

Enteric Microbial Flora, Bacterial Overgrowth, and Short-Bowel Syndrome

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Small intestinal bacterial overgrowth (SIBO) occurs commonly in short-bowel syndrome (SBS) and, in some instances, may result in significant problems. SIBO is characterized by a variety of signs and symptoms resulting from nutrient malabsorption caused by an increased number and/or type of bacteria in the small intestine. The anatomic and physiologic changes that occur in SBS together with medications commonly used in these patients facilitate the development of SIBO. Because many aspects related to SIBO in the SBS population remain poorly understood, it was our aim to review the current understanding of the gut flora and issues related to SIBO occurring in SBS.

Short-bowel syndrome (SBS) is a malabsorption syndrome resulting from extensive intestinal resection and may be either congenital or acquired.^{1–3} In infants, necrotizing enterocolitis and congenital intestinal anomalies frequently are responsible whereas multiple resections for Crohn's disease and massive resections owing to catastrophic mesenteric vascular events, radiation enteritis, adhesive obstruction, and trauma represent the more common causes of SBS in older children and adults.⁴ These patients frequently experience chronic diarrhea, dehydration, and macronutrient and micronutrient deficiencies requiring enteral or parenteral support at home. The importance of SBS lies not with its prevalence but rather on its effect on these patients' quality and duration of life, the high rate of associated complications, and the subsequent high costs involved in their care.⁵ A number of complications occur in SBS patients that can be related to either the altered bowel anatomy or its treatment (Table 1).^{1,2,6,7}

We acknowledge the absence of supportive published observational data; however, in our clinical experience, small intestinal bacterial overgrowth (SIBO) occurs commonly in SBS patients and, in some instances, appears to affect their lifestyle and the ability to successfully wean parenteral nutrition adversely. Nevertheless, many aspects related to SIBO in the SBS population remain poorly understood. In this review, it was our aim to determine from the evidence available from the literature the importance, prevalence, risk factors, and diagnosis of

SIBO in the setting of SBS to provide a better understanding of this important and treatable complication.

Normal Enteric Flora

The gastrointestinal tract in an individual typically contains approximately 400–500 distinct bacterial species, most of which are difficult to identify but are concentrated most highly in the distal small intestine and colon. The initial establishment of the enteric flora is influenced by a variety of host and external factors.^{8,9} Gut flora tends to parallel that of the mother because most bacterial species are acquired during the birthing process.⁹ Although some changes to the flora occur during the first few months of life and transient changes to the flora may occur during later stages of life, the gastrointestinal flora remain remarkably constant. This feature is based largely on recognition and tolerance of the infant-acquired flora by the gut immune system¹⁰ that, by sampling microbial antigens, identifies these as normal.

Mostly acid-tolerant aerobic organisms inhabit the oropharynx and upper gastrointestinal tract.^{9,11} Immunoglobulins present within the salivary secretions act as a first-line defense against ingested bacteria. Gastric acidity followed by exposure to bile in the duodenum further eliminates many of the ingested microorganisms, typically leaving bacterial counts of 10⁴/mL or less in the proximal small bowel and generally consisting of aerobic and facultative anaerobes. It has been found that in pathologic cases of SIBO, there are excessive bacterial counts in the proximal small bowel, commonly with bacterial species including *Streptococci*, *Bacteroides*, *Escherichia*, and *Lactobacilli*.⁸

In the nonresected human gastrointestinal tract, bacterial counts increase and a gradual transition from aerobic to anaerobic organisms occurs in more distal segments of the gut.^{9,11} Indeed, the terminal ileum is said to represent a transition zone between the aerobic flora

Abbreviations used in this paper: SBS, short-bowel syndrome; SIBO, small intestinal bacterial overgrowth.

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Table 1. Complications of SBS

Parenteral nutrition related
Hepatobiliary disease
Central venous catheter related
Catheter breakage
Central venous thrombosis
Sepsis
Bowel anatomy related
Malabsorptive diarrhea
Fluid and electrolyte level abnormalities
Micronutrient deficiencies
Oxalate nephropathy
Acid peptic disease
Anastomotic ulceration
SIBO

found in the proximal gut and the anaerobic organisms found in the colon. Once across the ileocecal valve, bacterial counts increase from 10^7 to 10^9 organisms/mL in the terminal ileum to approximately 10^{10} to 10^{12} organisms/mL in the colon. In the colon, predominantly fastidious anaerobic organisms such as *Bacteroides*, *Bifidobacteria*, *Clostridia*, and numerous other microbial organisms are typical residents. These bacteria play a role in the digestion of unabsorbed nutrients and assist in the modulation of immune functions in the lower gut.

Beneficial Effects of the Gut Flora

The normal gut flora provides a number of beneficial functions related to intestinal epithelial turnover, motility, blood flow, and mucosa-associated lymphoid tissue.^{12,13} Indeed, there is an intimate relationship among the intestinal epithelium, gut flora, and lymphoid tissue and, as such, the enteric flora is important in maintaining normal gastrointestinal and immune function and normal digestion of nutrients. Some of these effects have been best shown in experiments involving animals raised in a germ-free environment.^{12,13} In these animals, the lack of bacterial exposure results in thinning of the small-bowel villi with concomitant shortened crypts, a change in enterocyte shape from columnar to cuboidal, a reduction in the number and size of Peyer's patches, a reduction in lamina propria leukocyte infiltration, and a slowing of mucosal regeneration. Interestingly, and seemingly contradictory to the earlier-described findings, protein and carbohydrate absorption have been shown to be increased in germ-free animals,¹³ a finding corroborated by studies in which small-bowel bacteria were eliminated from animals previously raised in an otherwise normal microbial environment. Nevertheless, it is important to remember that, under normal circumstances, the degree to which nutrient absorption is impaired in the nonresected individual appears not to be

significant clinically. Furthermore, the introduction of microorganisms rapidly restores the normal appearance and function of the small intestinal epithelium.¹³ It is important to recognize that the relevance of these effects seen in animals requires confirmation in human beings.

Understanding the molecular mechanisms by which enteric microorganisms interact with the intestinal epithelium currently is being explored. Bacterial-enterocyte cross-talk has been identified recently by studies that have shown the ability of pathogens to impair the epithelial barrier and native bacteria to enhance this barrier.¹⁴ Further investigation in this area will lead to a greater understanding of the pathologic consequences of SIBO.

Other beneficial effects of the enteric flora include the production of micronutrients, such as vitamin K and folate, participation in the fermentation of unabsorbed carbohydrates by colonic bacteria to short-chain fatty acids, which can be absorbed subsequently through the colonic mucosa and be used as an energy source,¹⁵ and aiding in the metabolism and/or activation of medications, such as sulfasalazine. Bacterial competition with the host for micronutrients is rarely a significant problem; however, as discussed further later, an excess of small-bowel bacteria can deconjugate bile acids, making them unavailable for micellar solubilization, thus contributing to fat malabsorption.¹⁶ Finally, the normal gut flora is important to prevent luminal colonization with pathogenic bacteria.¹⁷

Deleterious Effects of the Gut Flora

Although even excess gut bacteria may have beneficial actions, luminal microorganisms also can have deleterious actions. Epithelial inflammation and varying degrees of villus atrophy, which may be confused with inflammatory diseases, may occur and result in impaired absorption.^{18,19} The degree of mucosal inflammation can vary considerably, both grossly and microscopically.¹⁸ Facultative anaerobes cause epithelial injury by direct adherence and production of enterotoxins, whereas aerobes produce enzymes and metabolic products that result in injury.^{20–22} Anaerobic organisms seem to be responsible primarily for the deleterious effects of SIBO and their suppression is necessary to allow normal ileal B₁₂ absorption.

Fat maldigestion and malabsorption mainly occur because of the deconjugation of bile acids by intraluminal bacteria, thus allowing their absorption by the jejunum and leading to insufficient concentrations for fat absorption.^{16,23} Bacterial deconjugation also may result in the production of substances, such as lithocholic acid, which

may exert toxic effects on the intestinal epithelium²⁴ and result in impaired absorption of not only fat but also carbohydrate and protein.²⁵ Because of the fat maldigestion and malabsorption that occurs in the setting of SIBO, deficiencies of the fat-soluble vitamins A, D, and E can occur. For reasons described previously, vitamin K deficiency is seen rarely in SIBO. Carbohydrate malabsorption also may result from the intraluminal degradation of sugars by enteric bacteria and from bacteria-related decreased enterocyte disaccharidase and brush-border hydrolase activity and impaired monosaccharide absorption.^{25,26} Although overt protein malnutrition is rare in SIBO, a reversible form of protein-losing enteropathy has been described.²⁷ The absorptive dysfunction and mucosal injury seen in SIBO, along with decreased levels of enterokinases that have been described in SIBO,²⁸ contributes to decreased amino acid and protein precursor uptake. Finally, SIBO has been associated with the production of toxins that may exert clinically relevant systemic effects. Examples include ammonia, D-lactate, alcohol, and bacterial peptidoglycans.^{29,30}

These negative effects of SIBO on nutrient digestion and absorption are largely responsible for the clinical features that occur. For example, the degradation of carbohydrates leads to the production of carbon dioxide, hydrogen, and methane that may be responsible for a variety of symptoms such as gas, bloating, distension, and abdominal discomfort. Fat malabsorption may lead to oxalate kidney stones, steatorrhea, and fat-soluble vitamin deficiencies with their associated symptoms. A secretory diarrhea may occur owing to the presence of hydroxylated fatty acids and deconjugated bile acids. B₁₂ malabsorption may result in megaloblastic anemia and neurologic symptoms related to subacute combined degeneration. Symptoms related to disturbed gastrointestinal motility also may occur in SIBO, perhaps owing to alterations in gut peptide elaboration as a consequence of differences in nutrient presentation to the respective parts of the gut.³¹⁻³⁵ A recent report identified a decreased number of interstitial cells of Cajal, the pacemaker cells of the intestine, in a patient with jejunal stasis and SIBO.³⁶ It is unknown at this time whether the pathologic consequences of SIBO are caused by an increased overall number of bacteria, the type of bacteria, or a combination of both situations.

Factors Protecting Against the Development of Small Intestinal Bacterial Overgrowth

Multiple factors both internal and external to the individual prevent excessive small-bowel bacterial colo-

nization and determine the types of bacteria present. The most important factors within the individual are normal small-bowel motility, which prevents the attachment of ingested organisms, and gastric acid, which destroys many organisms before they reach the small intestine. Further enzymatic digestion from pancreaticobiliary secretion³⁷ and the presence of adequate mucosal immunity also control the bacterial populations in the gut. Although the ileocecal valve traditionally has been considered an important factor in controlling the entry of colonic bacteria into the small intestine, its importance recently has been questioned, with overall small-bowel length¹⁸ and the presence of ileal peristalsis, in particular, suggested as the primary factors responsible for controlling the number of bacteria in the small bowel.³⁸ Finally, intestinal mucus normally traps bacteria intraluminally. As a result, in some instances, excess bacterial counts may be present but may not create any deleterious effects. The role of age and race on the risk for SIBO remains unclear but may be important.³⁹ Diet plays an important role in establishing and altering gut flora.⁴⁰ In infants, it is known that those fed human milk have greater *Bifidobacterium* populations than infants fed cow-milk formulas.⁴¹ In older children and adults, the type of food consumed will impact gut flora temporarily, in part because of the ability to enhance the selective growth of certain organisms already present in the gastrointestinal tract (see section on Treatment of Small Intestinal Bacterial Overgrowth in Short-Bowel Syndrome Patients). Finally, the gut flora also is influenced by external factors such as medications, geography, stress, lifestyle, and alcohol use.⁴² Taking the earlier-described factors into consideration, conditions that are associated with the presence of SIBO can be divided into those where stasis is present owing to either anatomic, functional, or multifactorial causes (Table 2).

Risk Factors for Developing Small Intestinal Bacterial Overgrowth in Short-Bowel Syndrome

There are 3 major bowel anatomies that occur in SBS patients: jejunocolic, end-jejunostomy, and jejunocolonic. The jejunocolic anatomy is present most commonly in those with SBS. Patients with this bowel anatomy do not have an ileum and usually do not have an ileocecal valve, anatomic factors that might increase the risk for SIBO. After massive intestinal resection, the remaining bowel attempts to increase fluid and nutrient absorption in compensation for lost bowel in a process referred to as *intestinal adaptation*.^{43,44} This process generally occurs during the first 2 years after the resection

Table 2. Conditions Associated With the Development of SIBO

Anatomic	Functional	Multifactorial
Enteroenteric fistulae	Intestinal dysmotility	Medications
Small-bowel diverticulosis	Inflammatory conditions	Immunodeficiency states
Surgically created blind loops	Autonomic neuropathy	Chronic pancreatitis
Strictures	Hypochlorhydria or achlorhydria	Cirrhosis
Resection of the ileocecal valve	Reduction of gut-associated lymphoid tissue after resection	Advanced age

and may result in structural and functional changes in the bowel that lead to both an increase in absorptive surface area (bowel dilatation primarily) and a slowing in the rate of bowel transit, thereby allowing increased time for absorption to occur.^{45,46} As the remnant small bowel dilates, peristalsis is less effective or ineffective at removing gut bacteria. Finally, the use of antisecretory medications to control gastric acid hypersecretion after massive resection may further predispose some SBS patients to develop excess bacterial colonization of the small intestine. The use of antimotility/antidiarrheal medications may play a similar role. Therefore, in SBS, the combination of altered bowel anatomy, decreased motility, and gastrointestinal acidity and bowel dilatation may contribute to the development of SIBO.

Consequences of Small Intestinal Bacterial Overgrowth in Short-Bowel Syndrome

Table 3 lists a number of potential consequences related to the presence of SIBO in SBS patients. A major pathophysiologic consequence of SIBO relates to the inflammatory epithelial changes that subsequently occur in the gut. The inflammation that occurs in the setting of SIBO is nonspecific, likely is caused by the overgrowth of more invasive strains of bacteria, and may result in a variety of epithelial changes including the blunting of the villi,⁴⁷ other less visibly apparent damage to the brush border, and/or the elaboration of inflammatory

cytokines/mediators that may disrupt or inhibit the absorptive process.^{20,39} These changes result in a reduction in the absolute or functional intestinal absorptive surface area with the subsequent development of symptoms attributed to SIBO such as gas, bloating, abdominal cramping, and diarrhea. Inflammation also may result in the development of anastomotic ulcerations and cause chronic bleeding and a microcytic anemia.¹⁸

The cause of inflammation in SIBO likely is multifactorial. Occasionally, certain bacterial species may invade the small-bowel mucosa resulting in an inflammatory response. More frequently, inflammation may occur as an inappropriate or overly aggressive reaction to absorbed bacterial antigens. In such instances, it is not uncommon to see other evidence of immune dysregulation including arthritis, especially large-joint arthritis, which often resembles that seen with inflammatory bowel disease. This finding was observed originally in patients with intestinal bypass for treatment of obesity and, at that time, was thought to occur as a complication of SIBO.⁴⁸

In SBS patients with an intact colon, a rare syndrome characterized by the development of neurologic symptoms ranging from lethargy, confusion, and poor school/work performance to seizures and coma and metabolic acidosis may occur.⁴⁹ This syndrome is thought to be caused by an increase in D-lactic acid levels, the dextro-isomer of lactic acid, in the blood. Development of this syndrome requires the following conditions: carbohydrate malabsorption with increased delivery of nutrients to the colon, bacterial flora that produces D-lactate, ingestion of large amounts of carbohydrate, and impaired D-lactate metabolism.⁵⁰ Excessive production of D-lactate occurs when the presence of abnormal gut flora overwhelms the normal metabolism of D-lactate and leads to an accumulation of this substance in the blood.^{51,52} Normally, the L isomer of lactic acid produced by most human bacterial organisms is absorbed and subsequently metabolized in the liver. Certain colonic bacteria (eg, some species of lactobacilli), however, may produce a combination of D and L isomers or exclusively D isomers. Impaired metabolizers of D-lactate seem to be at greatest risk for the development of this condi-

Table 3. Potential Consequences of SIBO

Variety of gastrointestinal symptoms
Failure to thrive in children
Malabsorption
Fat, carbohydrate, vitamin B ₁₂ , fat-soluble vitamins
Difficulty in weaning from parenteral nutrition
Caused by symptom-related decrease in oral intake and malabsorption
Gross and histologic bowel inflammation
Gastrointestinal bleeding
Bacterial translocation and endotoxemia
Endogenous sepsis/central line infections
Liver injury
D-lactic acidosis

tion.^{50,52} The optimal treatment of this condition is unclear and, currently, options include a carbohydrate-restricted diet and the use of antibiotics. Although this syndrome is not related to the presence of SIBO, it is not uncommon for both conditions to occur simultaneously.

It generally is accepted that infections, especially with gram-negative organisms, can result in increases in levels of liver test results and jaundice. The mechanism relates to the elaboration of endotoxins from these bacteria that then activate multiple inflammatory cytokines, including tumor necrosis factor, which interfere with the function of hepatocyte membrane transporters.^{53,54} The presence of endotoxemia in the absence of sepsis also can cause jaundice. Recently, it was shown that after intestinal resection in an animal, bacterial endotoxins and peptidoglycans were transported by the portal circulation to the liver, where they interfered with bile flow.⁵⁵ The presence of SIBO may predispose to bacterial translocation and lead to endotoxemia with subsequent sepsis and/or liver injury.^{56,57} Schimpl et al⁵⁸ studied bacterial overgrowth and translocation using a rat model of SBS and found that bacterial overgrowth occurred in all animals and bacterial translocation occurred more commonly in those with a jejunal resection compared with those with an ileal resection and, interestingly, occurred least commonly in those with both an ileal resection and a resection of the ileocecal valve. Nevertheless, it is important to recognize that, unlike in animals, bacterial translocation rarely has been shown and has not been proven to be of clinical significance in human beings, and SIBO per se has been shown not to be a major risk factor for liver injury in non-SBS patients,⁵⁹ so other factors such as parenteral nutrition and/or the absolute length of the remaining small bowel may be important cofactors.^{60,61} Similarly, the role of SIBO in recurrent sepsis, catheter-related sepsis in particular, remains speculative.

Diagnosis of Small Intestinal Bacterial Overgrowth in Patients With Short-Bowel Syndrome

The diagnosis of SIBO presents a number of difficulties and limitations. This is particularly so in the case of the SBS patient, who, as described later, presents a unique diagnostic challenge. Nonspecific clinical scenarios that may suggest the presence of SIBO include a worsening in stool output and weight loss in the adult SBS patient or failure to grow in the child SBS patient, abdominal cramping and foul smelling flatulence, especially if associated with more frequent stooling, and an unexpected plateau during the weaning of parenteral nutrition. On physical examination, the gradual devel-

opment of abdominal distention with a succussion splash may be seen. SIBO virtually always is present in patients with anatomic dilatation of the small bowel or delayed transit, although the relative role of SIBO in producing symptoms in this setting often is difficult to assess.

There is, as of yet, no widespread agreement as to the optimal test for SIBO. Culture of aspirated small-bowel fluid previously has been considered the gold standard. Unfortunately, this method is not without significant limitations, primarily because of the need for small-bowel intubation, which may result in contamination of the specimen during its transit into and through the small bowel and the difficulty in culturing the enteric flora, particularly anaerobic organisms. Indeed, it generally is regarded that more than 50% of the bacterial species in the gut are not culturable. In addition, it has been suggested that there may be patchy nonconfluent involvement along the upper gut, which may lead to a high rate of false-negative studies.^{62–64} Therefore, the reliability of the technique has been questioned and indirect methods of detecting SIBO have been developed as alternatives.

Hydrogen breath testing, the most commonly used alternative method to diagnose SIBO, uses carbohydrate (eg, glucose, lactulose, and xylose) as a substrate. In the presence of excessive bacteria in the small bowel, the substrate is metabolized, releasing hydrogen that subsequently is absorbed and then released in the expired air. It has been calculated that up to 80 g of glucose, which generally is absorbed rapidly in the small bowel, can be absorbed in the small bowel in patients with partial gastrectomy.⁶⁵ Therefore, a peak in hydrogen (usually > 10–20 ppm) in the breath sample after the oral administration of 80 g or less of glucose indicates SIBO. Nevertheless, false positives can occur owing to rapid intestinal transit with subsequent metabolism of the glucose within the colon by normal colonic bacteria.⁶⁶ Furthermore, it has been suggested that glucose as a substrate is limited by its rapid absorption in the proximal small bowel, which may result in missing SIBO that only is present in the more distal small bowel.⁶⁴ To overcome this limitation, lactulose, a nonabsorbable disaccharide, has been advocated because it will detect the presence of SIBO anywhere in the small bowel. Unfortunately, initial reports suggesting high sensitivity and specificity⁶⁷ have not been confirmed and the interpretation of this test is less reliable.^{68–70} In general, both the glucose and lactulose hydrogen breath tests have shown disappointing abilities to predict the results of small-bowel culture.⁶⁸ The hydrogen breath test also is limited by the fact that up to 27% of the population are

nonhydrogen producers,^{71,72} a limitation that may be overcome by simultaneous measurement of expired methane.

Despite its limitations, in the setting of SBS, where usually only a relatively short segment of jejunum is present, direct culture of small-bowel fluid is most useful in the diagnosis of SIBO. With regard to the use of hydrogen breath tests in SBS, although an increased fasting breath hydrogen result may be useful, it is difficult if not impossible to differentiate small bowel from colonic production of hydrogen (owing to rapid intestinal transit), and so we do not recommend their use, particularly with the use of lactulose as the substrate. We also do recommend caution using the response to an empiric antibiotic therapy as a means of diagnosing SIBO because the response may be difficult to interpret. For example, in those patients who do not seem to respond to antibiotics, it remains possible that SIBO still may be present. Similarly, in those patients who respond clinically to antibiotics, it may not necessarily occur because of the presence of SIBO because antibiotics may have more generalized and nonspecific effects on the gut flora. Indeed, caution is needed because the diagnosis of SIBO can set in motion a process of frequent antibiotic use that can lead to the performance of numerous tests if the symptoms do not respond or return.

Alternatives to direct culture of small-bowel fluid and the hydrogen breath test include the ¹⁴C (and ¹³C)-D-xylose breath test, which measures pulmonary excretion of labeled CO₂ produced from the bacterial fermentation of the labeled substrate. Although initial reports using this technique were promising, they have not been confirmed.^{73,74} Similarly disappointing results have occurred with the measurement of products of luminal bacterial metabolism in urine (eg, increased indicans) or blood (eg, increased D-lactate levels),⁷⁵ the ¹⁴C-glycolate breath test,⁷⁶ and the string test.⁷⁷ High fasting levels of hydrogen (>20 ppm) are common in SIBO but seem to lack both sensitivity and specificity.^{69,78} Finally, the direct culture of unwashed small-bowel mucosal biopsy specimens remains promising but requires further validation.⁷⁹

The determination of excess bacteria is much easier than determining the relationship between the excess counts and symptoms of SBS. Virtually all of the diagnostic techniques described are designed specifically to evaluate excess numbers of bacteria in the small bowel and do not determine whether or not the bacteria actually are doing any harm. As noted previously, a certain level of commensal bacteria is important but, more commonly, it is the presence of a particular species type in an

atypical location in the bowel in addition to an excess number that results in inflammation and the development of symptoms. In this instance, biopsy specimens of the small bowel may provide the best indication of whether or not the bacteria present actually are harmful. Inflammatory changes, villus blunting, and the presence of adherent or intracellular bacteria support the diagnosis of pathologic SIBO.

Prevalence of Small Intestinal Bacterial Overgrowth in Short-Bowel Syndrome

Very little is known about the prevalence of SIBO in patients with SBS. Furthermore, and importantly, although it might be expected to occur commonly after massive intestinal resection, the degree to which it creates problems necessitating intervention is not known. The lack of information regarding the prevalence of pathogenic and nonpathogenic SIBO in SBS likely is related to multiple factors including the nonspecificity of the symptoms attributed to SIBO and the limitations of the diagnostic tests and treatments that are available.

We recently reviewed the medical records of consecutive patients with SBS presenting to the University of Nebraska Intestinal Rehabilitation Program between October 2001 and September 2004 for the presence or absence of SIBO and its potential risk factors.⁸⁰ SIBO was considered present in those with either an abnormal colony count on distal duodenal aspirate (>10⁵ colony forming units/mL) or abnormal glucose hydrogen breath test (fasting H₂ > 20 ppm or increase in H₂ > 20 ppm < 60 min after ingestion). Forty-three of 87 patients evaluated during that time period were tested for SIBO, of whom 27 (63%) showed SIBO by this methodology. Specifically, 19 of 28 duodenal aspirates showed excessive growth of either aerobes only (10 of 19) or both aerobes and anaerobes (9 of 19). Six of 13 breath tests were abnormal with 4 showing an increased fasting breath hydrogen level. Although the results of the small-bowel aspirates may be of more interest diagnostically given the deficiencies of the hydrogen breath test that were noted previously, it is interesting to note that more than 50% of the breath test results still were interpreted as normal. Of a variety of potential risk factors evaluated, including patient characteristics, bowel anatomy, symptoms, time since onset of SBS, nutritional state, and body mass index, none was associated with the presence of SIBO. SIBO tended to be more prevalent in those with dilated small bowel (82% in dilated vs 59% in nondilated). Nevertheless, SIBO was present in the majority of SBS patients with nondilated bowel and either normal or

rapid transit on small-bowel barium-contrast study. Certainly, further work in this area is needed.

Treatment of Small Intestinal Bacterial Overgrowth in Short-Bowel Syndrome Patients

If future prospective studies confirm that SIBO is of clinical significance in the SBS population, treatment needs to be addressed. Because there currently are no controlled trials of any form of treatment for SIBO in SBS patients, recommendations on the basis of clinical experience therefore are necessary. Although it is not the intent of this article to review the treatment of SIBO in detail, and with the caveat noted earlier, the following briefly describes options that can be considered in the setting of SBS.

Once pathologic SIBO has been identified, microbial modification is the prime objective. The goal should not be to sterilize the gastrointestinal tract; rather the goal is to reduce the number of pathogenic bacteria present. A reassessment of the need for antimotility and antisecretory medications in each SBS patient should be undertaken because their elimination may be useful in some individuals.⁸¹ Because the culture of small-intestinal contents will not necessarily identify the specific species or strains of bacteria that are causing the clinical features of SIBO, a trial-and-error approach to antibiotic therapy can be used with success being judged on improvement in gas-related symptoms, reduction in stool output, and/or weight gain. Antimicrobial therapy should provide coverage for both aerobic and anaerobic organisms; monotherapy directed against anaerobes should be avoided. A single 10–14-day course of therapy usually will lead to an improvement in symptoms within 1–2 weeks. Because the underlying mechanism(s) responsible for causing SIBO are unlikely to change in most SBS patients, the periodic (eg, 7–14 days/mo) or, more commonly, continuous use of antibiotics may be necessary. In this circumstance, periodic rotation of the antibiotic used is advised to reduce the risk for antibiotic resistance. In those who have had objective diagnosis of SIBO but do not respond to antimicrobial therapy, it sometimes is useful to perform a qualitative culture with antimicrobial sensitivity testing of small-bowel contents.

Because of the concern over antimicrobial resistance, antibiotic-associated allergic reactions, and *Clostridium difficile* diarrhea associated with prolonged use of antibiotics, there is increasing interest in the use of prebiotics and probiotics in the management of SIBO. Despite the current interest in their use and their shown efficacy in some clinical applications,^{82–85} the role of these agents

in the management of SIBO remains unproven. Indeed, only anecdotal reports have suggested efficacy of probiotics in the management of SIBO in patients with SBS,^{86–88} a finding that may relate to the limited effect of the probiotic organisms on the overall number of luminal organisms present in this condition. Nevertheless, further studies in this area seem warranted given the low risk associated with their use. The only disadvantages of this therapy may be related to their cost and the potential for significant complications such as D-lactic acidosis in susceptible individuals or systemic infection in the immunocompromised patient.^{51,89}

As previously described, bowel dilatation often occurs during the period of intestinal adaptation after massive intestinal resection and may become so extreme as to facilitate the development of SIBO. Readily identifiable on barium-contrast small-bowel series, bowel dilatation may be alleviated by using surgical tapering with or without concomitant lengthening. Although uncontrolled case series have shown that these procedures may be beneficial in ameliorating symptoms of SIBO in some SBS patients, at least in the short term, the long-term consequences remain unknown.⁹⁰

Nutritional support remains an important part of the management of SIBO in SBS patients because the presence of SIBO may complicate adequate oral intake and contribute to the need for additional parenteral support in some of these patients.^{46,91} Carbohydrate restriction with a corresponding increase in fat and protein intake may be useful to decrease the development of gas-related symptoms and osmotic diarrhea, at least in children,⁵⁴ because most bacteria ferment only carbohydrate, and fat is an excellent calorie source. However, caution should be used because a high-fat diet in those with significant bile acid losses may aggravate stool output and increase the risk for oxalate nephropathy depending on the patients' bowel anatomy.⁹² Finally, despite a lack of evidence from controlled studies to support their use, other strategies for controlling recalcitrant SIBO in the SBS patient who has been described include intermittent bowel flushing with polyethylene glycol, use of prokinetic agents, and use of anti-inflammatory agents in those with overt or severe histologic intestinal inflammation.^{18,86} Caution is recommended if prokinetics are to be used because they may hinder absorption further owing to an acceleration in transit.

Conclusions and Future Directions

SIBO can be an important complication in the SBS patient and result in a variety of symptoms that may have deleterious effects on patient lifestyle and, possibly,

the ability to wean from parenteral nutrition. However, a number of unresolved issues exist that deserve further investigation.

1. The prevalence of SIBO in this population needs to be delineated better. Importantly, the identification of the optimal method of diagnosing this as a pathologic condition in the SBS patient and identifying specific bacterial populations that are important clinically and can be targeted therapeutically is needed.
2. Given the beneficial effects of the intestinal flora and the wide spectrum of clinical features and severity of SIBO, the ability to identify when an excess of enteric bacteria or atypical species is important clinically in an individual patient also is needed.
3. It would be useful to identify reliable risk factors that would lead to an increased suspicion by the clinician of clinically important excess bacterial colonization in the small bowel.
4. It also would be useful to characterize better the effect of SIBO on quality of life. In this regard, the development of a disease-specific quality-of-life instrument would be useful.
5. Effective treatment strategies need to be identified using appropriately powered and controlled studies in human beings. In addition to finding acceptable therapeutic agent(s), it also is important to determine the duration and frequency of treatment administration and how best to judge its success.
6. To conduct meaningful clinical investigations in this area, given the relative rarity of SBS, an effort needs to be made for centers involved in the management of intestinal failure to join forces and establish a collaborative clinical research initiative.

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