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Short Bowel Syndrome in Adults – Part 1

Physiological Alterations and Clinical Consequences



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Short bowel syndrome (SBS) is a malabsorptive condition resulting most commonly from extensive intestinal resection. It is associated with significant morbidity and mortality, a reduced quality of life and high health care costs. The management of patients with SBS is complex and requires a multidisciplinary approach including dietary, fluid and pharmacological management, co-morbid disease management and, occasionally, surgery. An understanding of the physiological alterations that occur in SBS is useful to understand the treatments employed. In Part 1 of this five-part series on SBS, we address the physiological alterations that occur, the clinical consequences of these changes including potential complications, and the adaptation process that the intestine undergoes in order to improve the body's ability to digest and absorb nutrients and fluid.

INTRODUCTION

Short bowel syndrome (SBS) is a disabling malabsorptive condition associated with a high frequency of complications and high utilization of healthcare resources. SBS generally does not become clinically apparent until about three-quarters of the small bowel (SB) have been removed. Because of the wide range in SB length and its capacity to compensate for bowel resection, the definition of SBS should not

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be based solely on the length of remaining bowel. Experts in intestinal failure have, instead, proposed defining SBS as a condition resulting from surgical resection, congenital defect, or disease-associated loss of absorption, characterized by the inability to maintain protein-energy, fluid, electrolyte, or micronutrient balances when on a normal diet.¹ Nevertheless, the presence of < 200 cm of remaining SB is often used in order to facilitate a clinical diagnosis.

Etiology and Epidemiology

In adults, the more common causes of SBS include multiple resections for Crohn's disease, massive resections due to catastrophic mesenteric vascular events, and malignancies (**Table 1**).^{2,3} Postoperative

vascular and obstructive catastrophes requiring massive intestinal resection seem to be increasing in incidence and in one recent series was the most common cause of SBS in adults.⁴ Notably, the operations leading to SBS after an open surgery appear to be different than after a laparoscopic approach – gastric bypass and cholecystectomy being most frequent with laparoscopy and colectomy, hysterectomy and appendectomy being the most common with the open approach in one series.⁵ The major mechanisms responsible after open surgery and laparoscopy appear to be adhesions and volvulus, respectively. While advances in the treatment of Crohn's disease may lead to a reduction in SBS, these improvements have not translated into a reduction in the need for home parenteral nutrition (PN).⁶

The incidence and prevalence of SBS are unknown because there are no reliable databases. Estimates are based on information from home PN registries, for which SBS is generally the most common indication. Two recent studies limited to SBS patients reported the majority of patients being female and > 50 years of age.^{2,3} The multifactorial etiology, uncertainty regarding intestinal length and varying definitions of SBS contribute to the difficulty of comparing reports. In the U.S., the annual prevalence of home PN has been estimated at approximately 120 per million, of whom about 25% have SBS; this amounted to about 10,000 adults in 1992.⁷ These numbers do not reflect patients with SBS who did not survive, were able to be weaned from PN during the index hospitalization, or were able to be successfully weaned from home PN and, therefore, likely underestimate the prevalence of SBS.

Relevant Anatomy and Physiology

Three bowel anatomies may occur in SBS and are generally described in terms of location of the anastomosis after resection:

- Jejunocolic
- Jejunoleocolonic
- End-jejunosomy

The clinical manifestations and outcome of SBS vary depending upon the remaining bowel anatomy and its residual function. Consequently, an appreciation of the bowel anatomies seen in SBS along with basic gastrointestinal physiological considerations is helpful to better understand the prognosis and guide patient management.

Table 1. Causes of Short Bowel Syndrome in Adults

- Mesenteric ischemia
- Postoperative complications
- Crohn's disease
- Trauma
- Neoplasms
- Radiation enteritis

Small Bowel

The proximal 100 to 150 cm of the jejunum is the primary site of carbohydrate, protein and water-soluble vitamin absorption.⁸ Fat absorption may extend over a larger length of SB if more fat is ingested. In a healthy adult, about 4 L of intestinal secretions (0.5 L saliva, 2 L gastric acid and 1.5 L pancreaticobiliary secretions) are produced in response to the food and drink consumed each day. Water absorption is a passive process resulting from the active transport of nutrients and electrolytes. Sodium transport creates an electrochemical gradient that drives the uptake of nutrients across the intestinal epithelium. Because the junctions between jejunal epithelial cells are considerable compared to other areas of the bowel, a rapid flux of fluids and nutrients occurs resulting in inefficient fluid absorption and iso-osmolar jejunal contents. Sodium absorption in the jejunum occurs against a concentration gradient, is dependent upon water fluxes and is coupled to the absorption of glucose.⁹ These factors become particularly important in the SBS patient who only has jejunum remaining.

In contrast to the jejunum, the ileum has tighter intercellular junctions resulting in less water and sodium flux.⁹ In the ileum, active transport of sodium chloride allows for significant fluid reabsorption and the ability to concentrate its contents. The distal ileum is also the primary site of carrier-mediated bile salt and B12 absorption. The ileum and proximal colon produce several hormones including glucagon-like peptides 1 and 2 and peptide YY that have transit/motility modulating (e.g., jejunal and ileal brake phenomena) and intestinotrophic properties.¹⁰ The benefit of the ileocecal valve in slowing transit and preventing reflux

Table 2. Factors Affecting Intestinal Adaptation

- Hyperphagia
- Remaining bowel anatomy
 - Colon present
 - Ileum present
- Luminal factors
 - Whole foods
 - Nutrients (short chain fatty acids, glutamine)
 - Pancreaticobiliary secretions
- Hormones/Growth factors
 - Trophic (GH, GLP-2, IGF-1, EGF, TGF-)
 - Antimotility (GLP-2, GLP-1, PYY)

GH=growth hormone; GLP-2=glucagon-like peptide-2; IGF-1=insulin-like growth factor-1; TGF- =transforming growth factor- ; GLP-1=glucagon-like peptide-1; PYY=peptide YY

of colonic contents into the SB remains controversial as the benefit may instead reflect the retention of a significant length of terminal ileum.¹¹

Colon

The colon has the slowest transit, tightest intercellular junctions and greatest efficiency of water and sodium absorption. In health, generally 1 to 1.5 L/day of fluid enters the colon, where all except about 150 mL are reabsorbed. In SBS, the colon plays a vital role in fluid and electrolyte balance given the capacity to accommodate and absorb up to 6 L daily.¹² Complete loss of the colon often leads to fluid and electrolyte disturbances. In addition to the resorptive capabilities of the colon, bacterial fermentation of malabsorbed carbohydrates to short chain fatty acids (SCFA) with subsequent absorption in the colon provides an additional 10-15% of energy needs or up to 1000 kcal daily.¹³ Thus, the colon becomes an important organ for fluid and electrolyte absorption and for energy salvage in SBS.

Stomach and Pancreaticobiliary

Massive enterectomy is associated with transient gastric hypergastrinemia and hypersecretion that may last up to 12 months postoperatively.¹⁴ This may occur as a result of the loss of inhibitory hormones produced in the proximal gut (e.g., gastric inhibitory peptide and vasoactive intestinal peptide). This increases the volume and lowers the pH of secretions entering the proximal SB potentially aggravating fluid losses and leading to peptic complications and impairment in the function of digestive enzymes, further contributing to fat maldigestion. The use of antisecretory medications including proton pump inhibitors or histamine 2 receptor antagonists reduces gastric secretions, prevents peptic complications and may lead to improved digestion and absorption.¹⁵ Although some SBS patients with extensive proximal SB resections may lose sites of secretin and cholecystokinin-pancreozymin (CCK-PZ) synthesis leading to diminished pancreaticobiliary secretions, the majority have extensive distal SB resections and demonstrate normal secretion of these substances.¹⁶ Resection of > 100 cm of terminal ileum decreases the reabsorption of bile acids into the enterohepatic circulation, resulting in a reduction in the bile salt pool, eventually exceeding the ability of the liver to synthesize adequate replacement.¹⁷ This bile acid deficiency results in impaired micelle formation and fat digestion, and manifests clinically as steatorrhea and fat soluble vitamin deficiencies. In addition, the entry of caustic bile acids into the colon causes net fluid secretion into the colon and accelerated colonic motility further increasing stool output.

Intestinal Adaptation

Intestinal adaptation is the process following intestinal resection whereby the remaining bowel undergoes macroscopic and microscopic changes in response to a variety of internal and external stimuli in order to increase its absorptive ability (**Table 2**).¹⁸ Enteral nutrients are of particular importance in promoting an adaptive response, presumably by stimulating pancreaticobiliary, gastrointestinal and gut hormone secretions.¹⁹ Adaptation is highly variable and usually occurs during the first two years following intestinal resection in adults. Both structural and functional adaptive changes can occur depending upon the extent and site of the intestine removed and the nutrient components of the diet (**Table 3**). The ileum is capable

(continued on page 34)

(continued from page 32)

of both morphologic and functional adaptation. While those with a jejunocolic anastomosis demonstrate functional SB adaptation, those with an end-jejunostomy show little to no adaptation. The colon also appears to undergo adaptive changes after massive intestinal resection.

Determining Remaining Bowel Anatomy and its Influence on Outcome

The large range of SB length, from about 300 to 800 cm in adults, underscores the importance of determining the SB length and segment/s remaining following any resection. The length and region of the SB remaining and the presence of even a part of the colon are important factors affecting the outcome of the patient with SBS. Establishing an accurate estimation of bowel length is often difficult as operative reports frequently record the amount of bowel removed rather than the amount remaining. SB length may also be estimated on a barium contrast SB series, which may also be useful to delineate other structural features such as the presence of bowel dilatation. Recently, computed tomography (CT) enteroclysis with three-dimensional reconstruction and calculation of SB length has been shown to provide similar information; however, this technique has not yet been adopted into clinical radiology practices.²⁰ Despite the importance of the remaining SB length in determining the clinical outcome in SBS patients,²¹ the ultimate determining factor of SBS severity and eventual outcome is the critical mass of functional intestinal absorptive epithelia remaining.

Because of differences in their adaptive ability, those with an ileal remnant have a better prognosis than those with only a jejunal remnant. In adults, terminal ileal resections > 60 cm generally require vitamin B12 replacement, while resections > 100 cm lead to disruption in the enterohepatic circulation resulting in bile salt deficiency and fat malabsorption.²² Extensive ileal resection also results in accelerated gastrointestinal transit due, in part, to the reduction in gut transit modifying hormones. The presence of the colon has been shown to be beneficial in SBS given its ability to absorb water, electrolytes and fatty acids, slow intestinal transit and stimulate intestinal adaptation. Indeed, those SBS patients with an end-jejunostomy are generally the most difficult to manage and are most likely to require permanent parenteral support.²³

Table 3. Adaptation-Related Intestinal Structural and Functional Changes

<ul style="list-style-type: none"> • Structural
<ul style="list-style-type: none"> ○ Remnant bowel dilation and elongation ○ Increase in intestinal wet weight, protein and DNA content ○ Villus lengthening and expansion in microvilli ○ Increase in crypt cell depth and enterocyte number ○ Increases in gut muscle thickness, circumference and length
<ul style="list-style-type: none"> • Functional
<ul style="list-style-type: none"> ○ Modified brush border membrane enzyme activity, fluidity and permeability ○ Up- or down-regulation of carrier-mediated transport ○ Slowing in the rate of transit allowing increased time for absorption to occur
<ul style="list-style-type: none"> • ? Gut microbiota, motor activity and barrier and immune functions

Complications

A variety of disorders may complicate the course of the patient with SBS. These complications may result from the underlying disease, altered bowel anatomy and physiology, or treatment modalities including PN and the associated central venous catheter (**Table 4**).^{24,25} Complications related to the altered bowel anatomy will be discussed below. Fluid, electrolyte and micronutrient complications will be discussed in future articles in this series.

Oxalate Nephropathy

Chronic kidney disease and calcium oxalate nephrolithiasis may complicate the course of SBS in those with a colon segment, occasionally leading to irreversible renal failure.²⁶ Normally, dietary oxalate is bound to intraluminal calcium and excreted in the stool. In SBS patients with fat malabsorption and a colon-in-continuity, calcium preferentially binds to unabsorbed fatty acids in the lumen leaving oxalate free to pass into the colon to be absorbed into the bloodstream and then filtered by the kidney. A reduction in bacterial breakdown of oxalate due to decreased *Oxalobacter formigenes* in the colon of SBS patients also contributes.²⁷ Furthermore, citrate usually prevents nucleation, the first step in renal stone formation; hypocitraturia is common in patients with malabsorption and is thought to be due to bicarbonate wasting in the stool. In the kidney, oxalate binds to calcium resulting in oxalate nephrolithiasis and risk of progressive obstructive nephropathy. To reduce the risk of this complication, correction of dehydration is of the utmost importance while use of calcium citrate supplementation, along with restriction of fat and oxalate-containing foods are advised. The clinical utility of *Oxalobacter formigenes* supplementation to increase oxalate destruction or cholestyramine to bind oxalate remains to be established. Urate nephrolithiasis is also relatively common in SBS patients with an ostomy and is related to chronic dehydration.

Metabolic Bone Disease

Osteomalacia, osteoporosis, osteopenia and secondary hyperparathyroidism may occur in SBS patients as a consequence of the PN, altered bowel anatomy causing malabsorption of macro- and micronutrients (especially vitamin D), medication use (e.g., corticosteroid use for treatment of an underlying disease) and other underlying patient factors such as gender, ethnicity, body size, and insufficient sun exposure.²⁶ An assessment of bone density should be undertaken in all SBS patients and repeated every 2-3 years; annually in the patient with osteoporosis. The identification of significant bone disease should lead to an assessment of calcium, phosphorus, magnesium, vitamin D (25-hydroxy vitamin D), and parathyroid hormone status and for the presence of metabolic acidosis. In patients receiving PN, an assessment of the PN formula and additives is warranted. Conventional management includes exercise, sunlight exposure, minimizing alcohol use

Table 4. Short Bowel Syndrome-Associated Complications

- Central venous catheter-related
 - Infection
 - Occlusion
 - Breakage
 - Central vein thrombosis
- Parenteral nutrition-related
 - Hepatic
 - Biliary
- Bowel anatomy-related
 - 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

and eliminating tobacco use. Calcium, magnesium and vitamin D replacement and correction of metabolic acidosis should be implemented as needed. Given the very poor bioavailability of bisphosphonates, intravenous agents are preferred in SBS.²⁸ Collaboration with an endocrinologist is encouraged.

Liver Dysfunction and Cholelithiasis

Hepatobiliary complications including steatosis, cholestasis and cholelithiasis occur commonly in

SBS patients and result both from contributions of the altered bowel anatomy and the PN required for support. For this reason, ‘intestinal failure-associated liver disease’ is the preferred term to describe these complications. Steatosis is more commonly seen in adults while cholestasis occurs more often in children; both can progress to end-stage liver disease. The mechanisms underlying the development of steatosis and cholestasis differ although overlap occurs.²⁹ The provision of > 1 g/kg/day of parenteral lipids and the presence of chronic cholestasis have been associated with the development of complicated liver disease.³⁰ Particularly in those with rapid worsening of liver tests, sepsis should be considered as should medications, supplements, other toxins, lack of enteral stimulation, altered bile acid metabolism, SB bacterial overgrowth, biliary obstruction, and co-existing chronic liver disease including viral, autoimmune and metabolic disorders. The composition of the PN should also be considered as excesses (energy content, dextrose, fat emulsion, methionine), deficiencies (choline, essential fatty acids, carnitine, taurine, glutathione) and duration of infusion (continuous versus cyclical) may contribute. The type of lipid emulsion (e.g., soybean-based [Intralipid, Fresenius Kabi or Liposyn, Abbott Laboratories], n-3 fish oil-based [Omegaven, Fresenius Kabi], combination of soybean, medium-chain triglycerides, olive oil and fish oil [SMOF, Fresenius Kabi]) may also be important. In the U.S., only the soybean-based lipid emulsion is currently available except by approval under a Food and Drug Administration investigational new drug application. Correction of an identified cause or alteration in PN or lipid composition often leads to an improvement in the liver tests. The clinical utility of ursodeoxycholic acid appears limited in this setting.²⁹ In those who continue to progress, consideration of intestinal transplantation (with or without liver transplantation) should be given.

Cholelithiasis, usually cholesterol stones, occurs in up to 40% of adults with SBS; the formation of biliary sludge is even more common.³¹ The predominant factor contributing to stone development is the reduced concentration of bile acids due to the altered enterohepatic circulation leading to lithogenic bile. Gallbladder stasis, related to reduced cholecystokinin secretion in those with limited enteral intake, also contributes. Complications of cholelithiasis appear to occur more commonly among SBS patients than the general population, hence prophylactic cholecystectomy

has been recommended in the SBS patient when abdominal surgery is being undertaken for other reasons.^{31,32}

Small Bowel Bacterial Overgrowth

Small bowel bacterial overgrowth (SBBO) appears to be common in SBS patients.³³ The presence of bowel dilatation and altered transit frequently seen in SBS, together with medications commonly used in these patients (e.g., acid suppressants and antimotility agents) is thought to facilitate the development of SBBO. In a recent retrospective pediatric study, SBBO was strongly and independently associated with PN use but was not associated with age, gender, underlying diagnosis, presence of ileocecal valve or antacid use.³⁴ Although SBBO may have potential benefit in terms of increasing energy extraction from malabsorbed carbohydrates, excess bacteria in the SB can induce inflammatory and atrophic changes in the gut impairing absorption, deconjugate bile acids resulting in fat maldigestion, consume vitamin B12 leading to deficiency, cause a number of gas-related symptoms and aggravate diarrhea leading to a reduction in oral intake, and potentially increase the risk of IFALD, central venous catheter infections and chronic gastrointestinal bleeding.

A number of limitations of the tests used to diagnose SBBO exist (i.e., most commonly SB aspirate with quantitative bacterial culture and hydrogen breath testing), which makes securing the diagnosis of SBBO in SBS challenging.³³ This is particularly so with breath testing, due to rapid transit in the shortened bowel making it difficult to differentiate SB versus colonic hydrogen production. As a consequence, empiric antimicrobial treatment is often provided. This may be reasonable in the setting of SBS given the high likelihood of SBBO; however, the goals of treatment need to be clearly identified given the nonspecific nature of the symptoms present and the potential adverse effects and expense involved with antimicrobial use. A variety of oral broad-spectrum antibiotics can be used with success based on improvement in symptoms, reduction in stool output and/or weight gain.³⁵ The continuous use of low-dose antibiotics in SBS may be necessary. To reduce the risk of antibiotic resistance, periodic rotation of the antibiotic used or use of a poorly absorbable antibiotic is advised. Although evidence from controlled studies to support their utility is lacking, other strategies for controlling SBBO include

(continued on page 38)

(continued from page 36)

limiting the use of antisecretory and ant motility agents, carbohydrate restriction, intermittent bowel flushing with polyethylene glycol, use of probiotic agents and bowel tapering operations.³⁶

OUTCOMES

SBS occurs in about 15% of adults undergoing intestinal resection; nearly 75% result from a single massive resection and the other 25% from multiple resections.³⁷ Approximately 70% of those with newly acquired SBS are eventually able to be discharged from the hospital.³⁸ Reports from the U.S. and France have demonstrated 2-year and 5-year survival rates for SBS at over 80% and 70%, respectively.^{39,40} Survival rates were lowest in the end-jejunostomy and ultra-short (< 30 cm without a colon) SB groups. PN-dependency at 1, 2 and 5 years was recently reported at 74%, 64% and 48%, respectively.³ In multivariate analysis, PN dependency was reduced with a remaining colon > 57% and a SB remnant length > 75 cm. In this study, over 25% of the patients who eventually weaned completely from PN did so > 2 years after their last bowel resection. Other factors affecting survival in SBS include the patient's age, primary disease process, co-morbid diseases, presence of chronic intestinal obstruction and the experience of the team managing the patient.²³

The quality of life of SBS patients is lower than population controls regardless of their PN requirement.⁴¹ Although the transition from hospital to home on PN leads to significant improvements in patients' quality of life,⁴² the quality of life remains worse in SBS patients on home PN compared to SBS patients not requiring PN.⁴³ Factors that seem to favor a better quality of life in home PN patients include strong self-esteem and good family/social support.^{44,45} The effective management of symptoms like diarrhea and prevention of complications is important for improving quality of life, reducing health care costs and improving survival in SBS. Recently, a SBS-specific quality of life instrument was shown to be valid, reliable and sensitive with excellent psychometric characteristics to measure treatment-induced changes in quality of life over time.⁴⁶ Studies using this instrument are awaited.

CONCLUSION

Short bowel syndrome is associated with significant morbidity and mortality, a reduced quality of life and high health care costs. In Part 1 of this five-part series on

SBS, we have reviewed the bowel-related physiological alterations that occur and the clinical consequences including potential complications. Subsequent parts of the series will review both conventional and novel treatment approaches in SBS and the importance of the oral diet and fluids in its management. ■

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