Small Bowel Bacterial Overgrowth: Presentation, Diagnosis, and Treatment

Virmeet V. Singh, MD and Phillip P. Toskes, MD

Address
Department of Medicine, Division of Gastroenterology, Hepatology and Nutrition, University of Florida, PO Box 100214, Gainesville, FL 32610-0214, USA.
E-mail: toskepp@medicine.ufl.edu

Current Gastroenterology Reports 2003, **5:**365–372
Current Science Inc. ISSN 1522-8037

Small bowel bacterial overgrowth (SBBO) syndrome is associated with excessive numbers of bacteria in the proximal small intestine. The pathology of this condition involves competition between the bacteria and the human host for ingested nutrients. This competition leads to intraluminal bacterial catabolism of nutrients, often with production of toxic metabolites and injury to the enterocyte. A complex array of clinical symptoms ensues, resulting in chronic diarrhea, steatorrhea, macrocytic anemia, weight loss, and less commonly, protein-losing enteropathy. Therapy is targeted at correction of underlying small bowel abnormalities that predispose to SBBO and appropriate antibiotic therapy. The symptoms and signs of SBBO can be reversed with this approach.

Introduction

When overgrowth of bacteria occurs in the small bowel proximal to the distal ileum, symptoms of vitamin malabsorption, malnutrition, and weight loss may occur. This clinical entity is known as blind loop, stagnant loop syndrome, or small bowel bacterial overgrowth (SBBO) syndrome. In this syndrome the enteric flora of the proximal small intestine resemble those of the healthy colon [1]. The high concentration of bacteria interferes with normal small bowel nutrient absorption, and patients develop malnutrition and such gastroenterologic symptoms as diarrhea, steatorrhea, and macrocytic anemia, which can significantly impair quality of life. Patients at risk are those with dysmotility syndromes, anatomic alterations of the gastrointestinal tract secondary to surgery, certain medical conditions, or advanced age. SBBO may also be an underappreciated cause of malnutrition in the elderly [2–4]. Treatment options are aimed at returning the small intestine to its normal bacterial environment, which includes treatment of predisposing conditions associated with bacterial overgrowth and antibiotic therapy [5••].

A comprehensive understanding of SBBO requires a sound knowledge of several key aspects of the gastrointestinal tract, including motility, physiology of nutrient absorption, and indigenous flora. In this review, emphasis is placed on pitfalls in the diagnosis of SBBO and recent trends in the management of this clinical condition.

Pathophysiology

Understanding the pathophysiology of SBBO involves an intimate knowledge of small bowel homeostasis, mechanisms of malabsorption, and predisposing factors for the disorder.

Homeostasis

In the healthy human host, control of the growth of enteric bacterial populations is multifactorial. The most important control mechanisms are the ability of gastric acid to inhibit or kill swallowed microorganisms and the cleansing effects of normal intestinal motility [1]. Other important mechanisms include immunoglobulins in the intestinal secretions and an intact ileocecal valve. Achlorhydria resulting from gastric mucosal atrophy, gastric resection, vagotomy, or highly effective antacid or antisecretory therapies permit viable swallowed bacteria to pass into the small intestine [6–9].

In the small bowel, the cleansing action of antegrade peristalsis, especially the migratory motor complex (MMC), is responsible for sweeping bacteria into the colon [10]. Thus, conditions that result in dysmotility of the small bowel are frequently complicated by bacterial overgrowth, which may not necessarily be symptomatic [1,6,7].

Stagnation of intraluminal flow and incomplete competence of the ileocecal sphincter account for the ordinarily higher bacterial counts in the distal ileum. In the colon, bacterial interaction, competition for nutrients, and the anaerobic environment attributable to bacterial metabolism are significant factors that control microbial populations.

Antibiotic therapy is known to alter microflora of the intestinal tract by the eradication or suppression of selected populations of bacteria while permitting resistant microbes to flourish. These effects depend on the composition of the native enteric flora and the spectrum of activity, dose, route of administration, duration of treatment, and pharmacokinetics of the antibiotic [11].

Table 1. Clinical conditions associated with bacterial overgrowth

Gastric
Hypochlorhydria or achlorhydria: atrophic gastropathy, gastrectomy, vagotomy
Sustained hypochlorhydria induced by proton-pump inhibitors
Surgery
Resection of diseased ileocecal valve
Afferent loop of Billroth II partial gastrectomy
Surgical blind loop (end-to-side anastomosis)
Anatomic
Intestinal obstruction (stricture, inflammation, neoplasm, radiation enteropathy)
Duodenal-jejunal diverticulosis
Gastrocolic or jejunocolic fistula
Dysmotility
Scleroderma
Idiopathic intestinal pseudoobstruction
Absent or disordered migrating motor complex
Diabetic autonomic neuropathy
Miscellaneous medical conditions
Crohn's disease
Chronic pancreatitis
Cirrhosis
Immunodeficiency syndromes
End-stage renal disease

There is some evidence to support a contributing role of the immune system in the regulation of the intestinal flora. Patients with SBBO may have altered levels of intraluminal secretory IgA or increased mucosal IgA immunocytes [12,13]. However, bacterial overgrowth in the elderly seems not to be related to immunosenescence [14]. Other modulating factors that are less well described include the bacterial production of bacteriocins, toxic metabolites, transfer of antibiotic resistance, and the role of the mucosa in elaborating growth factors. Little evidence is available to indicate a significant role for dietary composition or manipulation on regulation of the microbial population of the normal bowel [1].

Mechanisms of malabsorption

In general, malabsorption in SBBO can be attributed to the intraluminal effects of proliferating bacteria combined with the damage to small bowel enterocytes. A characteristic microscopic small bowel mucosal lesion is usually seen, consisting of villous blunting, loss of structural integrity of epithelial cells, and inflammatory infiltrate of the lamina propria. Various functional consequences of this damage have been detected, including diminished disaccharidase activity; decreased transport of monosaccharides, amino acids, and fatty acids; and protein-losing enteropathy [1].

Fat malabsorption (steatorrhea) in SBBO is a consequence of small intestine bacterial deconjugation of bile salts and impaired transport of lipid through the damaged small bowel enterocyte. Water-soluble conjugated bile salts are normally secreted to form mixed micelles with partially digested dietary lipids. These conjugated bile salts are not readily reabsorbed until they reach the ileum. When bacteria overgrow in the proximal small bowel, they deconjugate bile salts to form free bile acids, which are readily absorbed by the jejunum. This process may impair formation of the bile–salt–lipid micelle complex, so that dietary fat is malabsorbed. In addition, the free bile acids formed in SBBO may be toxic to the mucosa and contribute directly to the patchy mucosal lesion of SBBO [15]. Malabsorption of fat-soluble vitamins (vitamins A, D, E, and K) may occur as a consequence of general fat malabsorption, but this is seldom of any clinical significance.

Carbohydrate malabsorption may also be a consequence of SBBO. This may result from a combination of intraluminal carbohydrate degradation by bacteria and damage to the brush border disaccharidase functions of the small bowel mucosa. Furthermore, malabsorbed carbohydrates can be catabolized by small bowel and colonic bacteria to form short-chain organic acids that increase osmolarity of the intestinal fluid and contribute to diarrhea. Protein malabsorption results from a combination of impaired absorption of amino acids, intraluminal utilization of protein by bacteria, and protein-losing enteropathy caused by mucosal damage and leakage of protein into the lumen [1,16–18].

Cobalamin (vitamin B_{12}) deficiency that cannot be corrected by intrinsic factor but improves after antibiotic administration is a classic manifestation of SBBO. At the resident pH of the proximal small bowel, gastric intrinsic factor normally binds tightly to cobalamin, facilitating its absorption in the distal ileum. However, in SBBO, various anaerobic and facultative gram-negative aerobes competitively utilize dietary cobalamin. Intrinsic factor inhibits cobalamin utilization by aerobic bacteria but has no effect on the ability of gram-negative anaerobic flora to take up dietary cobalamin [19]. Although enteric bacteria also synthesize some cobalamin, they retain this vitamin, and thus it remains unavailable to the host for absorption. Paradoxically, cobalamin deficiency then ensues in patients with SBBO although they harbor large quantities of the vitamin within bacteria in their small bowel.

Two additional factors may contribute to the pathogenesis of diarrhea and other features of SBBO. First, such bacterial metabolites as free bile acids, hydroxylated fatty acids, and other organic acids stimulate secretion of water and electrolytes into the bowel lumen. This effect may contribute to the secretory diarrhea in SBBO. Second, experimental bacterial overgrowth in rats may induce further dysmotility of the bowel, which may encourage further bacterial overgrowth [20].

Predisposing factors

Various clinical disorders predispose patients to SBBO (Table 1). The common underlying factors of most of these conditions are 1) small intestinal stagnation or dysmotil-

Table 2. Symptoms associated with bacterial overgrowth

Bloating
Abdominal discomfort
Diarrhea
Weight loss
Weakness
Neuropathy

ity; or 2) decreased gastric acid secretion. Before the recognition of *Helicobacter pylori* infection as a common cause of duodenal ulcer disease, aggressive surgical management of this condition was common. The most frequent procedure was Billroth II gastrojejunostomy, which created a stagnant afferent loop that often resulted in bacterial overgrowth. Similarly, stagnant loops of intestine and bacterial overgrowth result from enteroenteric fistulae that complicate Crohn's disease or the surgical enterostomies often used to manage this disease. In patients with gastrocolic or gastrojejunocolic fistulae, massive overgrowth and severe malabsorption may develop [1].

Obstruction or dysmotility of the small bowel caused by such diverse problems as Crohn's disease, radiation enteropathy, adhesions, or tuberculosis may cause SBBO [1,21]. Other intestinal motility disorders, often coupled with hypochlorhydria, also predispose to SBBO. These disorders include scleroderma, chronic intestinal pseudoobstruction, diabetes mellitus, and cystic fibrosis [9,22,23]. Duodenal and jejunal diverticula may also be overgrown with bacteria, especially in patients with hypo- or achlorhydria [1].

Other clinical entities with a possible association with SBBO include chronic pancreatitis [24], end-stage renal disease, myotonic muscular dystrophy, fibromyalgia, chronic fatigue syndrome, and cirrhosis [25–29]. The underlying pathophysiologic mechanism of bacterial overgrowth described in these conditions has not been fully elucidated.

The importance of normal gastric acidity and normal intestinal motility is highlighted by experience in some patients with scleroderma and reflux esophagitis in whom symptomatic malabsorption developed when proton pump inhibitor therapy was substituted for less effective H_2 receptor antagonist therapy [30]. Indeed, the impact of highly effective antacid therapy, especially proton pump inhibitors, on the subsequent occurrence of SBBO is beginning to be appreciated [31]. Bacterial overgrowth has also been described in patients with various immunodeficiency syndromes, including chronic lymphocytic leukemia [32] and immunoglobulin deficiencies.

Healthy elderly subjects have been found to have SBBO without recognized problems with nutrient absorption, a condition known as simple colonization [3,6]. However, symptomatic SBBO may develop in the elderly as a consequence of dysmotility and hypo- or achlorhydria. In the elderly, the symptoms of malabsorption may be covert, leading to a delay in diagnosis. Because the elderly have less nutritional reserve than the young, these nutrient deficiencies are clinically much more devastating. Some authorities believe that SBBO may be the most common cause of clinically relevant malabsorption in the geriatric population [10,33].

Table 3. Clinical findings in small bowel bacterial overgrowth

Findings	Consequences
Cobalamin (vitamin B_{12}) deficiency	Peripheral neuropathy, megaloblastic anemia
Fat-soluble vitamin deficiency	
Vitamin A	Night blindness, xeropthalmia
Vitamin D	Osteomalacia, hypocalcemic tetany
Vitamin E	Neuropathy, hemolysis
Vitamin K	Coagulopathy
Hypoproteinemia and hypoalbuminemia	Edema
Fat malabsorption	Weight loss, steatorrhea, diarrhea
Carbohydrate malabsorption	Weight loss, diarrhea
Iron deficiency	Microcytic anemia

Clinical Features

The clinical consequences of SBBO are similar regardless of the underlying predisposing factors for overgrowth. However, individual symptoms vary depending on the nature of the primary small bowel abnormality (Tables 2 and 3).

Patients with small bowel strictures, obstruction, dysmotility, or surgically formed blind loops of bowel typically complain of variable abdominal discomfort, bloating, or periumbilical cramps, which may be followed over a period of several months or years by the development of diarrhea and malabsorption. In patients with scleroderma, Crohn's disease, chronic intestinal pseudoobstruction, radiation enteritis, or short bowel syndrome, it may be difficult to determine the extent to which symptoms and malabsorption are attributable to the primary disease or to SBBO. Small bowel diverticula, which may be multiple in the elderly, are generally asymptomatic for many years before bacterial overgrowth is sufficient to cause malabsorption, often a consequence of associated hypo- or achlorhydria [1].

Cobalamin malabsorption caused by SBBO results in macrocytic and megaloblastic anemia. In severe and prolonged cases, characteristic neurologic damage, including posterolateral spinal cord demyelinization, peripheral neuropathy, and cerebral cognitive defects, can develop. In one third of patients with SBBO severe enough to cause cobalamin deficiency, weight loss occurs that is associated with clinically demonstrable steatorrhea [1].

Malabsorption of fat-soluble vitamins can cause night blindness (vitamin A), osteomalacia and hypocalcemic tet-

any (vitamin D), coagulopathy (vitamin K), or vitamin E deficiency syndromes (neuropathy, T-cell abnormalities) [18]. Additionally, iron deficiency anemia may occur from internal blood loss, perhaps secondary to ulcerations within the stagnant bowel loops. Consequently, patients with SBBO may also have detectable fecal occult blood and hypochromic macrocytic anemia coincident with megaloblastic anemia [34].

Hypoproteinemia and hypoalbuminemia are common but reversible consequences of SBBO and can be severe enough to cause edema. Similarly, SBBO results in intraluminal catabolism of carbohydrates, dysfunction of mucosal disaccharides, and malabsorption of sugars [16]. The products of this disordered carbohydrate digestion, short-chain organic acids, may contribute to osmolar and pH changes in the colon and may aggravate watery diarrhea in SBBO.

Is SBBO the cause of the bloating, diarrhea, abdominal distention, and abdominal pain observed in patients with irritable bowel syndrome (IBS)? A recent study suggests that as many as 78% of 202 IBS patients may have SBBO [35]. However, this study suffered from such methodologic deficiencies as diagnosing SBBO by a lactulose-hydrogen breath test, and it lacked appropriate control subjects [36,37]. Indeed, a very recent preliminary study using quantitative cultures from the small bowel found that only 10% of patients with IBS had documented SBBO [38]. Although some patients with IBS probably have SBBO, this association is not likely to be common.

Diagnosis

Symptoms of diarrhea, weight loss, bloating, and flatulence in patients with a coexisting predisposition to SBBO, regardless of whether malabsorption has been demonstrated, should prompt the clinician to consider testing for bacterial overgrowth, especially if patients have failed to respond to empiric measures [10]. Any patients with a known predisposition to bacterial overgrowth who has diarrhea, steatorrhea, weight loss, and cobalamin deficiency should be evaluated for SBBO.

With the recent decline in surgery for the management of peptic ulcer disease, the diagnosis of SBBO is now considered most commonly in patients with problems other than those associated with gastrointestinal surgery. The lack of response of dysmotility syndromes (especially gastroparesis and IBS) and pancreatic insufficiency to pancreatic enzyme therapy is a frequent reason for referral to centers that specialize in testing for SBBO [39]. Differentiation of the symptoms of these disorders from similar symptoms that might be caused by superimposed SBBO is critical to the treatment of these patients and requires sophisticated testing. The history of gastrointestinal surgery in patients with symptoms of SBBO should prompt a review of whether that surgery resulted in construction of an afferent loop (Billroth II procedure, end-to-side or side-to-side small bowel anastomosis).

Recurrent symptoms of small bowel obstruction may result from strictures, adhesions, dysmotility, or intestinal pseudoobstruction, which can cause stasis and bacterial overgrowth. Dysphagia and other symptoms of systemic sclerosis should suggest scleroderma as an explanation of symptoms of malabsorption resulting from bacterial overgrowth. The barium small bowel series radiograph is an appropriate noninvasive study for these conditions and for small bowel diverticula or fistulae. Basic laboratory evaluations should include an analysis of fat in the stool to document steatorrhea and an intestinal culture.

Breath tests

The use of jejunal aspiration and culture for diagnosis of SBBO is cumbersome. The ongoing search for noninvasive diagnostic alternatives has led to the development of a variety of tests that measure the excretion of volatile metabolites produced by intraluminal bacteria in the expired breath. The most successful and popular methods analyze expired isotope-labeled CO_2 after timed oral administration of ^{14}carbon (^{14}C), ^{13}C-enriched substrates, or breath hydrogen after feeding of an unlabeled fermentable carbohydrate substrate [28,40•,41,42]. The first promising breath test for bacterial overgrowth was the bile acid or ^{14}C-cholylglycine test. This technique was based on the premise that small bowel bacteria in high concentrations would deconjugate this bile salt. However, the test was only moderately sensitive for detecting bacterial overgrowth, with a false-negative rate of 30% to 40% [43,44]. Furthermore, the specificity of this test was poor because of colonic bacterial deconjugation of unabsorbed bile salt in case of ileal damage or resection.

The ^{14}C-D-xylose breath test is more sensitive and specific [28]. Xylose is catabolized by aerobic gram-negative overgrowth flora. Both $^{14}CO_2$ produced by bacterial fermentation of xylose and unmetabolized xylose are absorbed by the proximal small bowel, eliminating the confusion of results caused by metabolization of substrate downstream by colonic bacteria. Following a 1-g oral dose of ^{14}C-D-xylose, elevated $^{14}CO_2$ levels were detected in the breath within 60 minutes in 85% of patients with SBBO. The sensitivity and specificity of the ^{14}C-D-xylose breath test are superior to those of the ^{14}C-bile acid test. Consequently, the ^{14}C-D-xylose test became a popular and reliable surrogate test for bacterial overgrowth. Although a few recent studies have raised doubts about the accuracy of this test [6,41,45,46], its rate of accuracy is 90% when compared with a properly performed intestinal culture and with attention focused on the first 30-minute breath analysis.

Because mammalian tissue does not generate hydrogen, detection of hydrogen in expired breath is considered a measure of the metabolic activity of enteric bacteria. This observation suggests that measurement of breath-hydrogen could circumvent the administration of a radioactive isotope in testing for bacterial overgrowth. Such a strategy would be useful for the study of children and fertile

Table 4. Antimicrobial agents for treatment of small bowel bacterial overgrowth

Antibiotic	Dosage (10-day course)
Amoxicillin–clavulanic acid	750 mg twice a day
Cephalexin+metronidazole	250 mg four times a day + 250 mg three times a day
Trimethoprim-sulfamethoxazole	One double-strength tablet twice a day
Ciprofloxacin	500 mg twice a day
Norfloxacin	400 mg twice a day
Colistin+metronidazole	250,000 IU/kg/d + 250 mg twice a day
Doxycycline	100 mg twice a day
Tetracycline	250 mg four times a day
Minocycline	100 mg twice a day
Chloramphenicol	250 mg four times a day

women, for whom breath tests using a radioactive isotope as the substrate are not recommended.

In individuals with bacterial overgrowth, excessive breath-hydrogen production has been detected in up to 30% of fasting patients and after oral administration of 50 to 80 g of glucose or 10 to12 g of lactulose [47]. Despite the simplicity of breath-hydrogen testing, numerous factors influence the results of this test. Antibiotics and laxatives must be avoided perhaps for weeks prior to breath-hydrogen testing. Bread, pasta, and fiber must not be consumed the night before the test because these foods cause prolonged hydrogen excretion. Cigarette smoking and exercise must be avoided before and during the test. Chlorhexadine mouthwash must be used before the test to eliminate oral bacteria, which may contribute to an early hydrogen peak after the substrate is given. Also, strict interpretive criteria are recommended, including two consecutive breath-hydrogen values more than 10 ppm above the baseline reading and recording of a clear distinction of the small bowel peak from the subsequent colonic peak (double-peak criterion). The poor sensitivity of breath-hydrogen testing may also result from inadequate fermentation by enteric flora (approximately 25%–40% of subjects harbor bacteria that do not ferment lactulose), rapid absorption of glucose in the proximal small bowel, a washout effect of concomitant diarrhea, or an acidic bowel lumen (which inhibits hydrogen generation) [48].

In a recent study Riordan *et al.* [42] examined the diagnostic value of the 10-g lactulose breath-hydrogen test and of a scintigraphic orocecal transit study, compared with small bowel culture. The sensitivity of the breath test alone to detect SBBO was only 16.7%, and the specificity was 70%. The combination of breath testing with scintigraphy increased specificity to 100%, but sensitivity was only 38.9%. Application of the double-peak criterion alone for interpretation of the lactulose breath-hydrogen test was thus inadequately sensitive to diagnose bacterial overgrowth, even with scintigraphy.

Other investigators have encountered similar problems with the sensitivity and specificity of either the lactulose or the glucose hydrogen-breath test compared with intestinal culture [49,50]. One controlled trial compared the glucose and lactulose hydrogen-breath tests with the 1-g ^{14}C-D-xylose breath test in 10 control subjects and 20 patients with culture-proven bacterial overgrowth. The ^{14}C-D-xylose test had a 95% sensitivity rate and a 100% specificity rate. In contrast, the breath-hydrogen test results were often uninterpretable or nondiagnostic [47].

Despite their ease of performance and avoidance of radioactive tracer, breath-hydrogen tests are not sufficiently sensitive or specific to justify their substitution for the ^{14}C-D-xylose breath test in noninvasive detection of intestinal bacterial overgrowth [48]. Furthermore, many authorities still regard small bowel aspiration for quantitative and qualitative culture specimens as the reference standard for diagnosis of SBBO [1,41,42]. Several nonradioactive breath tests using ^{13}C substrates such as ^{13}C-sorbitol appear to be promising [51].

Treatment

The main goals in the treatment of SBBO are 1) treatment of underlying small intestinal abnormality, when possible; 2) concentration on long-term antibiotic therapy when surgical management is not feasible; 3) adjunctive treatment of dysmotility, such as a prokinetic agent; and 4) nutritional support, particularly in patients with weight loss or vitamin deficiency.

Antibiotic therapy

Although bacterial overgrowth may be asymptomatic in many patients, the occurrence of compatible symptoms supported by positive test results for overgrowth should lead to a decision to treat. Antibiotic therapy is the cornerstone of treatment. Remarkable improvement in symptoms can be achieved in most patients.

Ideally, the choice of antimicrobial agent should be based on in vitro susceptibility testing of the bacteria in the small bowel of the individual patient. However, because this information is impractical to obtain in most cases, the choice of antibiotic is largely empiric and based on results of published series involving small intestinal cultures [52]. Whereas most patients with SBBO have aerobic and anaerobic overgrowth, in others malabsorption has been associated with overgrowth of purely aerobic flora. Therefore, the most effective antibiotic regimens generally include one or more drugs with activity against aerobic and anaerobic bacteria. Table 4 lists antimicrobial agents that have been effective in the treatment of bacterial overgrowth whether in controlled trials or based on extensive clinical experience [1,5••,10,53,54].

In most patients, a single course of treatment (10 days) markedly improves symptoms, and patients may remain free of symptoms for months. In others, symptoms recur

quickly, and acceptable results can only be obtained with cyclic treatment (1 of every 4 weeks). In still others, continuous treatment may be needed for 1 to 2 months [1]. If the antimicrobial agent is effective, a resolution or marked diminution of symptoms will be notable within several days of initiating therapy. Diarrhea and steatorrhea will decrease, and cobalamin malabsorption will be corrected.

No controlled trials offer guidance for the duration of treatment or management of refractory or recurrent patients. Decisions regarding management must be individualized, and benefits of therapy must be weighed against the risks of long-term antibiotic use, such as diarrhea, *Clostridium difficile* colitis, patient intolerance, bacterial resistance, and expense.

Historically, the treatment of first choice was tetracycline, 250 mg orally four times a day, with which improvement in symptoms and signs of malabsorption was expected within a week. Although recent experience suggests that up to 60% of patients with SBBO do not respond to tetracycline, some published studies still demonstrate the efficacy of doxycycline or minocycline as effective first-line therapy [3].

Amoxicillin–clavulanic acid, by virtue of its broad spectrum of antimicrobial activity [5••,52] and convenient twice-daily dosing regimen, has become a popular choice for empiric treatment of SBBO. Small uncontrolled trials have demonstrated the effectiveness of this antibiotic in improving symptoms and objective abnormalities in SBBO [23].

Alternative combination regimens that have also been used successfully include 1) cephalexin and metronidazole; 2) colistin and metronidazole; and 3) trimethoprim–sulfamethoxazole [1,5••]. Chloramphenicol has also been successful and may be acceptable for treatment of refractory patients. Antibiotics with activity that is largely limited to anaerobes, such as metronidazole or clindamycin, have a limited role as monotherapy. Conversely, antibiotics like penicillin or aminoglycosides that have poor activity against such enteric anaerobes as *Bacteroides* species should be avoided.

Recent successful experience with the fluoroquinolone ciprofloxacin in SBBO has been followed by a placebo-controlled randomized crossover trial that compared treatment of 10 symptomatic patients with the fluoroquinolone norfloxacin (800 mg/d), amoxicillin–clavulanic acid (1500 mg/d), or *Sacchromyces boulardii* (1500 mg/d) [54]. Both norfloxacin and amoxicillin–clavulanic acid brought a modest but significant short-term decrease in stool frequency and substantial improvement in the results of glucose-hydrogen breath testing. Probiotic treatment with *S. boulardii* did not result in any improvement in these outcome measures.

Prokinetic agents

Prokinetic agents, which may help to propel bacteria through the stagnant small bowel, would be attractive adjuncts to antibiotic therapy for SBBO. Animal studies suggest that enteric bacterial overgrowth may be favorably affected by prokinetic drugs [55,56,57•]. In a small study of humans with cirrhosis, orocecal transit time was decreased, and in four of five patients, bacterial overgrowth was abolished by treatment with cisapride [56]. Cisapride, however, has been withdrawn from the US market due to cardiotoxicity.

In one study of five patients with SBBO, low doses of octreotide (50 μg), given at bedtime so as not to impair the motor response to daytime feeding, stimulated motor activity, evoking phase III MMC activity that propagated at the same velocity as that of spontaneous complexes in healthy subjects [58]. In addition, this dosage of octreotide decreased nausea, bloating, vomiting, and abdominal pain in these patients and led to complete normalization of abnormal hydrogen-breath tests. Thus, low doses of octreotide may be a useful adjunct for SBBO in patients who do not respond to or are intolerant of antibiotics [59].

Encouraging results have also been obtained with octreotide and erythromycin in the treatment of scleroderma-associated dysmotility syndrome and SBBO [60]. However, relatively few patients have been studied with octreotide, and questions remain about its long-term side effects, the length of treatment required, the likelihood of recurrence, and whether combining octreotide therapy with antibiotics is reproducibly beneficial. The role of 5HT3 and 5HT4 agonist/antagonist therapy remains to be defined.

Probiotics

A recent resurgence of interest has been expressed in the concept that some enteric diseases may be ameliorated through manipulation of the intestinal flora with oral intake of live "probiotic" microbial supplements that change the enteric microbial balance. Probiotics have been studied in the management of inflammatory bowel disease, *C. difficile* colitis, and now SBBO. Unfortunately, studies of probiotic therapy for SBBO have so far shown disappointing or inconclusive results [61,62••].

Nutritional support

In addition to antibiotic therapy for SBBO, nutritional support is a crucial and integral component of management. Mucosal enterocyte damage may be incompletely reversible, and bacterial overgrowth may be refractory to antibiotic therapy. Dietary modifications may include a lactose-free diet or substitution of a large proportion of dietary fat with medium-chain triglycerides. Cobalamin deficiency is managed with monthly intramuscular injections of vitamin B_{12}. Correction of other deficient nutrients, such as calcium, magnesium, iron, and fat-soluble vitamins, may also be necessary.

Although correction of the underlying small bowel abnormalities is the primary goal of therapy, this is often not feasible. Most underlying conditions that predispose to SBBO are difficult, if not impossible, to reverse. Therefore, as in other chronic conditions, treatment is multifactorial and often long-term. Treatment should focus on eradica-

tion of the bacteria and correction of the severe malnutrition that results from bacterial overgrowth [5••,63].

Conclusions

Small bowel bacterial overgrowth is an increasingly recognized cause of malabsorption. Clinicians should maintain a low threshold for suspecting bacterial overgrowth as the cause of malabsorption because this entity is rather common and is also readily treatable. Serious malabsorption can be a consequence of bacterial overgrowth within the small intestine, resulting in clinically important deficiencies of several nutrients. Alterations in gastric acid secretion and intestinal motility provide the setting for development of bacterial overgrowth. The elderly, in particular, appear to be at increased risk for malabsorption secondary to SBBO. Bacterial overgrowth can be easily diagnosed with noninvasive breath tests and readily treated if the clinician's index of suspicion for this entity is high. Several nonradioactive breath tests using ^{13}C substrates such as ^{13}C-sorbitol are promising. Eradication of bacterial overgrowth by antibiotic therapy is safe and effective.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Gregg CR, Toskes PP: **Enteric bacterial flora and small bowel bacterial overgrowth syndrome.** In *Sleisenger and Fordtran's Gastrointestinal and Liver Disease,* edn 7. Edited by Feldman M, Friedman LS, Sleisenger MH. Philadelphia: WB Saunders; 2002:1783–1793.
2. Hoffmann JC, Zeitz M: **Small bowel disease in the elderly: diarrhoea and malabsorption.** *Best Pract Res Clin Gastroenterol* 2002, **16:**17–36.
3. Lewis SJ, Potts LF, Malhotra R, Mountford R: **Small bowel bacterial overgrowth in subjects living in residential care homes.** *Age Aging* 1999, **28:**181–185.
4. Riordan SM, McIver CJ, Wakefield D, *et al.*: **Small intestinal bacterial overgrowth in the symptomatic elderly.** *Am J Gastroenterol* 1997, **92:**47–51.
5. •• Desai A, Toskes PP: **Bacterial overgrowth syndrome.** *Curr Treat Opt Infect Dis* 2003, **5:**189–196.

A comprehensive review of current management strategies of the bacterial overgrowth syndrome.

6. Saltzman JR, Kowdley KV, Pedrosa MC, *et al.*: **Bacterial overgrowth without clinical malbsorption in elderly hypochlorhydric patients.** *Gastroenterology* 1994, **106:**615–623.
7. Husebye E, Skar V, Hoverstad T, Melby K: **Fasting hypochlorhydria with gram positive gastric flora is highly prevalent in healthy old people.** *Gut* 1992, **33:**1331–1337.
8. Lewis SJ, Franco S, Young G, O'Keefe SJ: **Altered bowel function and duodenal bacterial overgrowth in patients treated with omeprazole.** *Aliment Pharmacol Ther* 1996, **10:**557–561.
9. Gough A, Andrews D, Bacon PA, Emery P: **Evidence of omeprazole-induced small bowel bacterial overgrowth in patients with scleroderma.** *Br J Rheumatol* 1995, **34:**976–977.
10. Toskes PP: **Small intestinal bacterial overgrowth, including blind loop syndrome.** In *Infections of the Gastrointestinal Tract*, edn 2. Edited by Blaser M, Smith PD, Rardin JI, *et al.* Philadelphia: Lippincott Williams & Wilkins; 2002:291–300.
11. Levy J: **The effects of antibiotic use on gastrointestinal function.** *Am J Gastroenterol* 2000, **95(suppl 1):**S8–S10.
12. Riordan SM, McIver CJ, Wakefield D, *et al.*: **Serum immunoglobulin and soluble IL-2 receptor levels in small intestinal overgrowth with indigenous gut flora.** *Dig Dis Sci* 1999, **44:**939–944.
13. Kett K, Baklien K, Bakken A, *et al.*: **Intestinal B-cell isotype response in relation to local bacterial load: evidence for imuunoglobulin A subclass adaptation.** *Gastroenterology* 1995, **109:**819–825.
14. Riordan SM, McIver CJ, Wakefield D, *et al.*: **Luminal immunity in small-intestinal bacterial overgrowth and old age.** *Scand J Gastroenterol* 1996, **31:**1103–1109.
15. Wanitschke R, Ammon HV: **Effects of dihydroxy bile acids and hydroxyl fatty acids on the absorption of oleic acid in the human jejunum.** *J Clin Invest* 1978, **61:**178–186.
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. King CE, Toskes PP: **Protein-losing enteropathy in the human and experimental rat blind loop syndrome.** *Gastroenterology* 1981, **80:**504–509.
18. Saltzman JR, Russell RM: **Nutritional consequences of intestinal bacterial overgrowth.** *Comp Ther* 1994, **20:**523–530.
19. Welkos SA, Toskes PP, Baer H, *et al.*: **Importance of anaerobic bacteria in the cobalamin malabsorption of experimental rat blind loop syndrome.** *Gastroenterology* 1981, **80:**313–320.
20. Justus PG, Fernandez A, Martin JL, *et al.*: **Altered myoelectric activity in the experimental blind loop syndrome.** *J Clin Invest* 1983, **72:**1064–1071.
21. Husebye, 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.
22. Rose S, Young MA, Reynolds JC: **Gastrointestinal manifestations of scleroderma.** *Gastroenterol Clin North Am* 1998, **27:**563–564.
23. Virally-Monod M, Tielmans D, Kevorkian JP, *et al.*: **Chronic diarrhea and diabetes mellitus: prevalence of small intestinal bacterial overgrowth.** *Diab Metab* 1998, **23:**530–536.
24. Trespi E, Ferrieri A: **Intestinal bacterial overgrowth during chronic pancreatitis.** *Curr Med Res Opin* 1999, **15:**47–52.
25. Bauer TM, Schwacha H, Steinbruckner B, *et al.*: **Small intestinal bacterial overgrowth in human cirrhosis is associated with systemic endotoxemia.** *Am J Gastroenterol* 2002, **97:**2364–2370.
26. 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.
27. Casafont Morencos F, de las Heras Castano G, Martin Ramos L, *et al.*: **Small bowel bacterial overgrowth in patients with alcoholic cirrhosis.** *Dig Dis Sci* 1996, **41:**552–556.
28. Toskes PP: **The changing nature of small intestine bacterial overgrowth.** *Curr Gastroenterol Rep* 1999, **1:**267–268.
29. Morencos FC, de las Heras Castano G, Martin Ramos L, *et al.*: **Small bowel bacterial overgrowth in patients with alcoholic cirrhosis.** *Dig Dis Sci* 1995, **40:**1252–1256.
30. Fried M, Siegrist H, Frei R, *et al.*: **Duodenal bacterial overgrowth during treatment in outpatients with omeprazole.** *Gut* 1994, **35:**23–26.
31. Lewis SJ, Franco S, Young G, *et al.*: **Altered bowel function and duodenal bacterial overgrowth in patients treated with omeprazole.** *Aliment Pharmacol Ther* 1996, **10:**557–561.
32. Smith GM, Chesner IM, Asquith P, Leyland MJ: **Small intestinal bacterial overgrowth in patients with chronic lymphocytic leukaemia.** *J Clin Pathol* 1990, **43:**57–59.
33. Holt P: **Diarrhea and malabsorption in the elderly.** *Gastroenterol Clin North Am* 2001, **30:**427–444.
34. Giannella RA, Toskes PP: **Gastrointestinal bleeding and iron absorption in the experimental blind loop syndrome.** *Am J Clin Nutr* 1976, **29:**754–757.

35. 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.
36. Jones MP, Craig R, Olinger E: **Small intestinal bacterial overgrowth is associated with irritable bowel syndrome: the cart lands squarely in front of the horse.** *Am J Gastroenterol* 2001, **96:**3204–3205.
37. Riordan SM, McIver CJ, Duncombe VM, *et al.*: **Small intestinal bacterial overgrowth and the irritable bowel syndrome.** *Am J Gastroenterol* 2001, **96:**2506–2508.
38. Simren M, Ringstrom G, Agerfarz P, *et al.*: **Small intestinal bacterial overgrowth is not of major importance in the irritable bowel syndrome [abstract].** *Gastroenterology* 2003, **124(Suppl 1):**A-163.
39. Kumar A, Forsmark C, Toskes PP: **Small bowel bacterial overgrowth: the changing face of an old disease [abstract].** *Gastroenterology* 1996, **110:**A340.
40.• 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.
An evidence-based review of the physiologic basis of various breath tests and their applications, indications, and limitations in investigating a wide range of gastrointestinal diseases.
41. Lewis SJ, Young G, Mann M, *et al.*: **Improvement in specificity of [14C]d-xylose breath test for bacterial overgrowth.** *Dig Dis Sci* 1997, **42:**1587–1592.
42. 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.
43. King CE, Toskes PP, Guilarte TR, *et al.*: **Comparison of one gram 14C-xylose breath test to the 14C-bile acid breath test in patients with small intestine bacterial overgrowth.** *Dig Dis Sci* 1980, **25:**53–58.
44. Ferguson J, Walker K, Thomson AB: **Limitations in the use of 14C-glycocholate breath and stool bile acid determinations in patients with chronic diarrhea.** *J Clin Gastroenterol* 1986, **8:**258–262.
45. Valdovinos M, Camilleri M, Thomforde G, *et al.*: **Reduced accuracy of 14C-D-xylose breath test for detecting bacterial overgrowth in gastrointestinal motility disorders.** *Scand J Gastroenterol* 1993, **28:**963–968.
46. Riordan S, McIver C, Duncombe V, *et al.*: **Factors influencing the 1-gram 14C-D-xylose breath test for bacterial overgrowth.** *Am J Gastroenterol* 1995, **90:**1455–1460.
47. King CE, Toskes PP: **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.
48. Bishop WP: **Breath hydrogen testing for small bowel bacterial overgrowth: a lot of hot air?** *J Pediatr Gastroenterol Nutr* 1997, **25:**245–246.
49. 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.
50. MacMahon M, Gibbons N, Mullins E, *et al.*: **Are hydrogen breath tests valid in the elderly?** *Gerontology* 1996, **42:**40–45.
51. Wagner D, Bolt D, Currington C, *et al.*: **Clinical utility of the sorbitol breath test (SBT) to detect small intestinal bacterial overgrowth (SIBO) in the elderly [abstract].** *Gastroenterology* 2003, **124(Suppl 1):**A-165.
52. 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.
53. Toledo TK, DiPalma JA: **Antibiotics are effective in the treatment of bacterial overgrowth-related diarrhea.** *Am J Gastroenterol* 2000, **95:**3644–3645.
54. 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.
55. Wang X, Soltesz V, Axelson J, *et al.*: **Cholecystokinin increases small intestinal motility and reduces enteric bacterial overgrowth and translocation in rats with surgically induced acute liver failure.** *Digestion* 1996, **57:**67–72.
56. Pardo A, Bartoli R, Lorenzo-Zuniga V, *et al.*: **Effect of cisapride on intestinal bacterial overgrowth and bacterial translocation in cirrhosis.** *Hepatology* 2000, **31:**858–863.
57.• Madrid AM, Hurtado C, Venegas M, *et al.*: **Long-term treatment with cisapride and antibiotics in liver cirrhosis: effect on small intestinal motility, bacterial overgrowth, and liver function.** *Am J Gastroenterol* 2001, **96:**1251–1255.
A provocative study that suggests a possible role for prokinetics in the treatment of small bowel bacterial overgrowth.
58. Soudah HC, Hasler WL, Owyang C: **Effect of octreotide on intestinal motility and bacterial overgrowth in scleroderma.** *N Engl J Med* 1991, **325:**1461–1467.
59. Edmunds MC, Chen JD, Soykan I, *et al.*: **Effect of octreotide on gastric and small bowel motility in patients with gastroparesis.** *Aliment Pharmacol Ther* 1998, **12:**167–174.
60. Verne GN, Eaker EY, Hardy E, *et al.*: **Effect of octreotide and erythromycin on idiopathic and scleroderma-associated intestinal pseudoobstruction.** *Dig Dis Sci* 1995, **40:**1892–1901.
61. Stotzer PO, Blomberg L, Conway PL, *et al.*: **Probiotic treatment of small intestinal bacterial overgrowth by Lactobacillus fermentum KLD.** *Scand J Iinfect Dis* 1996, **28:**615–619.
62.•• Rolfe RD: **The role of probiotic cultures in the control of gastrointestinal health.** *J Nutr* 2000, **130(Suppl 2):**396S–402S.
A succinct review of the controversial role of probiotics in the prevention and treatment of a diverse spectrum of gastrointestinal disorders.
63. Gregg CR: **Enteric bacterial flora and bacterial overgrowth syndrome.** *Semin Gastrointest Dis* 2002, **13:**200–209.