Carol Rees Parrish, R.D., M.S., Series Editor

Nutritional Consequences of Small Intestinal Bacterial Overgrowth

John K. DiBaise

Small intestinal bacterial overgrowth (SIBO) is an increasingly recognized cause of malabsorption and is likely an under-recognized cause of a variety of nonspecific gastrointestinal symptoms. Disturbances in small bowel motility and gastric acid secretion are the principal predisposing factors providing a clue to patient groups at risk of this condition. The accurate diagnosis of SIBO remains problematic. Although simple, noninvasive breath tests are commonly used to diagnose SIBO, the gold standard test remains the culture of a small intestinal aspirate, which can be readily collected at the time of endoscopy. As reversal of the underlying condition predisposing to SIBO is unlikely, correction of any associated nutritional deficiencies is advised. Treatment with a broad-spectrum antibiotic is generally effective in relieving symptoms; however, repeated courses are often needed.

INTRODUCTION

Small intestinal bacterial overgrowth (SIBO) is characterized by a variety of signs and symptoms resulting from nutrient malabsorption when food, enteral feedings, medications such as lactulose or those containing sorbitol or fiber supplements interact with the bacteria. The symptoms may appear minor and nonspecific and lead to diagnostic confusion as these same signs and symptoms are often associated with an underlying disease process when present. SIBO implies a quantitative assessment of bacteria present in the small intestine. Although a certain level of commensal bacteria is important, it is the presence of a particular species type in an atypical location of the bowel, in addition to an excess number, that results in the development of the classical clinical manifestations of this condition. SIBO is usually defined as the presence of $>10^5$ colony forming units (cfu)/mL of bacteria in the proximal small intestine (1); however, it has been suggested that a lower colony count (e.g., $>10^3$ cfu/mL) may be adequate to induce symptoms as

John K. DiBaise, M.D., Professor of Medicine, Mayo Clinic, Scottsdale, AZ.

Table 1
Beneficial Metabolic Effects of the Enteric Microbiota

- Biotransformation of bile salts
- Production of micronutrients (e.g., vitamin K, biotin and folate)
- Participation in the fermentation of otherwise indigestible polysaccharides by colonic bacteria to short chain fatty acids
- Aiding in the metabolism and/or activation of medications (e.g., sulfasalazine, digoxin)
- Prevention of luminal colonization by pathogenic microorganisms

long as colonic-type bacterial species are identified. This clinical syndrome results predominantly from competition between the atypical and excessive bacteria in the proximal small bowel and the human host for ingested nutrients as well as from injury to the small bowel epithelium caused by these bacteria. Herein, the nutritional consequences of SIBO to the human host are discussed as are the patient groups at risk of developing this condition. The clinical approach to diagnosing and treating this condition is also briefly reviewed.

BENEFICIAL FUNCTIONS OF THE GUT MICROBIOTA

An intimate relationship exists among the intestinal epithelium, gut microbiota and lymphoid tissue and, as such, the commensal enteric microorganisms are important in maintaining normal gastrointestinal and immune function. Understanding the molecular mechanisms by which enteric microorganisms interact with the intestinal epithelium is currently being explored. Bacterial-enterocyte crosstalk has recently been identified by studies which have demonstrated the ability of pathogens to impair the epithelial barrier and native bacteria to enhance this barrier (2). A number of beneficial metabolic effects of the enteric microbiota with potential nutritional consequences have been described including the production of micronutrients (e.g., vitamin K, biotin, folate), and participation in the fermentation of otherwise indigestible polysaccharides by colonic bacteria to short chain fatty acids, which can subsequently be absorbed through the colonic mucosa and be utilized as an energy source (3) (Table 1). Recent evidence suggests that the gut microbiota is an important factor that participates in the extraction of calories from ingested dietary substances and helps to store those calories in host adipose tissue for later use. The evidence also suggests that there are differences in the gut microbiota between obese and lean individuals raising the possibility that differences in caloric extraction of ingested food substances may be determined by the composition of the gut microbiota (4,5). The normal gut microbiota also functions to prevent luminal colonization by pathogenic bacteria (6).

NUTRITIONAL CONSEQUENCES OF SIBO

A major pathophysiologic consequence of SIBO relates to the inflammatory epithelial changes that subsequently occur in the gut (7,8). The degree of mucosal inflammation can vary considerably both grossly and microscopically (7). The inflammation that occurs in the setting of SIBO is nonspecific and is likely due to the overgrowth of more invasive strains of bacteria. This inflammatory process may result in a variety of epithelial changes including the blunting of the villi (9), 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 (10). These changes result in a reduction in the absolute or functional intestinal absorptive surface area and play a role in the subsequent development of the symptoms attributed to SIBO such as gas, bloating, abdominal cramping, diarrhea and steatorrhea. The cause of inflammation in SIBO is likely multifactorial. Occasionally, certain bacterial species may invade the small bowel mucosa resulting in an inflammatory response. Facultative anaerobes cause epithelial injury by direct adherence and production of enterotoxins, while aerobes produce enzymes and metabolic products that result in injury (11,12). Anaerobic organisms seem to be primarily responsible for the deleterious effects of SIBO and their suppression is necessary to allow normal ileal B_{12} absorption. More frequently, mucosal inflammation

(continued on page 19)

(continued from page 16)

may occur as an inappropriate or overly aggressive reaction to absorbed bacterial antigens.

Fat maldigestion and malabsorption occur mainly due to the deconjugation of bile acids by intraluminal bacteria, allowing their absorption by the jejunum and leading to insufficient concentrations for micelle formation and fat absorption (13,14). Bacterial deconjugation may also result in the production of substances, such as lithocholic acid, which may exert toxic effects on the intestinal epithelium (15) and result in impaired absorption of not only fat, but also carbohydrate and protein (16). 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 rarely seen in SIBO.

Carbohydrate malabsorption may also result from the intraluminal degradation of sugars by enteric bacteria and from bacteria-related decreases in enterocyte disaccharidase and brush-border hydrolase activity, and impaired monosaccharide absorption (16,17). Indeed, lactose intolerance seems to be common in these patients and may contribute to the diarrhea that is often present. Although overt protein malnutrition is rare in SIBO, a reversible form of protein-losing enteropathy has been described (18). The absorptive dysfunction and mucosal injury seen in SIBO, along with decreased levels of enterokinases that have been described in SIBO (19), contributes to decreased amino acid and protein precursor uptake.

Vitamin B_{12} deficiency is caused by bacterial consumption involving predominantly anaerobic organisms within the intestinal lumen before it can be absorbed. Deficiencies of thiamine and nicotinamide have also been reported. In contrast, folate levels may be elevated in SIBO as a result of bacterial synthesis and its subsequent absorption.

These negative effects of SIBO on nutrient digestion and absorption, attributed to both the intraluminal effects of bacteria and damage to the small bowel mucosa, are largely responsible for the clinical features that are seen (Table 2). 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 due to the caustic effects of hydroxylated fatty acids and deconjugated bile acids. Vitamin B_{12} malabsorption may result in megaloblastic anemia and neurological symptoms related to subacute combined degeneration. Symptoms related to disturbed gastrointestinal motility may also occur in SIBO, perhaps due to alterations in gut peptide elaboration as a consequence of differences in nutrient presentation to the respective parts of the gut (20,21). It is unknown at this time whether the pathologic consequences of SIBO are due to an increased overall number of bacteria, the type of bacteria or a combination of both situations.

Table 2
Clinical Features Associated with Small Intestinal Bacterial Overgrowth

- Gas-bloat
- Flatulence
- Abdominal discomfort
- Diarrhea
- Steatorrhea
- Weight loss
- Features associated with micronutrient deficiencies (Vitamins B_{12}, A, D and E, iron, thiamine, nicotinamide)

FACTORS PROTECTING AGAINST SIBO

Multiple factors prevent excessive small bowel bacterial colonization and determine the types of bacteria present. The most important factors are normal small bowel motility, which prevents attachment of ingested organisms, and gastric acid, which destroys many organisms before they reach the small intestine. Further enzymatic digestion by pancreaticobiliary secretions and the presence of adequate mucosal immunity including immunoglobulins within the intestinal secretions also help to control the bacterial populations in the small bowel. Although the ileocecal valve has traditionally been considered an important factor in controlling the entry of colonic bacteria into the small intestine, its importance has recently been questioned

Table 3
Conditions Associated with the Development of Small Intestinal Bacterial Overgrowth

Anatomical
- Enteroenteric fistulae
- Small bowel diverticula
- Surgically-created blind loops
- Intestinal strictures
- Resection of the ileocecal valve (?)

Functional
- Intestinal dysmotility syndromes
- Hypo- or achlorhydria
- Inflammatory conditions
- Autonomic neuropathy
- Reduction of gut-associated lymphoid tissue

Miscellaneous
- Antisecretory and antimotility medications
- Immunodeficiency states
- Cirrhosis
- Radiation enteritis
- Diabetes mellitus
- Chronic pancreatitis
- Short bowel syndrome
- End stage renal disease
- Advanced age

with overall small bowel length (7) and the presence of ileal peristalsis, as the primary factors responsible for controlling the number of bacteria in the small bowel (22). Finally, intestinal mucus normally traps bacteria intraluminally. As a result, in some instances, excess bacterial counts may be present, but are not clinically important.

The role of age and race on the risk for SIBO remains unclear (10). Although asymptomatic colonization has been identified in an otherwise healthy elderly population, it has been suggested that SIBO may be the most common cause of malabsorption in the geriatric population presumably as a consequence of age-related dysmotility and hypochlorhydria (23). Diet plays an important role in establishing and altering gut flora (24); however, there is currently little evidence to support anything more than a temporary role for dietary manipulation on regulating the gut microbiota. The gut microbiota is also influenced by external factors such as medications (acid suppressants in particular), geography, stress, lifestyle, and alcohol use (25).

PATIENT GROUPS AT RISK OF SIBO

Taking the above into consideration, conditions that are associated with the presence of SIBO can be divided primarily into those where stasis/stagnation occurs within the small intestine and those where diminished gastric acid secretion is present (Table 3). Therefore, disturbances in small bowel transit and/or motility (e.g., chronic intestinal pseudo-obstruction, intestinal stricture, blind loop) and gastric acid secretion (e.g., achlorhydria, acid suppression) are the principal predisposing factors providing a clue to patient groups at risk of this condition. In many chronic conditions as described below, a multifactorial cause may be present.

Inflammatory Bowel Disease

SIBO commonly complicates Crohn's disease, particularly those individuals with previous intestinal resections, strictures and enteroenteric fistulae, and can be effectively treated by antibiotics (26). The glucose hydrogen breath test has been suggested to be a useful diagnostic test for small bowel strictures in Crohn's disease (27). Intestinal dysmotility that can occur in the setting of chronic intestinal inflammation and result in prolonged orocecal transit may also predispose the Crohn's patient to develop SIBO (28). It is often assumed that diarrhea in Crohn's disease is due to rapid intestinal transit; however, it is frequently multifactorial. Intestinal resection, bile salt deficiency related to terminal ileal disease or resection, toxic effect of bile salts in the colon, and SIBO in the setting of slowed transit sometimes related to the presence of intestinal strictures or postoperative blind loops may all contribute. SIBO does not appear to be a common occurrence in ulcerative colitis and although it had been suggested that the creation of an ileal pouch-anal anastomosis following colectomy may predispose to SIBO, asymptomatic chronic pouchitis was recently shown to be unrelated to SIBO (29).

Celiac Disease

A poor or absent response to a gluten-free diet may be seen in up to 30% of patients with celiac disease (30). A limited number of conditions including SIBO seem to be responsible (31). In this scenario, SIBO may be differentiated from other potential causes by its association with the presence of diarrhea and abdominal pain (31). Although the mechanism is unclear, intestinal dysmotility is suspected.

End Stage Renal Disease

Gastrointestinal symptoms are common in patients with chronic renal failure although the pathogenesis is unknown. SIBO also appears to be common in those with chronic kidney disease, particularly those requiring dialysis, and may be related to the variety of gastrointestinal motility derangements described in these patients (32,33). Hemodialysis has been shown to improve gastric motility; however, whether this reduces the risk of SIBO has not been demonstrated (34).

End Stage Liver Disease

SIBO appears to occur commonly in those with chronic liver disease, particularly those with more advanced forms involving portal hypertension (35). It may also be an independent risk factor for endotoxemia and spontaneous bacterial peritonitis (36), and has been suggested to play a pathogenic role in nonalcoholic fatty liver disease (37). The etiology seems to relate primarily to the presence of gastrointestinal dysmotility seen in this setting (38,39). Antibiotics and prokinetics improve SIBO associated with cirrhosis; liver transplantation has been shown to correct small bowel dysmotility.

Acute and Chronic Pancreatitis

SIBO may complicate the course of both acute and chronic pancreatitis and may be particularly prevalent, with reports of up to 40%, in those with associated pancreatic exocrine insufficiency (40–42). The mechanism is likely multifactorial including disease-related and treatment-related (e.g., opioid analgesics) intestinal dysmotility, hypochlorhydria and alterations in pancreaticobiliary secretions.

Diabetes Mellitus

SIBO occurs commonly in patients with diabetes mellitus, particularly those with gastroparesis (43,44). Although the pathophysiologic mechanism(s) remain incompletely defined, SIBO presumably occurs as a consequence of impaired gastrointestinal motility, which may, at least in part, be related to the presence of an underlying enteric and/or autonomic neuropathy. SIBO has recently been shown to be associated with the presence of cardiovascular autonomic neuropathy (45). Eradication of SIBO has been demonstrated to normalize orocecal transit in diabetics (46). An appreciation of the high prevalence of SIBO in those with diabetic gastroparesis underscores the need to address both issues when determining the optimal management strategy of these challenging patients.

Irritable Bowel Syndrome

Many patients with SIBO meet clinical criteria for irritable bowel syndrome and it has been suggested that SIBO may provide a unifying framework for understanding this condition (47). While initial reports suggested a high prevalence of SIBO in individuals with irritable bowel syndrome, subsequent reports have demonstrated a much lower prevalence, generally depending upon the diagnostic test used (48,49). Small bowel dysmotility has been suggested as the predisposing factor. A short course of antibiotic therapy may lead to an improvement in symptoms, although the duration of response remains uncertain (50).

Short Bowel Syndrome

SIBO can be an important complication in the patient with short bowel syndrome (SBS) and result in a variety of symptoms which may have deleterious effects on quality of life and, possibly, the ability to wean from parenteral nutrition (51). The anatomical and physiological changes that occur in SBS, together with medications commonly used in these patients, facilitate the development of SIBO. Unfortunately, at present, the identification of reliable risk factors in the SBS patient (e.g., bowel anatomy, length of remaining small bowel, presence of bowel dilatation) that should

Table 4
Factors That Can Influence Hydrogen Breath Tests

- Diet
- Exercise
- Tobacco smoking
- Recent use of antibiotics
- Rapid orocecal transit
- Methane producers with little or no hydrogen excretion
- Diagnostic criteria used

lead the clinician to have an increased suspicion of SIBO remains poorly defined (51).

Chronic Radiation Enteropathy

Chronic radiation enteropathy is often complicated by the development of SIBO. The underlying mechanism may be multifactorial including previous intestinal resections, intestinal strictures, epithelial dysfunction, intestinal dysmotility (52) and hypochlorhydria.

Immunodeficiency Syndromes

SIBO may complicate the course of a variety of immunodeficiency syndromes and has been reported in children and adults with common variable immunodeficiency, selective IgA deficiency and the acquired immunodeficiency syndrome among others (53,54). Although the mechanism(s) are unclear, the defect in immune function presumably plays a role.

DIAGNOSIS OF SIBO

Small Bowel Aspirate

SIBO should be considered in any individual with consistent symptoms, regardless of the presence of overt malabsorption, particularly when a predisposing anatomic or functional condition exists. The culture of aspirated small bowel fluid has traditionally been considered the gold standard in the diagnosis of SIBO, and despite significant limitations, is generally considered by most experts to be the preferred diagnostic test (55). A small bowel aspirate can be readily obtained during endoscopy, which is commonly performed in the evaluation of symptoms usually manifesting in the SIBO patient, by passing a sterile aspiration catheter through the working channel of the endoscope. Limitations include its invasiveness, expense, potential for contamination, potential for not detecting SIBO occurring in the more distal small intestine, and the difficulty in culturing the enteric microorganisms (47). Indeed, it is generally regarded that >50% of the bacterial species in the gut are not culturable. Therefore, the reliability of the technique has been questioned and indirect methods of detecting SIBO (e.g., hydrogen breath test; see below) have been developed as potential alternatives. It will be interesting to see whether recent improvements in the culture-independent, molecular microbial fingerprinting methods currently reserved for research can, in the future, be applied clinically in the diagnosis of SIBO and improve the utility of small bowel sampling via either fluid aspirate or mucosal biopsy.

Hydrogen Breath Testing

Bacteria are the sole source of hydrogen and methane in the gut. Hydrogen breath testing is the most commonly used alternative method to diagnose SIBO in clinical practice due to its low risk, inexpensive, portability and ease of use. Hydrogen breath testing utilizes an orally ingested carbohydrate (e.g., glucose, lactulose, xylose) as a substrate. In the presence of excessive bacteria in the small bowel, it is metabolized releasing hydrogen, which is subsequently absorbed and then released into the expired air. A rise in hydrogen (usually >20 parts per million (ppm)), generally within 90 to 120 minutes, in the breath sample after the oral administration of the substrate indicates SIBO. High fasting levels of hydrogen (>20 ppm) are also common in SIBO, but seem to lack both sensitivity and specificity (56,57). Despite a number of favorable characteristics of this diagnostic technique, several factors may influence the results of this test including diet, exercise, tobacco smoking, recent use of antibiotics, rapid orocecal transit, and the diagnostic criteria used (58) (Table 4). The hydrogen breath test is also

(continued on page 25)

(continued from page 22)

limited by the fact that up to 27% of the population are methane producers with little or no hydrogen excretion (59), a limitation that may be partly overcome by simultaneous measurement of expired methane. It is important to note that a lactose hydrogen breath test may be indicative of both lactose intolerance and/or SIBO. In addition, false positives can be seen in those with dumping syndrome and following gastric and intestinal resections. In general, hydrogen breath tests have demonstrated wide variations in sensitivity and specificity, hence, disappointing reliability to predict the results of small bowel culture (1,60).

Other Non-invasive Tests

Other noninvasive alternatives to direct culture of small bowel fluid and hydrogen breath testing are based on the detection of bacterial metabolites of either endogenous or exogenous substrates. The ^{14}C (and ^{13}C)-D-xylose breath test measures pulmonary excretion of radiolabeled CO_2 produced from bacterial fermentation of the labeled substrate. Initial reports using this technique suggested considerably better performance than the hydrogen breath test; however, more recent reports suggest widely ranging sensitivities and specificities (61,62). Disappointing results have also been seen with the measurement of products of luminal bacterial metabolism in urine (e.g., elevated indicans and cholyl-PABA) or blood (e.g., elevated D-lactate, short chain fatty acids and unconjugated bile acids) (63), and the ^{14}C-glycocholate breath test (64). The direct culture of unwashed small bowel mucosal biopsies remains promising, but requires further validation (65).

Ultimately, the determination of the presence of excess bacteria in the small bowel is much easier than determining whether the excess counts are responsible for the patient's symptoms. Although virtually all of the diagnostic techniques described are designed specifically to evaluate excess numbers of bacteria in the small bowel, they do not determine whether or not the bacteria are actually doing any harm. For this reason, biopsies of the small bowel may provide the best indication of whether or not the bacteria present are actually harmful. Inflammatory changes, villus blunting and the presence of adherent or intracellular bacteria, while uncommon, support the diagnosis of pathologic SIBO.

Because of the limitations and/or possibly the lack of wide-spread availability of the diagnostic tests of SIBO (66), it appears to be common clinical practice to provide empiric antibiotic treatment for individuals suspected of having SIBO. Caution is advised, however, when using the response to an empirical antibiotic therapy as a means of "diagnosing" SIBO as the response may be difficult to interpret and the diagnosis of SIBO can set in motion a process of frequent antibiotic use and the performance of numerous tests if the symptoms do not respond or return. For example, in those patients who do not seem to respond to antibiotics, it remains possible that SIBO may still be present. Similarly, in those patients who respond clinically to antibiotics, it may not necessarily occur because of the presence of SIBO, as antibiotics may have more generalized and nonspecific effects on the gut microbiota.

TREATMENT OF SIBO

Once pathologic SIBO has been identified, whenever possible, the underlying anatomic or functional disturbance should be corrected. Since this is usually not possible, the treatment tends to be multifactorial with the correction of the individual's nutritional state and microbial modification as the prime objectives. A reassessment of the need for antimotility and antisecretory medications, when applicable, should be undertaken (67). The use of prokinetic agents in the setting of intestinal dysmotility would appear to be beneficial to treat SIBO; however, little evidence exists to support their long-term efficacy in humans (68,69).

Nutritional intervention remains an important part of the management of SIBO. The initiation of a lactose-restricted diet, at least in the short-term, may result in a decrease of the development of gas-related symptoms and osmotic diarrhea in some individuals. Fat restriction with or without the addition of medium-chain triglycerides may be useful to reduce steatorrhea but is uncommonly needed in the absence of a coexisting cause of fat malabsorption (e.g., extensive intestinal resection or chronic pancreatitis with exocrine

Table 5
Antibiotic Options to Treat Small Intestinal Bacterial Overgrowth

Agent	*Dose*
Amoxicillin-clavulanate	500 mg PO 3 times/day
Cephalexin	250 mg PO 4 times/day
Chloramphenicol	250 mg PO 4 times/day
Ciprofloxacin	500 mg PO twice daily
Doxycycline	100 mg PO twice daily
Metronidazole	250 mg PO 3 times/day
Neomycin	500 mg PO twice daily
Norfloxacin	400 mg PO twice daily
Rifaximin	400 mg PO 3 times/day
Tetracycline	250 mg PO 4 times/day
Trimethoprim-sulfamethoxazole	1 double-strength tablet PO twice daily

PO = per os (by mouth)

insufficiency). The correction of micronutrient deficiencies when present, may also be necessary. In this regard, the periodic monitoring of micronutrient levels (e.g., fat-soluble vitamins, iron and vitamin B_{12} in particular) in SIBO patients should be considered. In the individual who presents with weight loss and malnutrition, nutritional supplements should be provided.

The goal when treating SIBO should not be to sterilize the gastrointestinal tract but rather to reduce the numbers of pathogenic bacteria present. As 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 is often used with success being judged on improvement in gas-related symptoms, reduction in stool output and/or weight gain. Given the diversity of organisms present in SIBO (70), antimicrobial therapy should provide coverage for both aerobic and anaerobic organisms; monotherapy directed against anaerobes should be avoided. Table 5 lists a variety of antibiotic regimens that have been proposed to treat SIBO. A variety of antibiotics have been reported to be effective in SIBO, but little objective evidence exists to favor one agent over another. In one of the few randomized, controlled trials of antibiotic therapy in SIBO, both amoxicillin-clavulanate and norfloxacin were shown to provide a modest reduction in stool frequency and lead to improvements in hydrogen breath testing (71). Recently, the poorly absorbed antibiotic, rifaximin, was shown to normalize the results of a glucose hydrogen breath test in substantially more individuals than those administered chlortetracycline (70% vs. 27%, respectively) (72).

A single seven-to-14 day course of antibiotic therapy will usually lead to an improvement in symptoms within a few days. Clinical response is generally used as a guide to the success or failure of the treatment, although in the occasional individual, repeat culture or breath testing may be considered. The duration of symptom improvement is highly variable and may depend upon the underlying cause of the SIBO (73). Because the underlying mechanism(s) responsible for causing SIBO are unlikely to change in most SBS patients, periodic (e.g., seven-to-14 days/month) or continuous use of antibiotics may be necessary. In this circumstance, periodic rotation of three or four different antibiotics is advised to reduce the risk of antibiotic resistance. Unfortunately, there are no controlled trials to offer assistance in the management of individuals with refractory or recurrent symptoms. In those who have had objective diagnosis of SIBO, but do not respond to antimicrobial therapy, clinical experience suggests that it may be useful to perform a qualitative culture with antimicrobial sensitivity testing of small bowel contents.

Because of the concern over the development of antimicrobial resistance, antibiotic-associated allergic reactions, *Clostridium difficile* diarrhea and the expense 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 demonstrated efficacy in some clinical applications, the role of these agents in the management of SIBO remains unproven (71,74). Indeed, only anecdotal reports have suggested efficacy of probiotics in the management of SIBO, a finding that may relate to the limited effect of the probiotic organisms on the overall number of luminal organisms present. Nevertheless, further studies in this area seem warranted given the low risk associated with their use. ■

References

1. Corazza GR, Menozzi MG, Strocchi A, et al. The diagnosis of small bowel bacterial overgrowth. Reliability of jejunal culture and inadequacy of breath hydrogen testing. *Gastroenterology*, 1990;98:302-309.
2. Kohler H, McCormick BA, Walker WA. Bacterial-enterocyte crosstalk: cellular mechanisms in health and disease. *J Pediatr Gastroenterol Nutr,* 2003;36:175-185.
3. Jorgensen JR, Fitch MD, Mortensen PB, Fleming SE. In vivo absorption of medium-chain fatty acids by the rat colon exceeds that of short-chain fatty acids. *Gastroenterology*, 2001;120:1152-1161.
4. Ley RE, Turnbaugh PJ, Klein S, Gordon JI. Microbial ecology: human gut microbes associated with obesity. *Nature*, 2006;444:1022-1023.
5. DiBaise JK, Zhang H, Crowell MD, et al. Gut microbiota and its possible relationship to obesity. *Mayo Clin Proc,* 2008;83:460-469.
6. Gorbach SL. Probiotics and gastrointestinal health. *Am J Gastroenterol,* 2000;95:S2-S4.
7. Kaufman SS, Loseke CA, Lupo JV, et al. Influence of bacterial overgrowth and intestinal inflammation on duration of parenteral nutrition in children with short bowel syndrome. *J Pediatr,* 1997;131:356-361.
8. Ament ME, Shimoda SS, Saunders DR, Rubin CE. Pathogenesis of steatorrhea in three cases of small intestinal stasis syndrome. *Gastroenterology*, 1972;63:728-747.
9. Toskes PP, Giannella RA, Jervis HR, et al. Small intestinal mucosal injury in the experimental blind loop syndrome. Light- and electron-microscopic and histochemical studies. *Gastroenterology*, 1975;68:193-203.
10. Riordan SM, McIver CJ, Wakefield D, et al. Small intestinal bacterial overgrowth in the symptomatic elderly. *Am J Gastroenterol,* 1997;92:47-51.
11. Riepe SP, Goldstein J, Alpers DH. Effect of secreted Bacteroides proteases on human intestinal brush border hydrolases. *J Clin Invest,* 1980;66:314-322.
12. Welkos SL, Toskes PP, Baer H. Importance of anaerobic bacteria in the cobalamin malabsorption of the experimental rat blind loop syndrome. *Gastroenterology*, 1981;80: 313-320.
13. Shindo K, Machida M, Koide K, et al. Deconjugation ability of bacteria isolated from the jejunal fluid of patients with progressive systemic sclerosis and its gastric pH. *Hepatogastroenterology*, 1998;45:1643-1650.
14. Tabaqchali S, Hatzioannou J, Booth CC. Bile-salt deconjugation and steatorhoea in patients with the stagnant-loop syndrome. *Lancet*, 1968;2:12-16.
15. Oumi M, Yamamoto T. A scanning electron microscope study on the effects of different bile salts on the epithelial lining of jejunal mucosa. *Med Electron Microsc,* 2000;33:11-15.
16. Giannella RA, Rout WR, Toskes PP. Jejunal brush border injury and impaired sugar and amino acid uptake in the blind loop syndrome. *Gastroenterology*, 1974;67:965-974.
17. Sherman P, Wesley A, Forstner G. Sequential disaccharidase loss in rat intestinal blind loops: impact of malnutrition. *Am J Physiol,* 1985;248:G626-G632.
18. King CE, Toskes PP. Protein-losing enteropathy in the human and experimental rat blind-loop syndrome. *Gastroenterology*, 1981;80:504-509.
19. Rutgeerts L, Mainguet P, Tytgat G, Eggermont E. Enterokinase in contaminated small-bowel syndrome. *Digestion*, 1974;10:249-254.
20. Stotzer PO, Bjornsson ES, Abrahamsson H. Interdigestive and postprandial motility in small-intestinal bacterial overgrowth. *Scand J Gastroenterol,* 1996;31:875-880.
21. Vantrappen G, Janssens J, Hellemans J, Ghoos Y. The interdigestive motor complex of normal subjects and patients with bacterial overgrowth of the small intestine. *J Clin Invest,* 1977;59:1158-1166.
22. Fich A, Steadman CJ, Phillips SF, et al. Ileocolonic transit does not change after right hemicolectomy. *Gastroenterology*, 1992;103:794-799.
23. Holt P. Diarrhea and malabsorption in the elderly. *Gastroenterol Clin North Am,* 2001; 30:427-444.
24. Finegold SM, Sutter VL. Fecal flora in different populations, with special reference to diet. *Am J Clin Nutr,* 1978;31:S116-S122.
25. Collins MD, Gibson GR. Probiotics, prebiotics, and synbiotics: approaches for modulating the microbial ecology of the gut. *Am J Clin Nutr,* 1999;69:1052S-1057S.
26. Castiglione F, Rispo A, Di Girolamo E, et al. Antibiotic treatment of small bowel intestinal overgrowth in patients with Crohn's disease. *Aliment Pharmacol Ther,* 2003; 18:1107-1112.
27. Mishkin D, Boston FM, Blank D, et al. The glucose breath test: a diagnostic test for small bowel stricture(s) in Crohn's disease. *Dig Dis Sci,* 2002;47:489-494.
28. Castiglione F, Del Vecchio Blancho G, Rispo A, et al. Orocaecal transit time and bacterial overgrowth in patients with Crohn's disease. *J Clin Gastroenterol,* 2000;31:63-66.
29. Lisowska A, Banasiewicz T, Marciniak R, et al. Chronic pouchitis is not related to small intestine bacterial overgrowth. *Inflamm Bowel Dis,* 2008;14:1102-1104.
30. Tursi A, Brandimarte G, Giorgetti G. High prevalence of small intestinal bacterial overgrowth in celiac patients with persistence of gastrointestinal symptoms after gluten withdrawal. *Am J Gastroenterol,* 2003;98:839-843.
31. Leffler DA, Dennis M, Hyett B, et al. Etiologies and predictors in nonresponsive celiac disease. *Clin Gastroenterol Hepatol,* 2007;5:445-450.
32. Strid H, Simren M, Stotzer PO, et al. Delay in gastric emptying in patients with chronic renal failure. *Scand J Gastroenterol,* 2004;39:516-520.
33. Strid H, Simren M, Stotzer PO, et al. Patients with chronic renal failure have abnormal small intestinal motility and a high prevalence of small intestinal bacterial overgrowth. *Digestion*, 2003;67:129-137.
34. Adachi H, Kamiya T, Hirako M, et al. Improvement of gastric motility by hemodialysis in patients with chronic renal failure. *J Smooth Muscle Res,* 2007;43:179-189.
35. Gunnarsdottir SA, Sadik R, Shev S, et al. Small intestinal motility disturbances and bacterial overgrowth in patients with liver cirrhosis and portal hypertension. *Am J Gastroenterol,* 2003;98:1362-1370.
36. Bauer TM, Steinbruckner B, Brinkmann FE, et al. Small intestinal bacterial overgrowth in patients with cirrhosis: prevalence and relation with spontaneous bacterial peritonitis. *Am J Gastroenterol,* 2001;96:2962-2967.

37. Sabate JM, Jouet P, Hanrois F, et al. High prevalence of small intestinal bacterial overgrowth in patients with morbid obesity: a contributor to severe hepatic steatosis. *Obes Surg,* 2008;18:371-377.
38. Gunnarsdottir SA, Sadik R, Shev S, et al. Small intestinal motility disturbances and bacterial overgrowth in patients with liver cirrhosis and portal hypertension. *Am J Gastroenterol,* 2003;98:1362-1370.
39. Soza A, Riquelme A, Gonzalez R, et al. Increased orocecal transit time in patients with nonalcoholic fatty liver disease. *Dig Dis Sci,* 2005;1136-1140.
40. Trespi E, Ferrieri A. Intestinal bacterial overgrowth during chronic pancreatitis. *Curr Med Res Opin,* 1999;15:47-52.
41. Van Felius ID, Akkermans LM, Bosscha K, et al. Interdigestive small bowel motility and duodenal bacterial overgrowth in experimental acute pancreatitis. *Neurogastroenterol Motil,* 2003;15:267-276.
42. Casellas F, Guarner L, Vaquero E, et al. Hydrogen breath test with glucose in exocrine pancreatic insufficiency. *Pancreas*, 1998;16:481-486.
43. Virally-Monod M, Tielmans D, Kevorkian JP, et al. Chronic diarrhea and diabetes mellitus: prevalence of small intestinal bacterial overgrowth. *Diabetes Metab,* 1998;43: 2373-2378.
44. Reddymasu S, Sarosiek I, Sostarich S, McCallum R. Incidence and predictors of small intestinal bacterial overgrowth in gastroparesis. *Gastroenterology*, 2008;134:A97 (abstract).
45. Zietz B, Lock G, Straub RH, et al. Small-bowel bacterial overgrowth in diabetic subjects is associated with cardiovascular autonomic neuropathy. *Diabetes Care,* 2000;23:1200-1201.
46. Cuoco L, Montalto M, Jorizzo RA, et al. Eradication of small intestinal bacterial overgrowth and oro-cecal transit in diabetics. *Hepato-Gastroenterol,* 2002;49:1582-1586.
47. Lin HC. Small intestinal bacterial overgrowth: a framework for understanding irritable bowel syndrome. *JAMA*, 2004;292:852-858.
48. Posserud I, Stotazer PO, Bjornsson ES, et al. Small intestinal bacterial overgrowth in patients with irritable bowel syndrome. *Gut*, 2007;56:802-808.
49. Pimentel M, Chow EJ, Lin HC. Eradication of small intestinal bacterial overgrowth reduces symptoms of irritable bowel syndrome. *Am J Gastroenterol,* 2000;95:3503-3506.
50. Pimentel M, Park S, Mirocha J, et al. The effect of a nonabsorbed oral antibiotic (rifaximin) on the symptoms of the irritable bowel syndrome: a randomized trial. *Ann Intern Med,* 2006 17;145:557-563.
51. DiBaise JK, Young RJ, Vanderhoof JA. Enteric microbial flora, bacterial overgrowth and short bowel syndrome. *Clin Gastroenterol Hepatol,* 2006;4:11-20.
52. Husebye E, Skar V, Hoverstad T, et al. Abnormal intestinal motor patterns explain enteric colonization with Gram-negative bacilli in late radiation enteropathy. *Gastroenterology*, 1995;109:1078-1089.
53. Pignata C, Budillon G, Monaco G, et al. Jejunal bacterial overgrowth and intestinal permeability in children with immunodeficiency syndromes. *Gut*, 1990;31:879-882.
54. Rubio-Tapia A, Hernández-Calleros J, Trinidad-Hernández S, Uscanga L. Clinical characteristics of a group of adults with nodular lymphoid hyperplasia: a single center experience. *World J Gastroenterol,* 2006;28:1945-1948.
55. Riordan SM, McIver CJ, Walker BM, et al. The lactulose breath hydrogen test and small intestinal bacterial overgrowth. *Am J Gastroenterol,* 1996;91:1795-1803.
56. Kerlin P, Wong L. Breath hydrogen testing in bacterial overgrowth of the small intestine. *Gastroenterology*, 1988;95:982-988.
57. Riordan SM, McIver CJ, Bolin TD, Duncombe VM. Fasting breath hydrogen concentrations in gastric and small-intestinal bacterial overgrowth. *Scand J Gastroenterol,* 1995;30:252-257.
58. Sellin JH, Hart R. Glucose malabsorption associated with rapid intestinal transit. *Am J Gastroenterol,* 1992;87:584-589.
59. Romagnuolo J, Schiller D, Bailey RJ. Using breath tests wisely in a gastroenterology practice: an evidence-based review of indications and pitfalls in interpretation. *Am J Gastroenterol,* 2002; 97:1113-1126.
60. Schiller LR. Evaluation of small bowel bacterial overgrowth. *Curr Gastroenterol Rep,* 2007;9:373-377.
61. King CE, Toskes PP, et al. Comparison of the 1-gram [14C]xylose, 10-gram lactulose-H2, and 80-gram glucose-H2 breath tests in patients with small intestine bacterial overgrowth. *Gastroenterology*, 1986;91:1447-1451.
62. Riordan SM, McIver CJ, Duncombe VM, et al. Factors influencing the 1-g 14C-D-xylose breath test for bacterial overgrowth. *Am J Gastroenterol,* 1995;90:1455-1460.
63. Kirsch M. Bacterial overgrowth. *Am J Gastroenterol,* 1990;85: 231-237.
64. Watson WS, McKenzie I, Holden RJ, et al. An evaluation of the 14C-glycocholic acid breath test in the diagnosis of bacterial colonisation of the jejunum. *Scott Med J,* 1980; 25:27-32.
65. Riordan SM, McIver CJ, Duncombe VM, Bolin TD. Bacteriologic analysis of mucosal biopsy specimens for detecting small-intestinal bacterial overgrowth. *Scand J Gastroenterol,* 1995;30:681-685.
66. Khoshini R, Dai SC, Lezcano S, Pimentel M. A systematic review of diagnostic tests for small intestinal bacterial overgrowth. *Dig Dis Sci,* 2007;8:1443-1454.
67. Fried M, Siegrist H, Frei R, et al. Duodenal bacterial overgrowth during treatment in outpatients with omeprazole. *Gut*, 1994;35:23-26.
68. Pardo A, Baroli R, Lorenzo-Zuniga V, et al. Effect of cisapride on intestinal bacterial overgrowth and bacterial translocation in cirrhosis. *Hepatology*, 2000;31:858-863.
69. Soudah HC, Hasler WL, Owyang C. Effect of octreotide on intestinal motility and bacterial overgrowth in scleroderma. *NEJM*, 1991;325:1461-1467.
70. Bouhnik Y, Alain S, Attar A, et al. Bacterial populations contaminating the upper gut in patients with small intestinal bacterial overgrowth syndrome. *Am J Gastroenterol,* 1999; 94:1327-1331.
71. Attar A, Flourie B, Rambaud JC, et al. Antibiotic efficacy in small intestinal bacterial overgrowth-related chronic diarrhea: a crossover, randomized trial. *Gastroenterology*, 1999;117:794-797.
72. Di Stefano M, Malservisi S, Veneto G, et al. Rifaximin versus chlortetracycline in the short-term treatment of small intestinal bacterial overgrowth. *Ali Pharmacol Ther,* 2000; 12:551-556.
73. Lauritano EC, Gabrielli M, Scarpellini E, et al. Small intestinal bacterial overgrowth recurrence after antibiotic therapy. *Am J Gastroenterol,* 2008;103:2031-2035.
74. Stotzer PO, Blomberg L, Conway PL, et al. Probiotic treatment of small intestinal bacterial overgrowth by Lactobacillus fermentum KLD. *Scan J Infect Dis,* 1996;28:1892-1901.