteral support, and improve patient quality of life

Target Audience
This activity has been designed to meet the educational needs of gastroenterologists, surgeons, and other clinicians involved in the management of patients with short bowel syndrome.

Requirements for Successful Completion
In order to receive credit, participants must view the activity and complete the post-test and evaluation form. A score of 70% or higher is needed to obtain CME credit. There are no pre-requisites and there is no fee to participate in this activity or to receive CME credit. Statements of Credit are awarded upon successful completion of the post-test and evaluation form.

Media: Enduring Material
Release and Expiration Dates: January 31, 2018 - January 30, 2019
Time to Complete: 15 minutes

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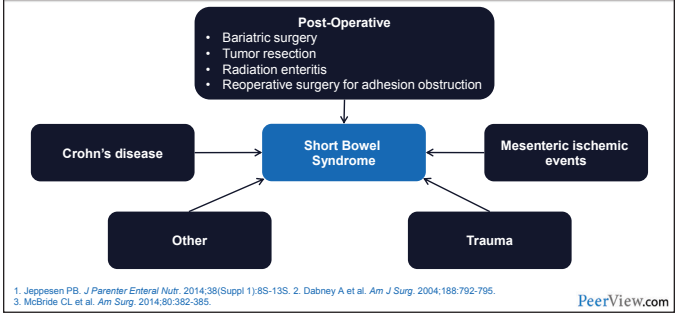
Causes and Symptoms of Short Bowel Syndrome

Short bowel syndrome (SBS) is a malabsorptive disorder associated with significant morbidity and mortality, reduced quality of life, and high healthcare costs.[1-3] Since intestinal dysfunction is only weakly correlated with the amount of intestine that is resected (ie, because of variable length of the human small bowel and ability to compensate for resection), the best definition of SBS is based upon the presence of significant malabsorption of both macronutrients and micronutrients. It is important to note that SBS is the most common cause of intestinal failure (IF), the state when an individual's gastrointestinal function cannot provide the body's nutritional requirements to maintain weight and support height in children.

Short bowel syndrome can occur when portions of the small intestine are missing or damaged at birth or have been surgically removed. In adults, SBS usually results from resection of the small intestine for Crohn's disease, trauma, radiation, or mesenteric ischemia; thus, it is critical that clinicians are aware of this condition and employ appropriate strategies to prevent intestinal dysfunction (Figure 1).

Figure 1. Etiology of Short Bowel Syndrome in Adults[1-3]



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The prognosis, clinical manifestations, and treatment of SBS vary depending upon the remaining bowel anatomy and its residual function. According to Dr. Iyer, "It is critically important to know what length of small bowel is left behind, and what part of the GI tract, because that really allows us to prognosticate with a pretty high degree of confidence." Because of differences in the ability to undergo adaptation, patients with an ileal remnant have a better prognosis than patients with only a portion of the jejunum remaining.[4,5] The presence of the colon is beneficial in SBS given its ability to absorb water, electrolytes, and fatty acids; slow intestinal transit; and stimulate intestinal adaptation. Patients with an end jejunostomy can be challenging and are the most likely to require permanent parenteral support (PS).[5]

Among potential clinical complications of SBS (Table 1), diarrhea tends to be the most bothersome and debilitating symptom for many patients.[5] Contributors to diarrhea after resection include loss of absorptive surface area, altered enterohepatic circulation (bile acid depletion, fat malabsorption), loss of hormonal feedback (glucagon-like peptide 1/peptide tyrosine tyrosine [GLP-1/PYY]), and gastric hypersecretion.[6] Intestinal failure-associated liver disease is a common and important concern in patients receiving parenteral nutrition (PN) and remains a major cause of morbidity and mortality in this population. Mild abnormalities in hepatic biochemistry are very common, seen in 30% to 40% of patients, and it should be noted that the risk of significant liver disease increases with longer duration of PN.[7]

Table 1. Clinical Complications Associated With SBS[1]

Bowel Anatomy–Related Complications	Central Venous Catheter–Related Complications	Parenteral Nutrition–Related Complications
• Malabsorptive diarrhea • Malnutrition • Fluid and electrolyte disturbances • Micronutrient deficiency • Essential fatty acid deficiency • Small bowel bacterial overgrowth • D-lactic acidosis • Oxalate nephropathy • Renal dysfunction • Metabolic bone disease • Acid peptic disease • Anastomotic ulceration/stricture	• Infection • Occlusion • Breakage • Central vein thrombosis	• Hepatic complications (ie, steatosis, cholestasis, fibrosis, cirrhosis) • Biliary complications (ie, gallstones)

In combination, all of these can lead to increased mortality, significant costs, and reduced quality of life

1. Parrish CR, DiBaise JK. *Gastroenterol Hepatol (N Y)*. 2017;13:600-608. PeerView.com

Managing the Patient With Short Bowel Syndrome

The goals of treatment for SBS are to relieve symptoms (decrease output), ensure adequate nutrition, increase absorptive potential of remnant intestine, and reduce or eliminate the need for parenteral nutrition. According to Dr. Iyer, if reduction/elimination is not possible, it is important to minimize or prevent the complications of PN. The initial evaluation of all patients with SBS should include a comprehensive assessment, and information obtained should include weight fluctuation; medication usage (including supplements and over-the-counter medications); presence of GI and other symptoms that may affect oral intake or fluid loss; potential signs/symptoms of micronutrient deficiencies; physical assessment for signs of dehydration and malnutrition; pertinent past medical, psychiatric, and surgical history, such as comorbidities and presence of bowel complications (eg, anastomotic strictures, chronic obstructions, enterocutaneous fistulae, and peritoneal drains); nutrition support history, such as an enteral and/or central venous access device, formula

used, the route and method of administration, and known prior complications; education, motivation, and support systems (eg, goals of care and quality-of-life considerations); and potential economic or other barriers.[8]

Dietary Approaches

It is important to note that dietary interventions (ie, oral diet and fluid management) are an essential component in the management of SBS. The basis of diet therapy is manipulation of food intake to maximize nutrient and fluid absorption, subsequently decreasing stool output. Although there are basic principles of diet therapy that apply to all patients with SBS (Table 2), individualizing to each patient's remaining bowel anatomy and educating on the importance of diet and fluid modifications are essential to optimize adherence and successful outcomes.[8]

Table 2. Diet Guidelines for SBS[1]

General tips	• Consume six to eight small meals or snacks per day, and start with a 3-day diet record • Tailor the diet to the patient, and outline what they can eat • Patients should chew foods well • Written diet materials available in the Patient Education section at www.ginutrition.virginia.edu
Protein	• Patients should consume a high-quality protein at each meal and snack
Carbohydrates	• Generous complex carbohydrate intake (eg, pasta, rice, potato, bread) is recommended • Limit simple sugars and sugar alcohols in both foods and fluids; lactose may be tolerated and does not always need to be avoided • Do not use supplemental nutrition drinks
Fat	• Limit fat to <30% in patients with a colon; may need to limit in patients without a colon • Include oils with essential fatty acids (eg, sunflower, soy, walnut)
Oxalate	• Limit if the colon is present; guarantee adequate urine output first
Fluids	• Consider oral rehydration solutions • Avoid sodas, fruit juices, fruit drinks, sweet teas, and liquid nutritional supplements • All fluids may need to be limited in some patients and intravenous fluids given
Salt	• Increase salt intake in patients with no colon; continue usual intake in patients with colon
Fiber	• Encourage some soluble fiber (in food) in patients with a colon segment

1. Parrish CR, DiBaise JK. *Gastroenterol Hepatol (N Y)*. 2017;13:600-608.

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Pharmacotherapy

It is important to recognize that, in addition to diet and fluid, medications may also be malabsorbed in patients with SBS. Thus, to maximize efficacy and safety, clinicians should consider the dose, formulation, frequency, and timing of administration of each drug in relation to meals, as well as closely monitor drug levels when possible.

In terms of pharmacologic therapy for SBS, several conventional medications are used for symptom relief. For example, antimotility agents such as loperamide are used to control diarrhea.[5] An initial dose of loperamide is typically two capsules or tablets (30 mL) taken 30 to 60 minutes prior to a meal and again at bedtime. The maximum recommended daily dose is eight tablets in generally healthy individuals, while a dose of up to four tablets taken four times daily may be needed in patients with SBS. According to Dr. Iyer, "These drugs are valid and useful for long-term use in these patients, and the basis for exceeding the recommended therapeutic doses is the recognized malabsorption of medications." Antisecretory agents (eg, proton pump inhibitors, octreotide) are used to minimize gastric acid hypersecretion, which causes an increase in acidic fluid volume entering the small bowel and contributes to diarrhea and fat maldigestion.

Octreotide, a somatostatin analog, increases small bowel transit time and reduces fluid losses, but tachyphylaxis often develops; according to Dr. Iyer, "The therapeutic effect that you get with an initial dose of octreotide wanes over time."

The structural and functional changes during intestinal adaptation are necessary to compensate for the sudden loss of digestive and absorptive capacity after massive intestinal resection. When the adaptive response is inadequate, patients are left with the requirement for PN and its associated morbidities.[9] Thus, several hormones have been studied as potential enhancers of the adaptation process, and two intestinal growth factors are currently available for use in patients with SBS who have been unable to wean themselves from parenteral support after the period of maximal intestinal adaptation.

Growth hormone was evaluated in a phase 3, prospective, randomized, placebo-controlled trial in 41 PN-dependent patients with SBS. After 2 weeks of stabilization and dietary optimization, patients were randomized to one of three treatment arms: recombinant human growth hormone (somatropin; 0.10 mg/kg taken subcutaneously once daily) plus glutamine, growth hormone (0.10 mg/kg taken subcutaneously once daily) without glutamine, and placebo plus glutamine. A significant reduction was seen in PN requirements in both groups treated with growth hormone at the end of the 4-week treatment period: 7.7 L per week (4.2 days/week) versus 5.9 L per week (3.0 days/week) versus 3.8 L per week (2.0 days/week), respectively (Table 3). Reduction in PN remained significantly reduced during a 12-week observation period only in the group treated with growth hormone plus glutamine. Peripheral edema and musculoskeletal complaints were common in the growth hormone–treated groups.[10] Though somatropin was approved in 2003 by the US Food and Drug Administration (FDA) as the first pharmacologic treatment of PN-dependent SBS, Dr. Iyer has noted that, "Growth hormone seems to have fallen out of favor, partly because of significant side effects."

Table 3. Growth Hormone, Glutamine, and an Optimal Diet Reduces PN in SBS[1]

Groups		Week 2 (mean ± SD)	Week 6 (mean ± SD)	Reduction (mean ± SD)
Volume of PN, L/week	Glutamine + diet	13.5 ± 7.8	9.7 ± 8.4	3.8 ± 2.4
	Growth hormone + diet	10.3 ± 5.6	4.5 ± 4.1	5.9 ± 3.8[a]
	Growth hormone + glutamine + diet	10.5 ± 4.5	2.7 ± 2.0	7.7 ± 3.2[b]
Calories of PN/week	Glutamine + diet	8,570 ± 3,042	5,937 ± 3,120	2,633 ± 1,341
	Growth hormone + diet	7,635 ± 3,530	3,296 ± 2,955	4,338 ± 1,858[c]
	Growth hormone + glutamine + diet	7,895 ± 3,374	2,144 ± 2,089	5,751 ± 2,082[b]
Frequency of PN, infusion days/week	Glutamine + diet	6 ± 2	4 ± 2	2 ± 1
	Growth hormone + diet	5 ± 2	2 ± 2	3 ± 2[a]
	Growth hormone + glutamine + diet	5 ± 2	1 ± 1	4 ± 1[b]

[a] $P < .05$, vs glutamine + diet (by parametric analysis). [b] $P < .001$, versus glutamine + diet (by parametric analysis). [c] $P < .01$, versus glutamine + diet (by parametric analysis).
1. Byrne TA et al. *Ann Surg*. 2005;242:655-661.

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Teduglutide, a GLP-2 analog, is a novel drug approved for the treatment of patients with SBS and intestinal failure. In phase 3 studies, teduglutide enhanced intestinal absorption and reduced PN requirements in patients with SBS-IF.[11,12] In the pivotal 24-week,

multicenter, multinational, double-blind, placebo-controlled trial (STEPS), 63% (27/43) of patients receiving teduglutide 0.05 mg/kg/day achieved the primary endpoint (20% to 100% reduction from baseline in weekly PS volume at weeks 20 and 24) compared with 30% (13/43) of patients receiving placebo ($P = .002$). Mean PS volume reductions were 4.4 L/week and 2.3 L/week among the treatment and placebo groups, respectively ($P \leq .001$; Figure 2). The most common adverse events reported in teduglutide-treated patients were gastrointestinal related, including abdominal pain, nausea, stoma complications, and abdominal distension.[11] Another recent study (STEPS-2) was a 24-month, open-label extension of STEPS to assess the long-term safety, tolerability, and clinical efficacy of teduglutide in patients with SBS-IF. Results from STEPS-2 demonstrated that long-term treatment with teduglutide resulted in sustained, continued reductions in PS requirements (Figure 2); notably, overall health and nutritional status were maintained despite PS reductions.[13]

Figure 2. Teduglutide: Results From STEPS and STEPS-2

Study	Treatment Received in STEPS/STEPS-2 (n)[b]	≥20% Reduction of Weekly PS, %	Mean Reduction in Weekly PS Volume, L/week[c]	Reduction in PS Volume From Baseline, %	Reduction of PS by ≥1 Day per Week, %
24-week STEPS[1,a]	Teduglutide (43)	63 (27/43)	4.4	34	54 (21/39)[d]
	Placebo (43)	30 (13/43)	2.3	17	23 (9/39)[d]
2-year STEPS-2[2]	Teduglutide/Teduglutide (30)	93 (28/30)	7.55	66	70 (21/30)
	Placebo/Teduglutide (29)	55 (16/29)	3.11	28[e]	48 (14/29)

[a] 76 patients went directly from STEPS to STEPS-2. [b] ITT population in STEPS, and the computer population in STEPS-2. [c] In STEPS-2, 10 patients in the teduglutide/teduglutide arm and two patients in the placebo/teduglutide arm achieved complete independence from parenteral support. Of the 12 subjects entering study 2 directly, six completed 24 months of treatment with teduglutide. Similar effects were seen. One of the six subjects was weaned off their PN/IV support while on teduglutide. [d] Based on evaluable (39 teduglutide and 39 placebo) patients. [e] Reduction from the start of teduglutide in STEPS-2.

1. Jeppesen PB et al. *Gastroenterology*. 2012;143:1473-1481. 2. Schwartz LK et al. *Clin Transl Gastroenterol*. 2016;7:e142.

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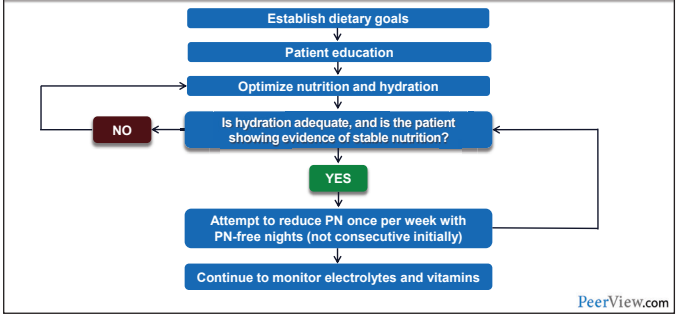
Because of a large variation in patient response with respect to teduglutide-induced parenteral support volume changes, which ranged from -1,993 mL/day to +329 mL/day, a recent post hoc analysis of STEPS aimed to identify characteristics of individual SBS patients who had the largest absolute teduglutide-induced parenteral support volume reductions. The authors associated reduced parenteral support volume with baseline parenteral support volume, bowel anatomy, and SBS features, suggesting that the findings may inform initial parenteral support volume adjustments and management of these severely disabled patients.[14] Another recent post hoc analysis was performed on adult patients who achieved complete parenteral support independence during treatment with teduglutide 0.05 mg/kg/day. Data were pooled from five teduglutide clinical trials (two phase 3 placebo-controlled trials and their respective extension studies), and it was found that oral or enteral autonomy is possible for some patients with SBS-IF who are treated with teduglutide, regardless of baseline characteristics and despite long-term parenteral support dependence.[15]

Prior to initiating therapy with a trophic agent, it is important to note the following patient characteristics: meets criteria for SBS; dependent on PN or IV fluids; has been optimized on diet therapy, anti-secretory drugs, and anti-diarrheal drugs; does not have contraindications (eg, active malignancy, intestinal obstruction); and is compliant/reliable with therapies.

Parenteral Nutrition

As mentioned previously, long-term use of PN is often associated with complications. Therefore, it is desirable, when possible, to wean SBS patients to an oral diet (Figure 3). During weaning, the most practical measures for assessing adequate hydration and nutritional status are oral intake, stool and urine output (key to monitor), serum electrolytes and visceral proteins, and body weight. Reductions can be made by either decreasing the days of PN infusion per week (preferable, especially from a quality-of-life perspective) or decreasing the PN infusion volume equally across all days of the week.[16]

Figure 3. Parenteral Nutrition Weaning: Practical Aspects



Conclusions

Short bowel syndrome demonstrates great variability, both in etiology and clinical manifestations. Although PN is essential in the postoperative period, its prolongation is associated with risks and complications that cause high morbidity and mortality. Thus, it is important to achieve enteral autonomy. Over the years, attempts have been made to improve patient management; indeed new drug therapies have been developed, such as somatotropin and teduglutide, which promote intestinal rehabilitation, improve the function of the remaining bowel, and allow a significant reduction in PN needs—with the ultimate goal of improving patient outcomes and quality of life.

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