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The Clinician's Toolkit for the Adult Short Bowel Patient Part II: Pharmacologic Interventions



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The care of patients with short bowel syndrome (SBS) varies considerably. Patients seek a reasonable return to a normal life after surgery resulting in SBS, as well as a path to optimize their health going forward. Clinicians involved in the management of these patients struggle with the complexity of care and heterogeneity between patients. Medications play a key role in addressing altered GI function and managing symptoms that result from extensive intestinal resection. The shotgun approach to medication management is well intentioned, but not recommended. Treatment should instead be individualized for each patient based on functional capacity of the remaining GI anatomy. A pharmacologic treatment plan should be developed using a methodical, stepwise approach. Medications utilized in the treatment of SBS include antimotility agents, antisecretory agents, antimicrobials (for treatment of bacterial overgrowth), and intestinal growth factors. The purpose of Part II of this series is to guide the clinician on the availability of medications and to develop a pharmacologic treatment plan that improves the quality of life for patients with SBS.

INTRODUCTION

Short bowel syndrome (SBS) is a complex malabsorptive disorder that most often results from an extensive intestinal resection due to a number of gastrointestinal pathologies. Management of SBS therefore is a challenge for clinicians nationwide and across multiple healthcare disciplines. Patients with SBS struggle to maintain adequate fluid, electrolyte, and nutritional status

and benefit from diet modification, oral rehydration solutions (ORS), supplemental electrolytes, minerals, and vitamins aimed at replacing intestinal losses, and medications that often target high stool or ostomy output. Parenteral nutrition (PN) or intravenous (IV) fluid/electrolytes may be required, especially during the process of intestinal adaptation that occurs within the initial months to years following extensive surgical resection.

The extent of malabsorption in patients with SBS will vary depending on the length and location of remaining bowel, its functional status, and the length of time since the last surgical resection. Treatment must therefore be individualized and

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take these factors into consideration. Medical management of SBS should focus on supportive care and symptom control. Pharmacologic treatment can work synergistically with dietary modification and ORS therapy to help control high stool outputs, minimize fluid and electrolyte losses, enhance intestinal absorption, and decrease PN/IV requirements. Medications are specifically targeted to treat the multiple factors that contribute to diarrhea in patients with SBS, including rapid intestinal transit, increased GI secretions, bacterial overgrowth, and malabsorption of fat and bile salts. Intestinal growth factor therapy offers another targeted approach in the treatment of SBS.

It is important to avoid the impulse to start multiple medications at the same time. This shotgun approach does not allow the clinician the ability to distinguish between what may be helping versus what is not, or worse, not allow the clinician to distinguish the source of potential adverse reactions. Patients with SBS often complain that the medical community fails to recognize the condition or appreciate its complexity. Healthcare professionals who are well-intentioned may be providing patients with inaccurate advice due to lack of experience managing SBS. Part I of this series discussed the role of diet and hydration therapies in the management of SBS.¹ The purpose of Part II is to guide the clinician on the availability and use of medications aimed at managing SBS.

Diarrhea Everywhere

Although patients with SBS deal with many challenging issues, high stool output often manifests as their primary complaint. Dealing with the need to make frequent trips to the bathroom and concern for fecal incontinence or a leaking ostomy have been reported to have a deleterious effect on lifestyle, physical function, activities of daily living, and the ability to travel.² This is why clinicians should make considerable effort to control stool output when managing patients with SBS. In addition to the tangible improvements in quality of life, decreasing stool output will potentially minimize the risk of complications resulting from malabsorption of fluids and nutrients. Short-term complications of high stool output include dehydration, electrolyte abnormalities, and metabolic acidosis. Long-term complications of high stool output can include

malnutrition, dehydration, chronic kidney disease, and metabolic bone disease.

First: Don't Make Diarrhea Worse

Medication Considerations

Essentially all orally administered medications are absorbed in the small intestine, so clinicians must anticipate impaired absorption in patients with SBS who often have rapid transit through the small intestine. Patients who have stomas may report the presence of unabsorbed tablet or capsule fragments within their ostomy effluent. Switching from a solid dosage form to a liquid formulation has been recommended as a method to improve absorption, but this recommendation is theoretical and not evidence based. In fact, liquid formulations may contribute to increased stool output if the liquid medication contains sugar alcohol/s. Sugar alcohols (sorbitol, mannitol, xylitol, maltitol, isomalt, erythritol, lactitol) are often added to liquid medication preparations to enhance solubility and palatability, but are potent cathartics that can lead to an osmotic diarrhea. See Table 1 for a list of commonly prescribed liquid preparations that contain sugar alcohol.

It is also problematic to use sustained, controlled, delayed, slow-release, or enteric-coated medications in patients with SBS as the reduced intestinal surface area will result in accelerated transit times and reduced absorptive capacity. It is important to note that patients do not just malabsorb food and liquids in SBS, but medications as well. This in turn will alter the intended pharmacokinetic properties of these medications. Instead, consider an immediate release oral dosage form, chewable oral formulation, or alternative administration routes (e.g., transdermal, sublingual, rectal, and subcutaneous) when available or appropriate.

Antidiarrheal Medications Used to Slow Intestinal Transit

Patients with SBS experience accelerated intestinal motility. Opioids or opioid receptor agonists are often used to slow intestinal transit by inhibiting intestinal smooth muscle contraction. This allows more time for fluid and nutrient absorption and an increased capacity of the small intestine. Opioid agonists may also contribute to an antidiarrheal effect through an inhibition of GI secretions.

Table 1. Commonly Prescribed Liquid Medications Containing Sugar Alcohol

Medication Oral Suspension	Sugar Alcohol Content
Acetaminophen (Tylenol) 160mg/5mL	Sorbitol
Acyclovir (Zovirax) 200mg/5mL	Sorbitol
Amantadine hydrochloride (Symmetrel) 50mg/5mL	Sorbitol
Amoxicillin / clavulanate (Augmentin) 200mg/28.5mg/5mL	Mannitol
Diphenoxylate and Atropine (Lomotil) 2.5mg/0.025mg/5mL	Sorbitol
Fer-In-Sol® (Ferrous sulfate) Liquid Iron Supplement	Sorbitol
Furosemide (Lasix) 10mg/mL	Sorbitol
Gabapentin (Neurontin) 250mg/5mL	Xylitol
Glycopyrrolate (Robinul) 1mg/5mL	Sorbitol
Guaifenesin (Mucinex) 100 mg/5mL	Sorbitol
Lacosamide (Vimpat) 10mg/mL	Sorbitol
Lansoprazole (Prevacid) 3mg/mL	Mannitol
Levetiracetam (Keppra) 100mg/mL	Maltitol
Loperamide (Imodium) 1mg/7.5mL	Glycerin
Magnesium Hydroxide (Milk of magnesia) 1200mg/15mL	Sorbitol
Magnesium Hydroxide (Concentrated milk of magnesia) 2400mg/10mL	Sorbitol
Metoclopramide (Reglan) 5mg/5mL	Sorbitol
Mycophenolate mofetil (CellCept) 200mg/mL	Sorbitol
Oseltamivir phosphate (Tamiflu) 6mg/mL	Sorbitol
Pyridostigmine bromide (Mestinon) 60mg/5mL	Sorbitol
Simethicone (Gas relief) 20mg/0.3mL	Maltitol
Sodium polystyrene sulfonate (Kionex) 15mg/60mL	Sorbitol
Valganciclovir (Valcyte) 50mg/mL	Mannitol
Valproic acid (Depakene) 250mg/5mL	Sorbitol

Loperamide in particular has been shown to not only slow gut transit, but also provide improved rectal function by increasing anal sphincter tone.³ Unlike its effect within the central nervous system (CNS), the bowel slowing effect of opioids is not impacted by the development of tolerance.⁴ Therefore, effective doses may remain constant for months to years.

Table 2 provides a list of antidiarrheal agents used to slow intestinal transit time in patients with SBS. Both loperamide and diphenoxylate are considered first-line antimotility agents, although loperamide is typically considered the preferred agent for initial therapy. If aggressive dosing of loperamide and/or diphenoxylate fails to achieve a desired response, it is reasonable to consider a more potent opioid narcotic. The advantages and disadvantages of each antimotility agent are provided in Table 2 and can be used as a guide for selecting the appropriate agent(s).

Tips for Use of Antidiarrheal Agents:

1. Check for *Clostridium difficile* prior to starting therapy, or when suspicion for infection arises (yes, even end jejunostomies and ileostomies can acquire C. diff infection).⁵
 - Antidiarrheal agents should be both scheduled and taken 30-60 minutes before meals/snacks to achieve maximum benefit.
 - Start with a single first-line agent, typically loperamide.
 - Dosage of loperamide should be escalated in a stepwise manner, allowing at least 2-3 days in the hospital setting while the patient is well monitored, and 3-5 days in the home setting after each dosage increase to assess response. Stop increasing dose if benefit is observed, adverse events occur, or the recommended maximum dosage is reached (see Table 2). Tolerance is typically limited by obstructive symptoms, so carefully monitor for the presence of nausea, vomiting, and abdominal pain or distention.
 - Advise patients to purchase/request generic loperamide in large bottle quantities (less costly). Avoid blister packs (sometimes difficult to open).

- If loperamide offers no benefit, or is not tolerated, switch to diphenoxylate/atropine.
- If loperamide provides partial (but suboptimal) improvement, add diphenoxylate/atropine and increase the dose in a stepwise manner as above.
- Consider use of systemic opioid narcotic agents if maximum recommended doses of the first-line agents fail.
- Start at a low dose (see Table 2) and advance in a stepwise manner as above.
- The use of opioid agents containing acetaminophen is considered by the FDA to have a lower abuse potential (C-III) when compared to the use of codeine or morphine as a single agent (C-II), which allows the ability to prescribe refills. But be cautious of the potential hepatotoxic effects of acetaminophen, especially when given long-term or at high doses. Patients should be instructed not to exceed 4g/day of acetaminophen or consume alcohol when using this drug.
- Consider stopping diphenoxylate and possibly stopping loperamide when switching to use of an opioid narcotic. It is daunting for patients to maintain this high pill count if stool output can be controlled with a stronger, single antidiarrheal agent.
- A bedtime dose (and sometimes a higher bedtime dose) may help minimize trips to the bathroom at night.
- Provide patients with guidelines for dosage titration as therapeutic response may vary with alterations in diet and/or changes in the course of their disease.
- Patients should be instructed to decrease or hold antimotility agents if they experience nausea, vomiting, or abdominal pain/cramping. They may also need to decrease the dose if they experience excessive CNS effects, such as sedation or mental status changes.

Medications Used to Reduce GI Secretions

Following extensive intestinal resection, gastric secretions are often increased for the first 6-12 months after surgery due to loss of feedback mechanisms from the resected bowel. The sheer volume of secretions then contributes to total fecal losses. Gastric hypersecretion will also result in the dumping of acidic contents into the proximal small bowel and can alter normal fat digestion through the denaturation of pancreatic enzymes and destabilization of bile acids. Treating gastric hypersecretion not only decreases the sheer volume of secretions, but also helps to restore the intestinal pH back to that which optimizes pancreatic enzyme and bile salt activity.

Table 3 provides a list of medications used to reduce GI secretions. Proton pump inhibitors (PPIs) are typically considered first-line agents and are highly effective early after intestinal resection. Histamine type 2 receptor (H_2) antagonists are considered second-line because of their decreased efficacy relative to PPIs in patients with high outputs.^{6,7} Even though the gastric acid hypersecretion response is typically transient following intestinal resection, the use of antisecretory agents is often continued long-term as attempts to stop the therapy can be associated with worsening stool output.⁶ It is still worthwhile to periodically try stopping therapy and measuring effect on stool volume—if it goes up without other changes, then the patient still needs it. The decision to continue antisecretory therapy long-term should be individualized based on observed benefit versus risk of adverse effects. Long-term use of PPIs has been associated with hypomagnesemia, osteoporosis, kidney disease, and vitamin B12 deficiency.⁸⁻¹⁰ However, the quality of evidence supporting these associations is consistently low to very low. The magnitude of absolute risk of developing an adverse effect with long-term use of a PPI for individual patients is in fact modest.¹¹ It is prudent to periodically reevaluate patients on long-term PPIs to ensure they are prescribed the lowest dose sufficient to manage their condition.

Clonidine and octreotide are alternative antisecretory agents that have been used in patients with SBS. Clonidine inhibits intestinal fluid secretion by stimulating alpha-adrenergic

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receptors on enteric neurons which can also result in reduced gastric and colonic motility. Although evidence supporting the use of clonidine in patients with SBS is limited, case reports are available that describe beneficial results.^{12,13} As it is an effective antihypertensive agent, use is often limited by reductions in blood pressure and development of orthostatic hypotension. Octreotide as a suppressive hormone is effective at reducing GI secretions and prolonging intestinal transit time. Its effectiveness can be limited by rapid development of tachyphylaxis; the physiologic effects of octreotide on GI hormones can be associated with adverse effects such as biliary stasis, cholelithiasis, liver dysfunction, and either hypoglycemia or hyperglycemia. Early use of octreotide following intestinal resection is often discouraged as it has been shown to reduce intestinal adaptation following resection in preclinical studies.^{14,15} Furthermore, use is limited by its high cost as well as the inconvenience and pain associated with subcutaneous injections three times daily. Octreotide is also available as a long-acting suspension for IM use every 4 weeks; however, it is costly and often denied by insurance.

Tips for Use of Antisecretory Agents:

- An antisecretory agent should be initiated immediately following extensive small bowel resection and maintained for at least 6 months.
- Use of a proton pump inhibitor (PPI) agent is typically preferred to a H₂ antagonist.
- Patients with SBS often require doses that are higher than those used for treatment of reflux disease due to malabsorption.
- H₂ antagonists, if effective, offer the advantage of compatibility with the PN formulation.
- The decision to continue PPI/H₂ antagonist therapy long-term should be individualized based on observed benefit versus risk of developing adverse effects.
- Monitor for acid rebound if PPI/H₂ antagonist therapy is discontinued, which

can manifest as a significant increase in stool volume.

- Octreotide may be considered when other measures fail to stabilize fluid and electrolyte balance (see limitations in Table 3). Its use should periodically be reevaluated for efficacy.
- Clonidine may offer an option for controlling diarrhea, but is rarely used in clinical practice due to its blood pressure lowering effect (see limitations in Table 3).

Other Medications Used in SBS (but maybe shouldn't be)

Patients with SBS may find themselves on a myriad of medications that offer little to no benefit that will not only increase pill burden, but can potentially worsen symptoms and nutrient losses. For this reason, medications used to treat SBS should be introduced in a stepwise manner that allows adequate time for assessment of efficacy/safety, and time for necessary dosage adjustment, before adding another agent. Medications that do not demonstrate a measurable clinical effect should be stopped. Agents with no proven benefit in the management of SBS include glutamine and probiotics. Although potential for harm is low, they are typically not recommended because they increase pill burden and create an unnecessary expense (again, with no benefit). Other agents with limited therapeutic benefit for treatment of SBS (and potential for harm if not used appropriately) include bile acid binders and pancreatic enzymes.

Bile acid binders, including cholestyramine, colestipol, and colesevelam, are specifically used for treatment of choleric diarrhea. This type of secretory diarrhea occurs in patients with limited ileal resections (<100 cm) and a colon-incontinuity. When bile salts enter the colon, they are metabolized by bacteria to form lithocholic acid, which is caustic to the colonic mucosa and thus stimulates water secretion. It is important to realize that choleric diarrhea is uncommon in patients with intestinal failure due to SBS as the length of ileal resection is typically > 100 cm. In the setting of extensive small bowel resections, bile acid binders can theoretically exacerbate diarrhea

Table 2. Antimotility Agents Used in Patients with SBS

Medication	Preparations	Adult Dose	Advantages	Limitations
Loperamide (Imodium®) Loperamide hydrochloride (Imodium Instants)	Tablets, 2 mg Capsules, 2 mg Oral liquid Available from UK or Canada on-line-dissolve instantly on your tongue (do not need water to take).	2-8 mg po QID	<ul style="list-style-type: none"> • Low cost • Does not cross blood-brain barrier • May improve rectal function • Usual maximum recommended dose is 16 mg/d, but able to push dose up to 32 mg/d in patients with SBS⁴ • Low risk for abuse • OTC availability 	<ul style="list-style-type: none"> • Low potency • Poorly absorbed and undergoes enterohepatic circulation; requires high doses to achieve desired effect in patients with significant ileal resection • Oral liquids may contain sugar alcohol • Dose limiting side effect is typically nausea
Diphenoxylate with atropine sulfate 0.025 mg per 2.5 mg dose (Lomotil®) Difenoxin with atropine sulfate 0.025 mg per 1mg dose (Motofen®)	Liquid, 2.5 mg/5 mL Tablets, 2.5 mg Tablet, 1 mg	2.5-5 mg po QID 1-2 mg po QID	<ul style="list-style-type: none"> • Low risk for abuse due to atropine component • Schedule IV-V • Able to prescribe refills 	<ul style="list-style-type: none"> • Low potency • Oral liquids may contain sugar alcohol • Tolerance limited by CNS and anticholinergic effects, such as dry mouth • Anticholinergic effects may be poorly tolerated in the elderly
Codeine phosphate (with acetaminophen 300 mg per tablet)	Tablets, 15, 30, 60 mg	15-60 mg po QID	<ul style="list-style-type: none"> • High potency • Lower risk for abuse than codeine/morphine provided as single agent • Able to prescribe refills 	<ul style="list-style-type: none"> • CNS effects • Hepatotoxicity related to high doses of acetaminophen • Risk for abuse (Schedule III)
Codeine sulfate	Tablets, 15, 30, 60 mg	15-60 mg po QID	<ul style="list-style-type: none"> • High potency 	<ul style="list-style-type: none"> • CNS effects • Risk for abuse (Schedule II) • No refills allowed
Tincture of Opium	Anhydrous morphine equivalent, 10 mg/mL	0.3-2 mL po QID *Avoid ordering in drops due to various dropper sizes	<ul style="list-style-type: none"> • High potency 	<ul style="list-style-type: none"> • CNS effects • Risk for abuse (Schedule II) • No refills allowed • High cost and may not be covered by insurance • Not readily available at many retail pharmacies • Unpleasant taste
Morphine sulfate	Oral solution, 20 mg/mL	0.1-0.5 mL po QID	<ul style="list-style-type: none"> • High potency 	<ul style="list-style-type: none"> • CNS effects • Risk for abuse (Schedule II) • No refills allowed

OTC, over the counter; po, by mouth; QID, 4 times per day

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Table 3. Medications Used to Reduce GI Secretions in Patients with SBS

Medication	Preparations	Adult Dose	Advantages	Limitations	
Proton Pump Inhibitor	Lansoprazole Oral capsule, delayed release Oral tablet disintegrating Oral powder for suspension	15-30 mg po BID	Highly effective at reducing gastric acid secretion	Not compatible with PN Long-term use has been associated with several adverse effects, but not well supported by evidence showing a causal relationship	
	Pantoprazole Oral tablet, enteric coated Injectable	20-40 mg po/IV BID	Parenteral dose can be administered via slow IV push	Acid rebound when medication stopped after long-term use This may be minimized by tapering dose or use of an H2 receptor antagonist	
	Omeprazole Oral capsule, delayed release Oral tablet, delayed release Oral powder for suspension	20-40 mg po BID	OTC availability for oral route		
	Esomeprazole Oral capsule, delayed release Oral tablet, delayed release Injectable	20-40 mg po/IV BID			
	Rabeprazole Oral tablet, enteric coated	20 mg po BID			
	Dexlansoprazole Oral capsule, delayed release	30-60 mg po BID			
	Histamine Receptor Antagonist	Famotidine Oral tablet Oral powder for suspension Injectable	20-40 mg po/IV BID	Parenteral dose can be added to PN formulation	Not as effective as PPI Requires reduced dose in patients with renal impairment
		Ranitidine Oral tablet Oral capsule Oral powder for suspension Injectable	150-300 mg po/IV BID	Parenteral dose can be administered via slow IV push	
		Cimetidine Oral tablet Oral solution Injectable	200-400 mg po/IV QID	Low incidence of side effects OTC availability for oral route	
		Nizatidine Oral tablet Oral capsule Oral solution	150-300 mg po BID		
Clonidine		Oral tablet	0.1-0.3 mg po BID	Availability of transdermal route	Lowers blood pressure and can cause orthostatic hypotension
		Transdermal patch	0.1-0.3 mg/24h patch every 7 days		
Octreotide		Injectable	100-250 mcg SC TID	Highly effective at reducing GI secretions	High cost Development of tachyphylaxis Side effects include biliary stasis, liver dysfunction, cholelithiasis, hypoglycemia, hyperglycemia Impairs intestinal adaptation Patients report significant injection discomfort
		Intramuscular Suspension (LAR Depot)	20 mg IM every 4 weeks		

po, by mouth; BID, twice daily; QID, 4 times per day

and fat malabsorption by binding up the few bile acids that are present. Another limitation to their use is that they can interfere with absorption of essentially any medication taken by mouth.

Tips for Use of Bile Acid Binders:

- Indicated for treatment of choleric diarrhea in patients with limited ileal resection (< 100cm) and colon-in-continuity.
- Do not use in patients with a jejunostomy or ileostomy.
- It is recommended that all other oral medications be administered at least 1 hour before or 4 hours after taking a bile acid binder.
- Monitor for development of worsening diarrhea, fat-soluble vitamin deficiencies, and impaired absorption of concomitant medications.

Pancreatic enzyme replacement therapy, a concentrated porcine derived formulation that contains lipase, amylase, and protease, has been considered for treatment of fat malabsorption when pancreatic insufficiency is suspected. It is important to recognize that pancreatic exocrine secretion is largely intact in patients with SBS. Pancreatic enzymes may not function normally due to gastric acid hypersecretion or in the setting of altered GI anatomy (e.g., roux en y) that results in inadequate mixing of pancreatic enzymes with nutrients.⁴ In practice, pancreatic enzyme replacement therapy is unlikely to benefit patients with SBS unless antisecretory agents fail to manage gastric acid hypersecretion (leading to pancreatic insufficiency) or if underlying pancreatic exocrine insufficiency exists.

Tips for Use of Pancreatic Enzyme Replacement:

- Note: pancreatic fecal elastase should not be used in SBS patients to assess pancreatic insufficiency as the high stool volume dilutes the elastase giving a factitious low result.
- Empiric use of pancreatic enzyme replacement therapy may be considered

for treatment of fat malabsorption when pancreatic insufficiency is suspected, such as:

- Chronic pancreatitis
- Pancreatic resection
- Roux-en-Y anastomosis or other similar altered GI anatomy that creates a mismatch between pancreatic enzymes and nutrients
- Starting dose is 500 lipase units/kg per meal and should be titrated as needed based on clinical symptoms, degree of steatorrhea, and fat content of the diet.

Adjunctive Therapies

Adjunctive agents that offer targeted treatment of an underlying condition include sodium bicarbonate for metabolic acidosis caused by high losses of bicarbonate (Table 4) and antibiotics for treatment of small intestinal bacterial overgrowth (SIBO) (Table 5). Several factors increase the risk of SIBO in patients with SBS, including altered GI anatomy and use of anti-motility and acid-suppressing agents that disrupt normal bacterial flora and permit overgrowth. Symptoms include diarrhea, abdominal pain, bloating, gas, and foul-smelling stool output. When treating this condition, repeated courses of antibiotic therapy are often necessary. Rotation of antibiotic agents and inclusion of antibiotic-free intervals may help decrease risk of developing resistant bacterial strains and improve overall long-term success in managing SIBO. If symptoms persist despite antibiotic therapy, consider reducing dosages of anti-motility and acid-suppressing medications.

Intestinotrophic Agents

Glucagon-like peptide-2 (GLP-2) Analog

Intestinal growth factor therapy offers a more targeted pharmacologic approach in the treatment of SBS. Glucagon-like peptide-2 (GLP-2) is an intestinal hormone that plays an important role in maintaining the structure and function of the intestine to facilitate absorption. GLP-2 is secreted by enteroendocrine L cells of the terminal ileum and proximal colon in response to luminal nutrients. Patients with an extensive intestinal resection are

Table 4. Medications/Agents Used to Treat Metabolic Acidosis

Medication/Agent	Preparations	Dosage
Sodium Bicarbonate Tablet	325 mg/650 mg (3.9 & 7.7 mEq of sodium and bicarbonate)	<ul style="list-style-type: none"> • Take 325-650 mg po TID • Titrate dose as needed • Take after meals
Sodium Bicarbonate Powder (kitchen "Baking soda")	Baking soda ½ teaspoon (26.8 mEq of sodium and bicarbonate)	<ul style="list-style-type: none"> • Titrate dose as needed • Take after meals
Sodium Citrate and Citric Acid	Bictra solution Cytra-2 solution Oracit solution Shohl's solution Generic solution	<ul style="list-style-type: none"> • Each solution contains 1 mEq of sodium and bicarbonate per 1 mL • Take 10-30 mL (diluted in 30-90 mL water) po TID • Take after meals

therefore thought to have limited GLP-2 secretion in response to a meal. Teduglutide is a recombinant human GLP-2 analog approved for use in adults and children 1 year of age and older with SBS who are dependent on IV fluid or parenteral nutrition. Patients enrolled in the STEPS trial were dependent on PN/IV at least 3 days per week, on a stable medical regimen, and at least 1 year out from their last intestinal resection.¹⁷ Sixty-three percent of patients receiving teduglutide achieved at least a 20% reduction in PN/IV volume requirements at week 20 and maintained that response at week 24, compared to 30% in the placebo group. At week 24, the PN/IV volume was reduced by a mean of 4.4 L/wk compared to baseline vs 2.3 L/wk in the placebo group. The greatest reductions in intravenous support were observed in those with higher baseline PN/IV volume requirements, whereas those with lower baseline PN/IV volume requirements and a colon-in-continuity were more likely to achieve enteral autonomy. Sustained efficacy has been demonstrated with long-term use of teduglutide.¹⁸

The most common side effects of teduglutide are abdominal pain, nausea, vomiting, abdominal distension, fluid overload, swelling/blockage of a stoma, and injection site reactions. As a growth factor, it has the potential risk for accelerated neoplastic and colon polyp growth although this has not been identified in post-marketing studies to date. In addition, biliary disease (cholecystitis, cholangitis, cholelithiasis) and pancreatitis have

been reported in the original clinical trials. Due to these potential risks, the FDA requires a risk evaluation and mitigation strategy (REMS) program that involves documentation that prescribers have been trained and are aware of these risks and that patients are informed. Teduglutide is an expensive medication that requires prior authorization to initiate therapy and renewal of authorization every 3-12 months, depending on the insurance provider. Patients may be required to apply for financial assistance programs to assist with high co-pay coverage. Insurance providers look for documentation that patients benefit from therapy (i.e., achieve at least a 20% reduction in PN/IV volume requirements) and have not developed complications before authorizing renewal of therapy.

Tips for Use of Teduglutide:

- Patients should meet all the following criteria before using Teduglutide:
 - Diagnosed with SBS.
 - Dependent on PN/IV therapy on a stable regimen.
 - Able to tolerate an oral diet. If patients are not eating and drinking, they are less likely to achieve benefit from the medication.

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- No history of any cancer within the past 5 years, particularly GI cancers.
- No active mucosal disease, including active Crohn's disease or strictures.
- Not pregnant or seeking to become pregnant.
- Already optimized on diet/hydration therapy, antidiarrheal agents, and antisecretory agents.
- Able to reliably adhere to the prescribed therapy and the necessary monitoring.
- A colonoscopy with removal of polyps should be done within 6 months prior to starting teduglutide, repeated at the end of 1 year of treatment, and subsequently done at least every 5 years.
- Teduglutide dose is 0.05 mg/kg subcutaneously once daily. Reduce dose by 50% for estimated glomerular filtration rate (eGFR) < 60 due to extensive renal excretion and prolonged elimination half-life seen in subjects with renal impairment.¹⁹ This can be accomplished by reducing the dose to 0.025 mg/kg daily or 0.05 mg/kg every other day.
- Teduglutide is provided as a kit that provides 30 vials. Each vial provides a

maximum dose of 3.8 mg. Therefore, when the daily dose exceeds 3.8 mg (i.e., for patients weighing >76 kg) the patient will require 2 kits per month.

- Close monitoring of nutrition and hydration status is required during the initial days to weeks of therapy to determine appropriate PN/IV weaning. Monitor urine output, weight, blood urea nitrogen (BUN), serum creatinine, and serum electrolytes/minerals weekly upon initiation of teduglutide. Frequency of monitoring can decrease after the first month of therapy, if stable. Weekly phone calls and routine clinic follow-up visits are required to ensure safe and appropriate use of teduglutide. More frequent follow-up may be required in individuals with cardiac comorbidities. Consider the following PN/IV weaning strategies:
 - Decrease overall parenteral fluid intake by increments of 10-20% if urine output exceeds baseline by 10-20%. Maintain a target urine output of 1-2 L daily.
 - Reduce parenteral calorie intake by increments of 10-20% if body weight exceeds target weight.
 - Reduce parenteral electrolyte/mineral intake and transition to oral supplementation as appropriate, based on laboratory monitoring.

Table 5. Antibiotics Used to Treat Intestinal Bacterial Overgrowth¹⁶

Medication	Dosage (for 7-14 days)	Efficacy
Metronidazole	250 mg po TID	43%-87%
Ciprofloxacin	500 mg po BID	43%-100%
Rifaximin	550 mg po TID	61%-78%
Amoxicillin-clavulanic acid	875 mg po BID	50%
Doxycycline	100 mg po BID	Not tested
Neomycin	500 mg po BID	33%-55%
Tetracycline	250 - 500 mg po QID	87.5%
Cephalexin	250 mg po QID	Not tested
Trimethoprim-sulfamethoxazole	1 double-strength tablet po BID	95%

- Incorporate oral multivitamin and mineral supplementation when PN frequency is less than 7 days per week.
- To monitor for biliary and pancreatic disease, check bilirubin, alkaline phosphatase, lipase, and amylase at baseline (within 6 months prior to starting teduglutide) and every 6 months.
- Monitor for increased absorption of oral medications, especially those medications with a narrow therapeutic index, by assessing drug levels (if available) and/or clinical response. Patients are at risk of drug toxicity if reductions in oral medication dosages are not taken, as appropriate. This often requires communication with

Table 6. Resources for Clinicians

Website Just for Clinicians to Get Answers About SBS

- **SBSCurbside.org** is a safe space (at no cost) for practicing clinicians to get answers to complex questions about adult patients with Short Bowel Syndrome (SBS).

➤ **SBSCurbside.org**

UVA Health GI Nutrition Site - ginutrition.virginia.edu

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the patient's primary care provider upon initiation of teduglutide.

Other GLP-2 analogs currently under investigation include glepaglutide and apraglutide. They have a longer elimination half-life, when compared to teduglutide, and offer the potential advantage of once weekly dosing. Neither are FDA approved as of yet.

Under Investigation

GLP-1 Analog

Another medication currently under investigation for treatment of SBS is vurolenatide. It is a long-acting GLP-1 analog that exhibits properties distinctly different than GLP-2. Like GLP-2, GLP-1 is secreted by enteroendocrine L cells of the terminal ileum and proximal colon in response to luminal nutrients and patients with extensive intestinal resection are thought to have limited GLP-1 secretion. The function of GLP-1 is to inhibit gastric emptying and slow intestinal motility and is thought to help mediate the so-called ileal break.²⁰ These properties may help improve nutrient absorption and decrease stool output when used in patients with SBS and offer another targeted treatment option.²¹ It is not a growth factor and therefore does not carry the risk of accelerating growth of abnormal cells, and as such, can be considered in those with underlying gastrointestinal cancers. There are currently several GLP-1 analogs approved for the treatment of type 2 diabetes mellitus. In addition to the GI effects of GLP-1, it plays an important role in glucose homeostasis by stimulating insulin synthesis and

insulin secretion in response to a meal. Its use can be associated with reduced food intake by its effect on promoting satiety. For those who may want to consider using an existing GLP-1 analog for treatment of SBS (not as a study participant), it is not likely to be authorized by insurance at this time.

CONCLUSION

Patients with SBS can experience debilitating diarrhea that can negatively impact health outcomes and quality of life. The medical management of diarrhea is challenging and requires a thoughtful, stepwise approach. Because diarrhea associated with SBS is due to multiple etiologies, and the patient population is heterogeneous, multiple medications may be required and an individualized approach is necessary to optimize the therapy plan. Remember, always consider the total pill burden in these patients. For more resources, see Table 6. ■

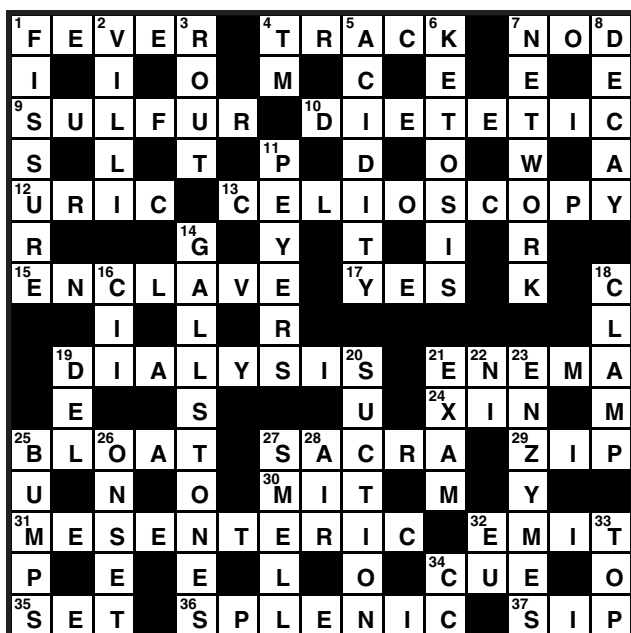
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Answers to this month's crossword puzzle:



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