ACG Clinical Guideline: Small Intestinal Bacterial Overgrowth

Mark Pimentel, MD, FRCP(C), FACG[1], Richard J. Saad, MD, FACG[2], Millie D. Long, MD, MPH, FACG (GRADE Methodologist)[3] and Satish S. C. Rao, MD, PhD, FRCP, FACG[4]

Small intestinal bacterial overgrowth is defined as the presence of excessive numbers of bacteria in the small bowel, causing gastrointestinal symptoms. This guideline statement evaluates criteria for diagnosis, defines the optimal methods for diagnostic testing, and summarizes treatment options for small intestinal bacterial overgrowth. This guideline provides an evidence-based evaluation of the literature through the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) process. In instances where the available evidence was not appropriate for a formal GRADE recommendation, key concepts were developed using expert consensus.

Am J Gastroenterol 2020;115:165–178. https://doi.org/10.14309/ajg.0000000000000501; published online January 8, 2020

INTRODUCTION

Small intestinal bacterial overgrowth (SIBO) has been recognized as a medical phenomenon for many decades. Although its definition has been debated, the principle concept is that the normal small bowel has lower levels of microbial colonization compared with the colon and this normal balance is significantly altered in SIBO. SIBO is defined as the presence of excessive numbers of bacteria in the small bowel causing gastrointestinal (GI) symptoms. These bacteria are usually coliforms, which are typically found in the colon and include predominantly Gram-negative aerobic and anaerobic species that ferment carbohydrates producing gas (1).

Since the late 1990s, there has been a resurgence in SIBO research which has been further enhanced by the increasing knowledge of the gut microbiome and its roles in human health and disease (2). These include a series of articles linking SIBO to diseases such as irritable bowel syndrome (IBS) (3,4), inflammatory bowel disease (IBD) (5), systemic sclerosis (6), motility disorders (7,8), cirrhosis (9), fatty liver (10), postgastrectomy syndrome (11), and a variety of other conditions. Although these findings are important, a recent consensus document identified a number of strengths and weaknesses in the published work in this area (12). As such, an effort has been underway to re-evaluate the criteria for the diagnosis of SIBO and define the optimal methods for diagnostic testing to identify this condition. Furthermore, treatment for SIBO has been largely empirical, has not undergone the scrutiny of sponsored clinical trials, and requires appraisal. In this guideline, we provide an evidence-based evaluation of the literature and assess the current unmet needs in SIBO research.

The guideline is structured in sections, each with recommendations, key concepts, and summaries of the evidence. Each recommendation statement has an associated assessment of the quality of evidence and strength of recommendation based on the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) process. The GRADE system was used to evaluate the quality of supporting evidence (13). A "strong" recommendation is made when the benefits clearly outweigh the negatives and/or the result of no action. "Conditional" is used when some uncertainty remains about the balance of benefits and potential harms. The quality of the evidence is graded from high to low. "High" quality evidence indicates that further research is unlikely to change the authors' confidence in the estimate of effect, and that we are very confident that the true effect lies close to that of the estimate of the effect. "Moderate" quality evidence is associated with moderate confidence in the effect estimate, although further research would be likely to have an impact on the confidence of the estimate, whereas "low" quality evidence indicates that further study would likely have an important impact on the confidence in the estimate of the effect and would likely change the estimate. "Very low" quality evidence indicates very little confidence in the effect estimate, and that the true effect is likely to be substantially different than the estimate of effect.

Key concepts are statements that are not amenable to the GRADE process either because of the structure of the statement or because of the available evidence. In some instances, key concepts are based on extrapolation of evidence and/or expert opinion. Tables 1 and 2 summarize the recommendations and key concepts, respectively, in this guideline.

DEFINITION OF SIBO

SIBO can be most inclusively defined as a clinical syndrome of GI symptoms caused by the presence of excessive numbers of bacteria within the small intestine (potential thresholds are discussed below). This definition implies that there must be a measurable and excessive bacterial burden within the small bowel, and that this microbial overgrowth has resulted in specific GI signs and/or

[1]Medically Associated Science and Technology (MAST) Program, Cedars-Sinai Medical Center, Los Angeles, California, USA; [2]Michigan Medicine, University of Michigan, Ann Arbor, Michigan, USA; [3]Division of Gastroenterology and Hepatology, University of North Carolina, Chapel Hill, North Carolina, USA; [4]Division of Gastroenterology/Hepatology, Augusta University, Augusta, Georgia, USA. **Correspondence:** Mark Pimentel, MD, FRCP(C), FACG. E-mail: pimentelm@cshs.org.
Received February 13, 2019; accepted November 12, 2019

Table 1. Summary and strength of GRADED recommendations for SIBO

Diagnosis of SIBO
1. We suggest the use of breath testing (glucose hydrogen or lactulose hydrogen) for the diagnosis of SIBO in patients with IBS (conditional recommendation, very low level of evidence).
2. We suggest using glucose hydrogen or lactulose hydrogen breath tests for the diagnosis of SIBO in symptomatic patients with suspected motility disorders (conditional recommendation, very low level of evidence).
3. We suggest testing for SIBO using glucose hydrogen or lactulose hydrogen breath tests in symptomatic patients (abdominal pain, gas, bloating, and/or diarrhea) with previous luminal abdominal surgery (conditional recommendation, very low level of evidence).
Other conditions associated with SIBO
4. We suggest against the use of breath testing for the diagnosis of SIBO in asymptomatic patients on PPIs (conditional recommendation, very low level of evidence).
5. We suggest testing for methane using glucose or lactulose breath tests to diagnose the overgrowth of methane-producing organisms (IMO) in symptomatic patients with constipation (conditional recommendation, very low level of evidence).
Treatment of SIBO
6. We suggest the use of antibiotics in symptomatic patients with SIBO to eradicate overgrowth and resolve symptoms (conditional recommendation, low level of evidence).

IBS, irritable bowel syndrome; IMO, intestinal methanogen overgrowth; PPI, proton-pump inhibitor; SIBO, small intestinal bacterial overgrowth.

symptoms. For example, the pathologic fermentation of nutrients that would ordinarily be completely absorbed in the small intestine could lead to the production of excess gas and bloating.

The objective measurement of bacteria in the small intestine was initially achieved through quantitative culture of aspirates acquired from the proximal small bowel, akin to urine culture for urinary tract infection (14). However, the threshold cutoff for the definition of a positive culture has been controversial, both in the published literature and among experts in the field. The most recent North American Consensus found that the literature points more accurately to a bacterial colony count of $\geq 10^3$ colony-forming units per milliliter (CFU/mL) in a duodenal/jejunal aspirate as diagnostic of SIBO (12). This is based on a collation of the literature among normal subjects in trials. It should be noted that the bacterial colony counts in SIBO are based on growth of culturable bacteria.

An alternative method for the diagnosis of SIBO is the measurement of exhaled hydrogen gas on the breath, after the ingestion of a fixed quantity of a carbohydrate substrate such as glucose or lactulose (15,16). Although popular, it is an indirect method of assessing whether there are excessive amounts of bacteria in the small bowel. Similar to the quantitative culture of small bowel aspirates, the published literature and expert opinion has varied widely regarding both the details of breath testing techniques and the definition of a positive test for SIBO. With these limitations in mind, the most recent published criteria on breath testing recommend a rise in exhaled hydrogen of at least 20 parts per million (ppm) above baseline within 90 minutes of oral ingestion of either 75 g of glucose or 10 g of lactulose, as diagnostic of SIBO (12).

The signs and/or symptoms of SIBO can arise from the malabsorption of nutrients, alteration in intestinal permeability, inflammation, and/or immune activation that arises from the pathologic bacterial fermentation within the small bowel (17). Such symptoms can include, but may not be limited to, nausea, bloating, flatulence, abdominal distension, abdominal cramping, abdominal pain, diarrhea, and/or constipation. In extreme cases, signs can include steatorrhea, weight loss, anemia, deficiencies in fat soluble vitamins, and/or mucosal inflammation of the small bowel. These are usually associated with extraordinary causes of SIBO such as iatrogenic (postsurgical blind loop) or scleroderma (18).

Evidence suggests that abdominal pain, bloating, gas, distension, flatulence, and diarrhea are the most common symptoms described in patients with SIBO and prevalent in more than two-thirds of patients (19–21). In severe cases, nutritional deficiencies including vitamin B12, vitamin D, and iron deficiencies can occur, but in most cases, these are subtle or undetectable (22). Some patients may also manifest fatigue and poor concentration (23). However, no single symptom can be specifically attributed to SIBO. Symptoms often masquerade as other diagnoses such as IBS, functional diarrhea, functional dyspepsia, or bloating. This is due in part to the varied presentation of patients with SIBO and the number of underlying risk factors that can lead to the development of SIBO. For example, in a patient with chronic pancreatitis, it is difficult to determine whether diarrhea results from exocrine insufficiency or from coexistent SIBO and to what extent symptoms are related to pancreatic insufficiency vs SIBO. Similarly, in patients with Crohn's disease, particularly those having undergone ileocecal valve resection, symptoms of abdominal pain, boating, and diarrhea could result from SIBO vs that of active inflammation, bile acid malabsorption, or postoperative strictures. Indeed, several studies have attempted to assess this in a systematic manner. For example, Jacobs et al. (21) obtained aerobic and anerobic duodenal cultures from subjects undergoing antroduodenal manometry and compared 38 subjects with culture-positive SIBO to 74 subjects with culture-negative SIBO and reported no differences in the intensity, frequency, and duration of abdominal pain or in bloating, fullness, belching, indigestion, nausea, vomiting diarrhea, and gas. Therefore, close attention should be paid not only to a patient's symptom profile but also to risk factors for SIBO and any history of previous attempts to treat other underlying conditions, when evaluating SIBO as a possible diagnosis in a patient presenting with unexplained abdominal pain, gas, bloating, diarrhea, and/or malabsorptive symptoms.

DIAGNOSIS OF SIBO

Breath testing

Quantitative measurement of breath hydrogen and/or methane is a relatively inexpensive, noninvasive, easy, and widely available test. Since the clinical definition of SIBO is unclear in the absence of validated patient-reported outcomes (PROs), the use of breath testing for SIBO is recognized as a key concept in Table 2 but not a GRADEable guideline. Newer mail-in kits are available for home testing for patients not able to travel or in remote locations. Often these kits are directed to laboratories with Clinical Laboratory Improvement Amendments certification and as such have more stringent validation/calibration supervision as compared to clinicians offices. However, diet precautions before test, substrate ingestion, and breath test collection occur in a home setting that may not be strictly controlled.

The premise of breath tests is that human cells are incapable of producing hydrogen and methane gases (24). Consequently, if these gases can be detected in breath samples, it must signify another source such as the fermentation of carbohydrates by microbes in the gut, their subsequent absorption into the blood stream, and their expiration through the lungs (25). This principle has led to the development of several carbohydrate substrate-based breath tests. Here, after ingestion of a carbohydrate load and its exposure to bacteria, the sugar is rapidly fermented to produce hydrogen gas along with short-chain fatty acids. Methanogenic archaea in turn use hydrogen as a substrate for the production of methane (26,27). A rise in the concentrations of hydrogen in breath samples facilitates a diagnosis of SIBO, whereas the North American Consensus recommended that the presence of methane levels ≥10 ppm is diagnostic of methanogenic overgrowth (Figure 1a–c) (12). However, some experts recommend a rise of 10 ppm in methane levels, and this requires confirmation. The carbohydrates traditionally used as substrates in breath testing for SIBO are glucose and lactulose, with each substrate possessing unique characteristics. Historically, breath testing was performed using a radiolabeled substrate (e.g., xylose), which could be detected on exhaled breath samples, if excess bacteria were present (28). However, this technique is no longer used because of safety concerns regarding radiolabeled substrates (14).

A recent North American Consensus article provides some guidelines for standardized methods of performing and interpreting breath test results (12). Before breath testing, it is recommended that patients avoid use of antibiotics for 4 weeks and avoid promotility agents and laxatives for at least 1 week. The day before the breath test, fermentable foods (e.g., complex carbohydrates) should be avoided, and patients should fast for 8–12 hours. In addition, during the breath test, patients should avoid smoking and minimize physical exertion. The North American Consensus recommends administering 75-g glucose or 10-g lactulose, either taken with or followed by 1 cup of water (~250 mL). The breath samples should be measured for hydrogen and methane. As noted previously, an increase in hydrogen concentrations of ≥20 ppm from baseline within 90 (12)–120 (29) minutes is recommended to be diagnostic of SIBO (Figure 1a).

Although methane is increasingly important and recognized, it creates a nomenclature problem in the SIBO framework. For methane, a concentration of ≥10 ppm at any point during the test is indicative of methanogen colonization. However, methanogens are not "bacteria" (representing the "B" in SIBO) but belong to the domain Archaea and may also overgrow in the colon and not just the small intestine. As such, we have proposed a new term, intestinal methanogen overgrowth (IMO), for methanogens rather than SIBO (Figure 1b).

Table 2. Summary of key concepts in SIBO

1. The most common symptom of SIBO is bloating.
2. Vitamin deficiencies in SIBO are not common and are usually seen in patients with an iatrogenic or structural abnormality of the bowel such as blind loop syndrome. Note: Folate may be elevated in SIBO as bacteria produce folate.
3. The cause(s) of SIBO in patients are varied, and this may need to be determined in order to best prevent a recurrence of SIBO (see Table 3).
4. Breath testing is useful for identifying SIBO noninvasively before antibiotic treatment.
5. During breath testing, it is important to use the correct dose of glucose (75 g) and lactulose (10 g) for standardization purposes.
6. Based on an evidence-based approach from the literature, a colony count of $\geq 10^3$ CFU/mL is most suggestive of SIBO when using duodenal culture.
7. The presence of excessive methane on breath testing does not indicate SIBO, since methanogens are not bacteria (they are archaea). A better term would be IMO.
8. *Methanobrevibacter smithii* appears to be the key methanogen responsible for breath methane production.
9. Constipation is associated with elevated levels of breath methane and stool *M. smithii*.
10. Targeting methanogens may reduce methane production and improve constipation.
11. A proportion of subjects with IBS are found to have SIBO, based both on breath testing and on culture.
12. There is a lack of consistent data to support recommending specific probiotics in the treatment of SIBO.
13. There is currently no basis for the use of fecal microbiota transplant in the treatment of SIBO.
14. A focus on prevention of SIBO is important to avoid the need for repeated courses of antibiotics. Treatment of the underlying cause represents the primary mode of prevention.
15. In subjects with an abnormal breath test, retesting after treatment may correlate with symptom improvement and may be confirmed by normalization of hydrogen or methane levels.

CFU/mL, colony-forming units per milliliter; IBS, irritable bowel syndrome; IMO, intestinal methanogen overgrowth; SIBO, small intestinal bacterial overgrowth.

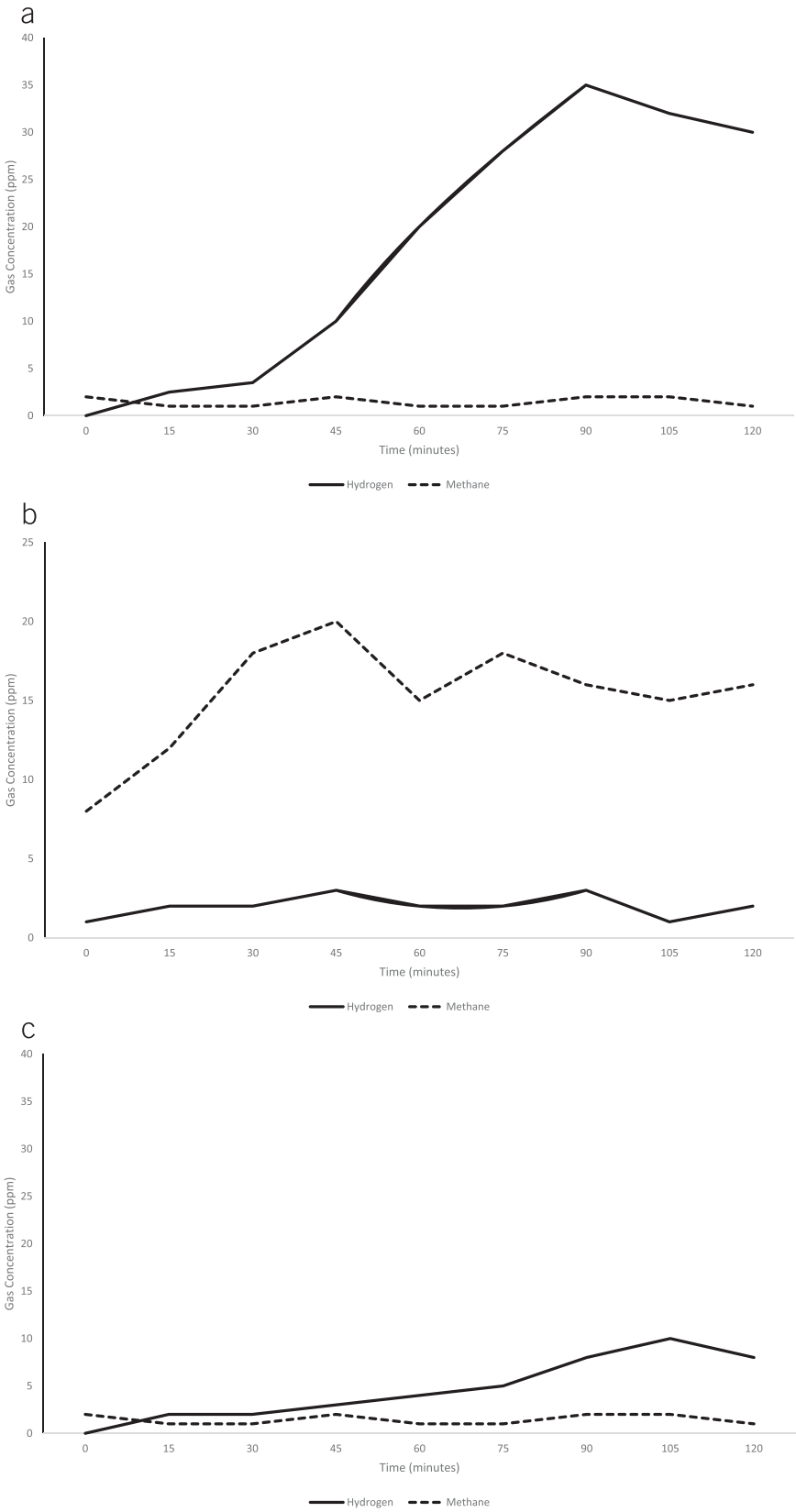

Figure 1. Breath test examples. (**a**) Hydrogen-positive breath test to suggest small intestinal bacterial overgrowth. (**b**) Methane-positive breath test to suggest intestinal methanogen overgrowth. (**c**) Normal breath test. ppm, parts per million.

Irrespective of the nomenclature, a change in or measured level of hydrogen or methane that remains below the threshold levels noted above should be considered a negative test (Figure 1c). When using lactulose as a substrate, an initial peak from bacterial overgrowth in the small intestine followed by a second peak from colonic bacterial fermentation has been described. However, per the new consensus statement, a second peak is not required, but the first peak must occur within 90 minutes of substrate administration for the test to be considered positive. According to a systematic review by Khoshini et al. (14), the sensitivity of lactulose has ranged from 31% to 68% and specificity has ranged from 44% to 100%, whereas the sensitivity of glucose breath testing has varied from 20% to 93% and specificity from 30% to 86% when compared with cultures of aspirates from the small bowel. Recently, the use of fructose as a monosaccharide substrate for persons with diabetes with suspected SIBO has been evaluated because a 75-g glucose load can cause acute hyperglycemia and gut dysmotility and possibly impact the breath test results. In this study, when compared with duodenal aspirates, the use of a fructose solution as the substrate in persons with diabetes yielded similar sensitivity, specificity, and diagnostic accuracy (48%, 71%, and 58%, respectively) for the diagnosis of SIBO when compared with glucose solution in persons without diabetes (30). Although not studied, lactulose may be preferred for diabetic subjects as a nonabsorbed carbohydrate. In addition to hydrogen and methane, hydrogen sulfide (H_2S) is another gas produced by gut bacteria, but a commercial testing system is not yet available. A recent study evaluated the role of H_2S in patients undergoing a workup for SIBO (31). However, a cutoff value for diagnosis of SIBO using H_2S gas needs to be validated and its utility determined.

Small bowel aspiration and culture

Small bowel aspirate and culture is often considered the gold standard for the diagnosis of SIBO. Standardized techniques for aseptic collection of small bowel aspirate samples are lacking, as methods differ regarding the placement of the device for sample aspiration and the amount of fluid collected, as well as sample handling and subsequent culture. In general, during an upper endoscopy, a deep duodenal intubation can be achieved while minimizing suction during the insertion of the scope through mouth and stomach and preventing cross-contamination of secretions from outside the duodenum as described (20,21). In 1 technique, a 2-mm Liguory catheter (COOK Medical, Bloomington, IN) with multiple side holes is passed through the biopsy channel of an upper endoscope into the third and fourth portions of the duodenum. Using gentle suction, approximately 3–5 mL of duodenal fluid is aspirated, and the specimen is sent to a microbiology laboratory for aerobic/anaerobic culture (20,21). Wearing of sterile gloves both by the endoscopist and assistant when assembling the catheter and collecting samples and placing a sterile cap on the syringe are all key components for proper specimen collection and handling. Once obtained, the specimen should be promptly transferred to a microbiology laboratory with rapid processing for aerobic and anaerobic cultures. It is important to communicate with the laboratory personnel regarding use of appropriate media and not to report results as positive or negative but to describe the growth of organisms as a precise colony count in CFU/mL. Historically, a level of $\geq 10^5$ CFU/mL had been used for identifying pathological bacterial infection in humans, including a diagnosis of SIBO. However, in the case of SIBO, this cutoff appears too stringent and lacks validation (25,32). Healthy controls have $<10^3$ CFU/mL in the small bowel, and concentrations above 10^5 CFU are almost exclusively seen in patients with gastrectomy (14). These levels were often from patients with Billroth I or II and blind loops or segments of intestinal stasis out of continuity with the digestive flow. Therefore, a concentration of $\geq 10^3$ CFU/mL is now generally considered diagnostic of SIBO and has been recommended by the North American Consensus (12). Diagnosis of SIBO using small bowel aspiration and culture is time-consuming, expensive, and is an invasive procedure which requires sedation and carries the usual risks of endoscopy, but is technically simple and can be widely performed outside of specialized referral centers or research environment. In 1 study (20), the diagnostic agreement of small bowel aspirates with breath testing was ~65%, indicating that using 1 testing method may not definitively diagnose SIBO and that additional testing may be necessary, particularly in patients with persistent symptoms and a high likelihood of SIBO.

Although published data are limited, there is a growing list of studies assessing SIBO by 16S ribosomal RNA (rRNA) gene sequencing in a cohort of subjects with IBS (33). In this study, sequencing of a small cohort of subjects revealed lower microbial diversity in the duodenum in subjects with IBS compared with subjects without IBS. The most significant findings were increases in *Escherichia/Shigella* ($P = 0.005$) and *Aeromonas* ($P = 0.051$) and decreases in *Acinetobacter* ($P = 0.024$), *Citrobacter* ($P = 0.031$), and *Microvirgula* ($P = 0.036$). In another study, Kerckhoffs et al. found higher levels of *Pseudomonas* in the small bowel of subjects with IBS compared with healthy controls (34). These results were mirrored in stool samples from the same cohort. In the largest study to date, sequencing was able to validate SIBO as $>10^3$ CFU/mL by culture on MacConkey agar based on correlation to symptoms, sequencing, and breath testing results (35). In the same study, using a cutoff of $>10^3$ CFU/mL also correlated with a positive hydrogen breath test (i.e., a rise in hydrogen ≥ 20 ppm above baseline) at 90 minutes and also correlated with the clinical symptoms of bloating and urgency (35).

Another study sequenced microbes in duodenal samples and rectal biopsies from subjects with IBS and controls (36) and also found higher numbers of bacteria in the small bowel in subjects with IBS. However, a study of jejunal aspirates using culture and PCR of 16S rRNA genes found no significant correlation between glucose breath test results and bacterial levels (37). Large-scale studies are currently underway to evaluate this further.

Newer techniques

It is recognized that the current breath tests have low sensitivity and specificity and that additional validation studies are needed for standardization (38). The lactulose breath test has been criticized for high false-positive values (because of the accelerated transit and colonic fermentation in some individuals) and the glucose breath test for being absorbed in proximal duodenum and therefore having low sensitivity for detecting distal SIBO—in other words, missing overgrowth in distal small bowel (12,14,39). A unique orally ingested capsule technology is also underdevelopment that can measure *in vivo* hydrogen and carbon dioxide after ingestion of a carbohydrate meal and may provide a better alternative to current breath hydrogen measurement techniques (40). Additional capsule technologies that can sample

small bowel bacteria (small bowel capsule detection system) are also emerging, and these technologies could provide a more direct and accurate evaluation of SIBO (41).

Recommendations

1. We suggest the use of breath testing (glucose hydrogen or lactulose hydrogen) for the diagnosis of SIBO in patients with IBS (conditional recommendation, very low level of evidence).

IBS is one of the most commonly evaluated condition with ties to SIBO, which has allowed this association to be graded in this guideline. Although the rate of SIBO in IBS is debated, meta-analyses suggest that up to 78% of IBS subjects suffer from SIBO (42). Although there remains a question of cause or effect in IBS, there is little controversy that a subset of subjects with IBS have SIBO. This evidence is now based on meta-analysis, and other evidence such as 16S rRNA gene sequencing continues to support this concept (33,34,36).

Further evidence that IBS is associated with microbiome dysbiosis (or SIBO) is based on the successful use of antibiotics in the treatment of IBS. Although this will be discussed in more detail below, in 2015, the U.S. Food and Drug Administration (FDA) approved a nonabsorbed antibiotic, rifaximin, for the treatment of IBS with diarrhea based on the existing understanding that one possible underlying cause of IBS is perturbation of the microbiome. A subset of subjects with IBS who participated in the TARGET 3 trial that supported approval of rifaximin (43) also underwent breath testing. Recently presented data suggested that the optimal benefit of rifaximin was seen in subjects with IBS with abnormal baseline hydrogen levels during the lactulose breath test (44). In fact, 76% of subjects with an initial positive breath test that became negative following a course of antibiotics were defined as a responder, based on the primary FDA outcome measure. This further supports that altered microbial levels could play a role in IBS.

Recommendations

2. We suggest using glucose hydrogen or lactulose hydrogen breath testing for the diagnosis of SIBO in symptomatic patients with suspected motility disorders (conditional recommendation, very low level of evidence).
3. We suggest testing for SIBO using glucose hydrogen or lactulose hydrogen breath testing in symptomatic patients (abdominal pain, gas, bloating, and/or diarrhea) with previous luminal abdominal surgery (conditional recommendation, very low level of evidence).

OTHER CONDITIONS ASSOCIATED WITH SIBO

There are a number of mechanisms responsible for maintaining the relatively sterile milieu of the small intestine (Table 3). Deficiency or breakdown in one or more of these mechanisms can result in the abnormal accumulation of bacteria in the small bowel. As such, in almost all instances, SIBO is an epiphenomenon related to something else, usually a condition that leads to stasis in the small intestine. Table 4 provides a list of conditions that have historically been linked to SIBO, which include small bowel mechanical problems or motility disorders. However, conditions such as malabsorption, altered immunity, postgastric and colon surgeries, and systemic disorders can also be important. SIBO is not only associated with several conditions (Table 4) but can also cause malabsorption, vitamin deficiencies, and other problems. These data are based on animal and human studies, and in some cases, reversibility has been demonstrated after successful treatment of SIBO, supporting a cause-and-effect relationship.

Table 3. Mechanisms for maintaining small bowel ecological homeostasis

Mechanism	Rationale
Gastric acid	Most ingested bacteria in food cannot survive the acidic stomach.
Pancreatic enzymes	Digestive enzymes in the proximal small bowel may also digest bacterial products. Efficient digestion of nutrients leaves less substrates for bacteria.
Bile acids	As detergents, bile acids can have an effect on bacterial membranes.
Small bowel motility	Migrating motor complexes and other events cleanse the small intestine of debris during fasting.
IC valve	The IC valve protects the small bowel from retrograde movement of colonic flora into the small bowel.
Immune system	Mucosal immunity may be important in the maintenance of a stable microbiota of the intestinal lumen.

IC, ileocecal.

The small bowel has an inherent cleansing function with recurring antegrade peristalsis and migratory motor complexes organized into 3 phases. Of these, the phase III migrating motor complex (MMC) is an intense phasic and tonic contractile event that begins in the stomach or proximal bowel and sweeps through toward the colon, propelling chyme, secretions, and bacteria, and offering a natural protection against SIBO (7,45). This organized bioprotective mechanism may be disturbed by motility disorders including neuropathy or myopathy (examples include scleroderma and diabetes) or by medications such as opioids, antidiarrheals, or anticholinergics, which can reduce propulsive movements and facilitate bacterial overgrowth. Likewise, postsurgical changes such as gastrojejunostomy with a blind loop or injury to the vagus nerve may each provide an opportunity for bacterial overgrowth. Although strictures causing partial or fixed obstruction would be obvious causes of stagnation and have been considered to be risk factors for SIBO, there are currently no solid peer-reviewed publications validating this. Colectomy, either partial or complete, and especially with loss of the ileocecal valve, will allow retrograde movement of colonic contents resulting in colonization of the small bowel with bacteria normally found in the large intestine (46). Studies in patients with anatomical risk factors from intrinsic causes such as small bowel diverticulosis or fistula formation or iatrogenic consequences such as post–Roux-en-Y, ileocolonic anastomosis, or post–radiation stricture/adhesion formation have all shown a higher prevalence of SIBO (8,21,32,46–50). Advanced age and female gender are also associated with a higher likelihood of SIBO, perhaps because of delays

Table 4. Conditions associated with small intestinal bacterial overgrowth

Category	Specific condition
Mechanical causes	Small bowel tumor Volvulus Intussusception Postsurgical causes
Systemic disease	Diabetes Scleroderma Amyloidosis
Motility	IBS Pseudo-obstruction Visceral myopathies Mitochondrial diseases
Medications	Opiates Potent antisecretory agents
Malabsorptive conditions	Pancreatic insufficiency Cirrhosis (altered bile acid composition) Other malabsorptive conditions
Immune-related	Human immunodeficiency virus Combined variable immunodeficiency IgA deficiency
Other	Aging (the elderly) Small bowel diverticulosis

IBS, irritable bowel syndrome; IgA, immunoglobulin A.

in gut transit (51,52). Other systemic diseases known to alter motility and which are associated with SIBO include Parkinson disease, chronic renal failure, amyloidosis, systemic sclerosis, hypothyroidism, and diabetes mellitus (53–57). Although these many mechanisms for SIBO development are intuitive, multicenter randomized controlled trials of diagnosis and treatment of SIBO in these above-stated conditions are lacking, and thus from an evidence-based perspective, higher level data are needed here.

Immune function and inflammation

Evidence supports an association between SIBO and various immunodeficiency syndromes, such as immunoglobulin A deficiency and common variable immunodeficiency (58–61). Patients with celiac disease (62,63) are also known to have SIBO. In the case of Crohn's disease, 16.8% of those in endoscopic remission had SIBO, and the presence of SIBO on breath testing was associated with ongoing GI complaints (64).

Several other conditions have been associated with SIBO, including cirrhosis and spontaneous bacterial peritonitis (65), chronic pancreatitis (66), cystic fibrosis (67), IBS (25), fibromyalgia (68), alcoholism (69), and multiple sclerosis (70), but the potential mechanism(s) underlying these relationships remains unclear.

Recommendations

4. We suggest against the use of breath testing for the diagnosis of SIBO in asymptomatic patients on proton-pump inhibitors (PPIs) (conditional recommendation, very low level of evidence).

Gastric acidity and proton-pump inhibitors

Gastric acidity plays an important role as a gatekeeper preventing the overgrowth of bacteria in the upper GI tract. Patients with hypochlorhydria or achlorhydria, secondary to autoimmune gastritis, or partial or total gastrectomy are at increased risk of SIBO (11,71,72). PPIs are among the most common medications used to treat patients suffering from unexplained GI symptoms and are also used to treat gastroesophageal reflux disease, ulcers, and functional dyspepsia. Spiegel et al. described an association between PPI use and SIBO (73), and most studies have shown a higher risk of developing SIBO in PPI users (21,74–77). For example, a retrospective study that included data from 1,263 duodenal aspirates noted that PPI use was significantly more prevalent in patients with positive duodenal culture results compared with those with negative cultures (52.6% vs 30.2%) (74). Similarly, a meta-analysis of 19 studies with more than 7,000 subjects confirmed an up to 3-fold higher risk of SIBO with PPI use (77). In a study by Compare et al. (78), 42 patients with nonerosive esophagitis were given 8 weeks of PPI therapy. All patients had negative glucose hydrogen breath tests before PPI use. On follow-up, 26% of the patients tested positive for SIBO on the breath test, and significantly higher rates of bloating, flatulence, abdominal pain, and diarrhea were reported. However, the association between SIBO and PPI is complex. Although most studies did not find a relationship between the duration of PPI therapy and SIBO, some have suggested that double-dose PPI therapy is more likely to be associated with SIBO than single dose. However, a recent meta-analysis concluded that it was not possible to determine whether dose, duration, and type of PPI exposure had an effect on the risk of developing SIBO because of insufficient data from previous studies and stated that "more high-quality evidence is still required" (77). Interestingly, another study showed that SIBO was independent of PPI use in patients with IBS, and that a positive methane breath test was less common in patients on PPI (79). This may be due to the fact that methanogens require hydrogen for the production of methane (discussed below), although this remains to be determined.

Finally, a recent large-scale deep sequencing study was presented examining the role of PPI in the development of alterations in the small bowel microbiome (80). The study demonstrated that SIBO was not seen by culture or sequencing and no changes in microbial diversity were observed. This further supports the lack of concrete evidence for the development of SIBO because of PPI therapy.

Recommendations

5. We suggest testing for methane using glucose or lactulose breath tests to diagnose the overgrowth of methane-producing organisms (IMO) in symptomatic patients with constipation (conditional recommendation, very low level of evidence).

Methane production and IMO

One aspect of breath testing that has become very intriguing is the role of methane. Multiple studies and 1 meta-analysis (81–84) have demonstrated that a positive methane breath test is associated with constipation (odds ratio = 3.51, confidence interval [CI] =

2.00–6.16), and the level of methane on the breath is proportional to the degree of constipation (81). The North American Consensus defines a positive methane breath test as the presence of methane levels of ≥10 ppm during the breath test (12). Methane infusion into the small intestine has been shown to slow transit in a canine model (85), suggesting a direct causal relationship between the overgrowth of methane-producing organisms and constipation. This is supported by *in vitro* experiments demonstrating that methane can augment contractility and delay ileal peristaltic conduction velocity (86) through effects on cholinergic neurons (87). As will be discussed, methane may be important in disease conditions and may also be useful as a predictor of treatment.

Although methane is interesting, it is also a conundrum. Methane is produced not by bacteria, but by archaea. Archaea are prokaryotic organisms and represent the third domain in the 3-domain system of life, distinct from both bacteria and eukaryotes (88), from which they can be differentiated through their rRNA and cell wall characteristics. In humans, excess methane production (i.e., levels high enough to result in a positive methane breath test) appears to be caused by *Methanobrevibacter smithii*, which is the predominant methanogen in the human gut (89,90). The problem then becomes one of nomenclature. Excessive methane production cannot be caused by "bacterial" overgrowth, but is rather due to archaeal overgrowth, so the term IMO may be more appropriate than "SIBO" or "methane-SIBO." Furthermore, although methanogens do occur in the small bowel, individuals with positive methane breath tests also exhibit increased methanogen levels in stool, suggesting they may occur throughout the intestinal tract. Therefore, it may not be altogether correct to use the term "small intestinal" overgrowth, and as such, IMO may be more accurate.

TREATMENT OF SIBO

Antibiotics

Recommendations

6. We suggest the use of antibiotics in symptomatic patients with SIBO to eradicate overgrowth and resolve symptoms (conditional recommendation, low level of evidence).

The use of antibiotics has been the cornerstone of therapy for the treatment of SIBO (Table 5). Indeed, based solely on anecdotal evidence, it has been a longstanding common practice to use empiric antibiotic therapy in those with risk factors for and a clinical presentation suggestive of SIBO. As the consequences of antibiotic use have increased, including the development of resistant bacteria, adverse reactions, and rise of opportunistic infections such as *Clostridioides difficile*, a more cautious approach is needed. Before considering antibiotic therapy, an effort should be made to objectively diagnose SIBO. In general, the evidence for the use of antibiotics in SIBO has been limited to small clinical trials of poor to modest quality. The antibiotics assessed in these clinical trials have included amoxicillin-clavulanic acid, chlortetracycline, ciprofloxacin, doxycycline, metronidazole, neomycin, norfloxacin, rifaximin, tetracycline, and trimethoprim-sulfamethoxazole. A meta-analysis was performed on 32 clinical trials assessing the safety and efficacy of rifaximin in the treatment of SIBO through March of 2015 (91). The analysis included 7 randomized clinical trials, 24 cohort studies, and 1 randomized crossover trial comprising a total of 1,331 patients. There was considerable heterogeneity among the trials, including the method of SIBO diagnosis; dose of rifaximin, which ranged from 600 to 1,600 mg a day; and duration of therapy, which ranged from 5 to 28 days. Only 1 study compared rifaximin with placebo. With these limitations in mind, the overall success of therapy with an intention-to-treat was 70.8% (CI = 61.4–78.2), and adverse reactions occurred in 4.6%. Two subsequent clinical trials have since been performed which assessed rifaximin efficacy in treating SIBO. This included a trial of 18 patients with SIBO after surgery for colorectal cancer, which was diagnosed by the glucose breath test (92). Each participant received 10 days of rifaximin at a total daily dose of 1,200 mg, of whom 33% responded based on follow-up glucose breath testing. The second trial assessed 17 cirrhotic patients with SIBO diagnosed by the glucose breath test (93). Subjects received 7 days of rifaximin at 200 mg 3 times daily and exhibited a 76% response rate based on repeat breath testing (93).

Table 5. Suggested antibiotics for treatment of small intestinal bacterial overgrowth

Antibiotic	Recommended dose	Efficacy
Nonabsorbable antibiotic		
Rifaximin	550 mg t.i.d.	61%–78%
Systemic antibiotic		
Amoxicillin-clavulanic acid	875 mg b.i.d.	50%
Ciprofloxacin	500 mg b.i.d.	43%–100%
Doxycycline	100 mg q.d. to b.i.d.	[a]
Metronidazole	250 mg t.i.d.	43%–87%
Neomycin	500 mg b.i.d.	33%–55%
Norfloxacin	400 mg q.d.	30%–100%
Tetracycline	250 mg q.i.d.	87.5%
Trimethoprim-sulfamethoxazole	160 mg/800 mg b.i.d.	95%

[a]In the study, no testing performed to reassess small intestinal bacterial overgrowth, although all participants had other objective measures of improvement.

Three clinical trials have assessed ciprofloxacin. The first of these compared treatment with 500 mg of ciprofloxacin twice daily for 10 days to treatment with metronidazole 250 mg 3 times daily, in a cohort of 29 patients with Crohn's disease and SIBO (94). The presence of SIBO was confirmed by the glucose breath test, and response to treatment was determined by the repeat glucose breath test. All 14 patients treated with ciprofloxacin responded, compared with 13 of 15 (86%) patients treated with metronidazole (94). In the second trial, 6 patients with nonalcoholic steatohepatitis were confirmed to have SIBO by the glucose breath test. These patients were treated with 500-mg ciprofloxacin twice daily for 5 days, after which only 1 remained positive (95). In the third trial, 10 patients with cystic fibrosis and SIBO based on the glucose breath test were treated with 35- to 50-mg ciprofloxacin per kg per day, and after an unspecified duration of therapy, 9 of 10 patients responded to treatment, as determined by the repeat breath test (96).

In a single study assessing elderly nursing home residents, 9 of 62 residents tested positive for SIBO by glucose breath testing (97) Those testing positive received 10 days of doxycycline, 100 mg a day, for 4 consecutive months. No follow-up breath testing was performed, but those with an initial positive breath demonstrated weight gain and increased body mass index at the end of 4 months,

whereas those with a negative breath experience a decrease in weight and body mass index. There has been 1 randomized, placebo-controlled trial which assessed the efficacy of norfloxacin treatment, 400 mg twice daily for 10 days, in 15 subjects with IBS and SIBO diagnosed by culture of small bowel aspirates (98). All 4 subjects who consented to retesting for SIBO responded to treatment, but none of the 7 subjects who received placebo responded. A crossover clinical trial compared the effects of 7 days of treatment with either amoxicillin-clavulanic acid (875 mg twice daily) or norfloxacin (400 mg twice daily) in 10 patients with SIBO diagnosed by the glucose breath test (99). Based on the repeat breath test, the response rate for amoxicillin-clavulanic acid was 50%, compared with 30% for norfloxacin. A single study assessed the response of 7 days of tetracycline at a total daily dose of 1 g given to 24 adults with jejunal cultures positive for *Escherichia coli*. After therapy, 21 of the 24 (87.5%) demonstrated negative jejunal cultures (100). Fianlly, in an open trial of 20 Brazilian children diagnosed with SIBO by the lactulose breath test, treatment with trimethoprim-sulfamethoxazole in combination with metronidazole was found to result in a response rate of 95% (101).

As SIBO frequently recurs following a course of antibiotic therapy, it is common practice to retreat with another course of antibiotics. This practice of antibiotic retreatment is solely based on anecdotal evidence and expert opinion. As such, there are no universally accepted treatment approaches to therapy. One published study assessed the frequency of SIBO recurrence in 80 adults following a course of antibiotic therapy and found recurrence rates of 12.6% at 3 months, 27.5% at 6 months, and 43.7% at 9 months (102). Although no clinical trials have been published regarding the use of repeat antibiotic therapy for recurrent SIBO, there is a study which evaluated the use of repeat antibiotics to treat SIBO and prevent recurrence in 51 patients with systemic sclerosis who had a significant risk of SIBO recurrence (103). In this study, 7 days of norfloxacin 400 mg twice daily was alternated once monthly with 7 days of metronidazole 250 mg 3 time daily for 3 consecutive months. Both the presence of SIBO and SIBO resolution was assessed by glucose breath testing, with 52% of subjects exhibiting eradication of SIBO and significant improvement of intestinal symptoms after treatment (103).

Two studies have assessed the efficacy of neomycin in the treatment of IMO. We note that both of these studies used methane levels $\geq$3 ppm to define positivity, not methane levels $\geq$10 ppm as more recently recommended by the North American Consensus. The first was a placebo-controlled trial of 84 IBS patients with IMO based on lactulose breath testing (104). Ten days of neomycin dosed at 500 mg twice daily reduced methane levels on repeat breath testing to below 3 ppm in 20% of patients, compared with 1% of those receiving placebo. The second study was a retrospective chart review of 74 patients with IMO, as determined by the lactulose breath test (105). In this study, patients received either neomycin only (500 mg twice daily), rifaximin only (400 mg 3 times daily), or both antibiotics, for 10 days. Reduction of methane to undetectable levels (below 3 ppm) on repeat breath testing was 33% in subjects treated with neomycin alone, 28% in subjects treated with rifaximin alone, and 87% in subjects treated with both antibiotics (105).

Diet

There are a variety of proposed mechanisms by which dietary manipulation may be beneficial in the treatment of SIBO. However, the dominant theme in diet manipulation for SIBO is the reduction of fermentable products. In most cases, this involves a low fiber approach as well as avoidance of alcohol sugars and other fermentable sweeteners such as sucralose. In addition, prebiotics such as inulin should also be avoided. However, the data on using diet for SIBO are principally extensions of the data from IBS. A recent meta-analysis of low FODMAP (Fermentable Oligo-, Di-, Mono-saccharides And Polyols) and gluten-free diets in IBS noted that there was no good evidence to support gluten-free approaches and "very low quality evidence" for low FODMAP diets (106).

Despite the conclusions of the meta-analysis, data do support that a low FODMAP diet is associated with fewer fermentation products, as assessed by the breath test. In 1 study, daily hydrogen output was far higher when FODMAPS were ingested (107). A study by McIntosh et al. that compared the effect of low vs high FODMAP diets on symptom severity, metabolomic markers, and the microbiome in subjects with IBS also found a small decrease in hydrogen production in subjects who consumed a low vs a high FODMAP diet (108).

Probiotics

The concept of using probiotics to treat a condition with excessive bacteria seems counterintuitive. However, a study in rats suggest that the effects of probiotics may include prokinetic actions (109). Perhaps, shifts in bacteria may also be facilitated by this type of treatment effecting a change in symptoms or gas pattern on breath testing.

In an uncontrolled study, administration of *Bifidobacterium infantis* 35624 did not appear to affect hydrogen production during breath testing, but rather resulted in an increase in methane, such that twice the number of subjects met the criteria for positive methane production ($\geq$10 ppm) after treatment as did before (110). Another study examined the open label use of a proprietary probiotic cocktail on IBS subjects with or without SIBO. Although this was a small study with only 5 subjects with IBS/SIBO, these subjects appeared to have >70% improvement in clinical symptoms, compared with 10.6% in IBS subjects without SIBO (111).

A meta-analysis has recently examined the existing trials of probiotics in SIBO and found that probiotics appeared to reduce hydrogen production with an odds ratio of 1.61 (CI = 1.19–2.17), but the studies were mostly small and of poor quality (112). However, the associated SIBO-causing conditions were mixed, and although there may have been some improvement in symptoms such as abdominal pain, stool frequency was not impacted by probiotic therapy (112). A recent controlled study showed that probiotics may cause SIBO and D-lactic acidosis leading to gas and bloating, and that withdrawal of probiotics combined with a course of antibiotics led to resolution of symptoms (23).

Fecal microbiota transplant

Although concrete data on the effects of fecal microbiota transplant (FMT) on SIBO are limited, there are some important anecdotes that warrant discussion. The most important of these is a recent study in which the investigators screened donor patients for SIBO based on the lactulose breath test (113), although a positive breath test did not preclude donation of fecal material. Interestingly, subjects with *C. difficile* receiving stool from donors with a positive lactulose breath test exhibited more GI symptoms after FMT, although this did not reach statistical significance.

Even more concerning is that more recently, the FDA has issued warnings about multidrug resistant organisms passed on to recipients during FMT (114).

Another interesting case report illustrates another concern with FMT in the context of SIBO (115). In this case, the authors describe severe constipation in a subject who underwent FMT for a *C. difficile* infection. It was later determined that the recipient acquired the phenotypes of constipation and a methane-positive breath test from the FMT donor (115).

GUIDANCE FOR TRIAL DESIGN

Most of the GRADE eligible recommendations described in these SIBO guidelines have low levels of evidence to support them. This has to do with the grading criteria, which require large effect sizes in double-blind clinical trials. These trials ordinarily involve therapeutics and not diagnostics. However, these guidelines also demonstrate that SIBO represents a significant unmet need—despite the large population affected by this condition, there are few treatment options that have undergone the scrutiny of large-scale randomized trials. Clearly, improved diagnostics and treatments are needed to help these patients. In this section, we outline the important path that these tests and treatments would need to follow to gain use in clinical practice. Table 6 outlines a proposed guideline on study design and outcomes in SIBO clinical trials.

Screening

Trials for SIBO will need to follow a path to identify subjects for inclusion. Although endoscopic culture of the small bowel for SIBO could be a potential standard for diagnosis, it has not been established as a gold standard because of limitations of the technology and access to more distal small bowel and associated risks. Indirect techniques such as breath testing can be used, but would require scrutiny in studies to demonstrate the correlation between parameters on breath testing and specific symptoms in SIBO.

Based on the North American Consensus, a positive breath test should be based on the following parameters until studies guide the literature in a better direction to include:

- Positive lactulose or glucose breath test for hydrogen (rise above baseline ≥20 ppm by 90 minutes)
- Positive lactulose or glucose breath test for methane (≥10 ppm at any point during testing)

It is important to recognize the limitations of breath testing, and therefore, in the enrollment of clinical trials, it is crucial to also have symptoms present. The most prominent symptom of SIBO is bloating. As such, this symptom should be considered mandatory for enrollment in a clinical trial and the primary enrollment symptom. However, other features of SIBO could also be examined as secondary symptoms, such as diarrhea, abdominal pain, flatulence, belching, and even constipation (in the case of methane). Although there is no threshold for bloating, in the absence of a validated PRO, this primary symptom of SIBO should be experienced by the patient during entry enrollment a minimum of 50% of days.

Outcome measures

In the case of classic SIBO with a positive hydrogen breath test, endpoints should be an improvement in bloating in conjunction with normalization of the hydrogen breath test (postintervention rise in hydrogen <20 ppm above baseline within 90 minutes of

Table 6. Proposed study enrollment and outcome considerations for small intestinal bacterial overgrowth clinical trials

Gas type	Study stage	Proposed criteria
H_2 positive	Enrollment	H_2 ≥ 20 ppm within 90 minutes of lactulose or glucose and bloating (moderate to severe) at least 50% of days Or Sterile method duodenal aspirate with coliform count on appropriate agar of > 10^3 CFU/mL[a] and bloating (moderate to severe) at least 50% of days
	Postintervention outcome measure	Primary outcome measure: reduction of bloating severity or frequency by 50% plus normal H_2 breath test (<20 ppm at or before 90 minutes) or duodenal aspirate on <10^3 CFU/mL[a] Key secondary outcome: reduction in diarrhea if part of inclusion criteria Exploratory secondary endpoints: Improvements in abdominal pain, urgency, belching, flatulence, and frequency of stool
CH_4 positive	Enrollment	CH_4 ≥ 10 ppm at any point during the first 90 minutes of the breath test and constipation (<3 CSBM/week)
	Postintervention outcome measure	Primary outcome measure: improvement in constipation severity (increase in number of CSBM/week by >1 and normalization of CH_4 (no CH_4 ≥ 10 ppm within 90 minutes) Key secondary outcome: improvement in bloating by >50% (frequency or severity) Exploratory secondary endpoints: improvements in abdominal pain, straining, incomplete evacuation, SBM, and belching

[a]Note that duodenal aspirates may be considered an undue burden and risk to study subjects being performed before and after clinical interventions.
CFU/mL, colony-forming units per milliliter; CSBM, complete spontaneous bowel movements; ppm, parts per million; SBM, spontaneous bowel movements.

lactulose or glucose). A key secondary endpoint in hydrogen subjects could be diarrhea or loose stool. Other symptoms would be exploratory secondary endpoints.

Methane would be considered a special case. Since constipation is a key feature of methane, these symptoms could be considered as the primary symptom and endpoint with bloating as a key secondary outcome. For methane, a postintervention methane of no greater than 10 ppm would be considered successful eradication. However, since methane production and constipation have been shown to be correlated, a key secondary endpoint could be reduction in methane from baseline with corresponding reduction in constipation.

FUTURE DIRECTIONS

As this guideline points out, although indirect measures for SIBO evaluation using breath testing are the most practical approach to SIBO research, part of the challenge is that current breath testing technology provides an incomplete picture of the fermentation dynamics in the gut. Figure 2 illustrates the interrelationship between classes of organism in the gut and their fermentation products. The reason hydrogen has not correlated with symptoms clearly in clinical trial could be that hydrogen is consumed in the gut to produce methane and H_2S gases. As such, measuring only methane and hydrogen produces an incomplete picture. Future studies are examining the role of measuring all 3 gases during breath testing. The value of these in overgrowth assessment may provide greater clarity and symptom correlation. Also, it is important to develop validated questionnaires and PROs for SIBO, as symptoms lack specificity. Furthermore, advancements are taking place in indirect microbiome testing. One such area is to assess breath volatile substances by mass spectroscopy. This work is in the early stages but offers a great deal of promise for future considerations. As these unfold, what was once SIBO may become a collection of conditions named for the specific organism(s) that are responsible for the phenotype.

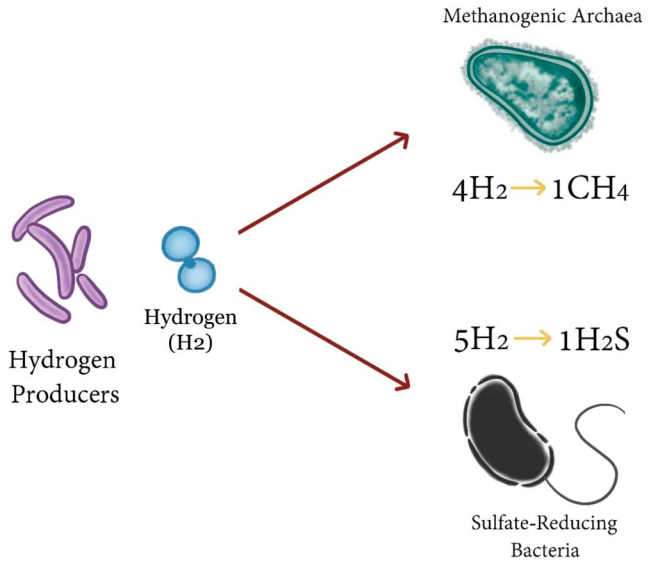

Figure 2. Gas dynamics in the gastrointestinal tract.

ACKNOWLEDGEMENTS

This guideline was produced in collaboration with the Practice Parameters Committee of the American College of Gastroenterology. The committee gives special thanks to Scott Fink, MD, who served as guideline monitor for this document, and to Bryan G. Sauer, MD, MSc, FACG, who assisted with the GRADE methodology process.

CONFLICTS OF INTEREST

Guarantor of the article: Mark Pimentel, MD, FRCP(C), FACG.
Specific author contributions: M.P., R.J.S., M.D.L., B.G.S., and S.S.C.R. wrote, reviewed, and edited the manuscript. All authors have approved the final submission.
Financial support: None to report.
Potential competing interests: S.S.C.R. has received grant support from Progenity and Salix Pharmaceuticals (now Bausch Health) and is on the advisory boards for Progenity and Salix Pharmaceuticals. M.D.L. is a consultant for Takeda, Pfizer, Janssen, UCB, AbbVie, Valeant, Salix, Target Pharmasolutions, and Prometheus, and has received grant support from Pfizer and Takeda. R.J.S. is a consultant for Takeda. MP has equity in Gemelli Biotech and is a consultant for Synthetic Biologics. M.P. is also a consultant for and received grant support from Salix Pharmaceuticals. Cedars-Sinai has a licensing agreement with Bausch Health and Gemelli Biotech.

REFERENCES

1. Sachdev AH, Pimentel M. Antibiotics for irritable bowel syndrome: Rationale and current evidence. Curr Gastroenterol Rep 2012;14:439–45.
2. Turnbaugh PJ, Ley RE, Hamady M, et al. The human microbiome project. Nature 2007;449:804–10.
3. Pimentel M. The prevalence of small intestinal bacterial overgrowth in irritable bowel syndrome: IBS vs healthy controls (not historical definitions). Gut 2008;57:1334–5.
4. Majewski M, McCallum RW. Results of small intestinal bacterial overgrowth testing in irritable bowel syndrome patients: Clinical profiles and effects of antibiotic trial. Adv Med Sci 2007;52:139–42.
5. Shah A, Morrison M, Burger D, et al. Systematic review with meta-analysis: The prevalence of small intestinal bacterial overgrowth in inflammatory bowel disease. Aliment Pharmacol Ther 2019;49:624–35.
6. Tauber M, Avouac J, Benahmed A, et al. Prevalence and predictors of small intestinal bacterial overgrowth in systemic sclerosis patients with gastrointestinal symptoms. Clin Exp Rheumatol 2014;32:S-82–7.
7. Vantrappen G, Janssens J, Hellemans J, et al. The interdigestive motor complex of normal subjects and patients with bacterial overgrowth of the small intestine. J Clin Invest 1977;59:1158–66.
8. Husebye E, Skar V, Høverstad T, et al. Abnormal intestinal motor patterns explain enteric colonization with gram-negative bacilli in late radiation enteropathy. Gastroenterology 1995;109:1078–89.
9. Fukui H, Wiest R. Changes of intestinal functions in liver cirrhosis. Inflamm Intest Dis 2016;1:24–40.
10. Fialho A, Fialho A, Thota P, et al. Small intestinal bacterial overgrowth is associated with non-alcoholic fatty liver disease. J Gastrointestin Liver Dis 2016;25:159–65.
11. Paik CN, Choi MG, Lim CH, et al. The role of small intestinal bacterial overgrowth in postgastrectomy patients. Neurogastroenterol Motil 2011;23:e191–6.
12. Rezaie A, Buresi M, Lembo A, et al. Hydrogen and methane-based breath testing in gastrointestinal disorders: The North American consensus. Am J Gastroenterol 2017;112:775–84.
13. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol 2011;64:383–94.
14. Khoshini R, Dai SC, Lezcano S, et al. A systematic review of diagnostic tests for small intestinal bacterial overgrowth. Dig Dis Sci 2008;53:1443–54.
15. Levitt MD, Bond JH Jr. Volume, composition, and source of intestinal gas. Gastroenterology 1970;59:921–9.

16. Gasbarrini A, Corazza GR, Gasbarrini G, et al. Methodology and indications of H2-breath testing in gastrointestinal diseases: The Rome consensus conference. Aliment Pharmacol Ther 2009;29(Suppl 1):1–49.
17. Ghoshal UC, Ghoshal U. Small intestinal bacterial overgrowth and other intestinal disorders. Gastroenterol Clin North Am 2017;46:103–20.
18. Polkowska-Pruszynska B, Gerkowicz A, Szczepanik-Kulak P, et al. Small intestinal bacterial overgrowth in systemic sclerosis: A review of the literature. Arch Dermatol Res 2019;311:1–8.
19. Erdogan A, Rao SS. Small intestinal fungal overgrowth. Curr Gastroenterol Rep 2015;17:16.
20. Erdogan A, Rao SS, Gulley D, et al. Small intestinal bacterial overgrowth: Duodenal aspiration vs glucose breath test. Neurogastroenterol Motil 2015;27:481–9.
21. Jacobs C, Coss Adame E, Attaluri A, et al. Dysmotility and proton pump inhibitor use are independent risk factors for small intestinal bacterial and/or fungal overgrowth. Aliment Pharmacol Ther 2013;37:1103–11.
22. Zaidel O, Lin HC. Uninvited guests: The impact of small intestinal bacterial overgrowth on nutritional status. Pract Gastroenterol 2003;7: 27–34.
23. Rao SSC, Rehman A, Yu S, et al. Brain fogginess, gas and bloating: A link between SIBO, probiotics and metabolic acidosis. Clin Transl Gastroenterol 2018;9:162.
24. Baker J, Eswaran S, Saad R, et al. Abdominal symptoms are common and benefit from biofeedback therapy in patients with dyssynergic defecation. Clin Transl Gastroenterol 2015;6:e105.
25. Rezaie A, Nikfar S, Abdollahi M. The place of antibiotics in management of irritable bowel syndrome: A systematic review and meta-analysis. Arch Med Sci 2010;6:49–55.
26. Krajmalnik-Brown R, Ilhan Z-E, Kang D-W, et al. Effects of gut microbes on nutrient absorption and energy regulation. Nutr Clin Pract 2012;27:201–14.
27. Gaci N, Borrel G, Tottey W, et al. Archaea and the human gut: New beginning of an old story. World J Gastroenterol 2014;20:16062–78.
28. Newman A. Breath-analysis tests in gastroenterology. Gut 1974;15: 308–23.
29. Erdogan ALY, Badger C, Hall P, et al. What is the optimal threshold for an increase in hydrogen and methane levels with glucose breath test (GBT) for detection of small intestinal bacterial overgrowth (SIBO)? Gastroenterology 2014;146:S-532.
30. Bhagatwala JSA, Leelasinjaroen P, Tetangco E, et al. Investigation of small intestinal bacterial overgrowth (SIBO) in diabetics using fructose breath test. Gastroenterology 2018;154:53–4.
31. Lin ECK, Pichetshote N, Rezaie A, et al. Measurement of hydrogen sulfide during breath testing correlates to patient symptoms. Gastroenterology 2017;152:205–6.
32. Pyleris E, Giamarellos-Bourboulis EJ, Tzivras D, et al. The prevalence of overgrowth by aerobic bacteria in the small intestine by small bowel culture: Relationship with irritable bowel syndrome. Dig Dis Sci 2012;57: 1321–9.
33. Giamarellos-Bourboulis E, Tang J, Pyleris E, et al. Molecular assessment of differences in the duodenal microbiome in subjects with irritable bowel syndrome. Scand J Gastroenterol 2015;50:1076–87.
34. Kerckhoffs AP, Ben-Amor K, Samsom M, et al. Molecular analysis of faecal and duodenal samples reveals significantly higher prevalence and numbers of Pseudomonas aeruginosa in irritable bowel syndrome. J Med Microbiol 2011;60:236–45.
35. Leite G, Villanueva-Millan MJ, Celly S, et al. 4—First large scale study defining the characteristic microbiome signatures of small intestinal bacterial overgrowth (SIBO): Detailed analysis from the reimagine study. Gastroenterology 2019;156:S-1–2.
36. Li G, Yang M, Jin Y, et al. Involvement of shared mucosal-associated microbiota in the duodenum and rectum in diarrhea-predominant irritable bowel syndrome. J Gastroenterol Hepatol 2018;33:1220–6.
37. Sundin OH, Mendoza-Ladd A, Morales E, et al. Does a glucose-based hydrogen and methane breath test detect bacterial overgrowth in the jejunum? Neurogastroenterol Motil 2018;30:e13350.
38. Erdogan A, Rao SS, Gulley D, et al. Possible underestimation of SIBO in IBS patients: Is lack of glucose breath test standardization responsible? Neurogastroenterol Motil 2015;27:1192–3.
39. 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; 96:1113–26.
40. Kalantar-Zadeh K, Berean KJ, Ha N, et al. A human pilot trial of ingestible electronic capsules capable of sensing different gases in the gut. Nat Electronics 2018;1:79–87.
41. Singh S, Allan N, Wahl C, et al. Sa1717—Development of a swallowable diganostic capsule to monitor gastrointestinal health. Gastroenterology 2019;156:S-376.
42. Shah ED, Basseri RJ, Chong K, et al. Abnormal breath testing in IBS: A meta-analysis. Dig Dis Sci 2010;55:2441–9.
43. Lembo A, Pimentel M, Rao SS, et al. Repeat treatment with rifaximin is safe and effective in patients with diarrhea-predominant irritable bowel syndrome. Gastroenterology 2016;151:1113–21.
44. Rezaie A, Heimanson Z, Israel RJ, et al. Lactulose breath testing predicts the response to rifaximin—Program no. P299. World Congress of Gastroenterology at ACG 2017 Meeting. Orlando, FL, 2017.
45. Code CF, Marlett JA. The interdigestive myo-electric complex of the stomach and small bowel of dogs. J Physiol 1975;246:289–309.
46. Rao SSC, Tan G, Abdulla H, et al. Does colectomy predispose to small intestinal bacterial (SIBO) and fungal overgrowth (SIFO)? Clin Transl Gastroenterol 2018;9:146.
47. Bures J, Cyrany J, Kohoutova D, et al. Small intestinal bacterial overgrowth syndrome. World J Gastroenterol 2010;16:2978–90.
48. Petrone P, Sarkisyan G, Fernandez M, et al. Small intestinal bacterial overgrowth in patients with lower gastrointestinal symptoms and a history of previous abdominal surgery. Arch Surg 2011;146:444–7.
49. Yamini D, Pimentel M. Irritable bowel syndrome and small intestinal bacterial overgrowth. J Clin Gastroenterol 2010;44:672–5.
50. Kim DB, Paik CN, Kim YJ, et al. Positive glucose breath tests in patients with hysterectomy, gastrectomy, and cholecystectomy. Gut Liver 2017; 11:237–42.
51. Newberry C, Tierney A, Pickett-Blakely O. Lactulose hydrogen breath test result is associated with age and gender. Biomed Res Int 2016;2016: 1064029.
52. Choung RS, Ruff KC, Malhotra A, et al. Clinical predictors of small intestinal bacterial overgrowth by duodenal aspirate culture. Aliment Pharmacol Ther 2011;33:1059–67.
53. Barboza JL, Okun MS, Moshiree B. The treatment of gastroparesis, constipation and small intestinal bacterial overgrowth syndrome in patients with Parkinson's disease. Expert Opin Pharmacother 2015;16: 2449–64.
54. Lauritano EC, Bilotta AL, Gabrielli M, et al. Association between hypothyroidism and small intestinal bacterial overgrowth. J Clin Endocrinol Metab 2007;92:4180–4.
55. Mulak A, Bonaz B. Brain-gut-microbiota axis in Parkinson's disease. World J Gastroenterol 2015;21:10609–20.
56. 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;67:129–37.
57. Jigar Bhagatwala SWY, Erdogan A, Leelasinjaroen P, et al. Altered small bowel motility and small intestinal bacterial overgrowth: Time to target the culprit? Gastroenterology 2016;150:97.
58. 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;44:939–44.
59. Kett K, Baklien K, Bakken A, et al. Intestinal B-cell isotype response in relation to local bacterial load: Evidence for immunoglobulin A subclass adaptation. Gastroenterology 1995;109:819–25.
60. Belitsos PC, Greenson JK, Yardley JH, et al. Association of gastric hypoacidity with opportunistic enteric infections in patients with AIDS. J Infect Dis 1992;166:277–84.
61. Pignata C, Budillon G, Monaco G, et al. Jejunal bacterial overgrowth and intestinal permeability in children with immunodeficiency syndromes. Gut 1990;31:879–82.
62. Lasa JS, Zubiaurre I, Fanjul I, et al. Small intestinal bacterial overgrowth prevalence in celiac disease patients is similar in healthy subjects and lower in irritable bowel syndrome patients. Rev Gastroenterol Mex 2015; 80:171–4.
63. Rubio-Tapia A, Barton SH, Rosenblatt JE, et al. Prevalence of small intestine bacterial overgrowth diagnosed by quantitative culture of intestinal aspirate in celiac disease. J Clin Gastroenterol 2009;43:157–61.
64. Sanchez-Montes C, Ortiz V, Bastida G, et al. Small intestinal bacterial overgrowth in inactive Crohn's disease: Influence of thiopurine and biological treatment. World J Gastroenterol 2014;20:13999–4003.
65. Bauer TM, Steinbrückner B, Brinkmann FE, et al. Small intestinal bacterial overgrowth in patients with cirrhosis: Prevalence and relation

with spontaneous bacterial peritonitis. Am J Gastroenterol 2001;96:2962–7.
66. Therrien A, Bouchard S, Sidani S, et al. Prevalence of small intestinal bacterial overgrowth among chronic pancreatitis patients: A case-control study. Can J Gastroenterol Hepatol 2016;2016:7424831.
67. Fridge JL, Conrad C, Gerson L, et al. Risk factors for small bowel bacterial overgrowth in cystic fibrosis. J Pediatr Gastroenterol Nutr 2007;44:212–8.
68. Pimentel M, Wallace D, Hallegua D, et al. A link between irritable bowel syndrome and fibromyalgia may be related to findings on lactulose breath testing. Ann Rheum Dis 2004;63:450–2.
69. Gabbard SL, Lacy BE, Levine GM, et al. The impact of alcohol consumption and cholecystectomy on small intestinal bacterial overgrowth. Dig Dis Sci 2014;59:638–44.
70. Zhang Y, Liu G, Duan Y, et al. Prevalence of small intestinal bacterial overgrowth in multiple sclerosis: A case-control study from China. J Neuroimmunol 2016;301:83–7.
71. Saltzman JR, Kowdley KV, Pedrosa MC, et al. Bacterial overgrowth without clinical malabsorption in elderly hypochlorhydric subjects. Gastroenterology 1994;106:615–23.
72. Husebye E, Skar V, Høverstad T, et al. Fasting hypochlorhydria with gram positive gastric flora is highly prevalent in healthy old people. Gut 1992;33:1331–7.
73. Spiegel BM, Chey WD, Chang L. Bacterial overgrowth and irritable bowel syndrome: Unifying hypothesis or a spurious consequence of proton pump inhibitors? Am J Gastroenterol 2008;103:2972–6.
74. Franco DL, Disbrow MB, Kahn A, et al. Duodenal aspirates for small intestine bacterial overgrowth: Yield, PPIs, and outcomes after treatment at a Tertiary Academic Medical Center. Gastroenterol Res Pract 2015;2015:971582.
75. Lombardo L, Foti M, Ruggia O, et al. Increased incidence of small intestinal bacterial overgrowth during proton pump inhibitor therapy. Clin Gastroenterol Hepatol 2010;8:504–8.
76. Ratuapli SK, Ellington TG, O'Neill MT, et al. Proton pump inhibitor therapy use does not predispose to small intestinal bacterial overgrowth. Am J Gastroenterol 2012;107:730–5.
77. Su T, Lai S, Lee A, et al. Meta-analysis: Proton pump inhibitors moderately increase the risk of small intestinal bacterial overgrowth. J Gastroenterol 2018;53:27–36.
78. Compare D, Pica L, Rocco A, et al. Effects of long-term PPI treatment on producing bowel symptoms and SIBO. Eur J Clin Invest 2011;41:380–6.
79. Giamarellos-Bourboulis EJ, Pyleris E, Barbatzas C, et al. Small intestinal bacterial overgrowth is associated with irritable bowel syndrome and is independent of proton pump inhibitor usage. BMC Gastroenterol 2016;16:67.
80. Weitsman S, Leite G, Celly S, et al. 979—A large scale evaluation of the small intestinal microbiome in subjects on proton pump inhibitors. Gastroenterology 2019;156:S-206.
81. Chatterjee S, Park S, Low K, et al. The degree of breath methane production in IBS correlates with the severity of constipation. Am J Gastroenterol 2007;102:837–41.
82. Attaluri A, Jackson M, Valestin J, et al. Methanogenic flora is associated with altered colonic transit but not stool characteristics in constipation without IBS. Am J Gastroenterol 2010;105:1407–11.
83. Hwang L, Low K, Khoshini R, et al. Evaluating breath methane as a diagnostic test for constipation-predominant IBS. Dig Dis Sci 2010;55:398–403.
84. Kunkel D, Basseri RJ, Makhani MD, et al. Methane on breath testing is associated with constipation: A systematic review and meta-analysis. Dig Dis Sci 2011;56:1612–8.
85. Pimentel M, Lin HC, Enayati P, et al. Methane, a gas produced by enteric bacteria, slows intestinal transit and augments small intestinal contractile activity. Am J Physiol Gastrointest Liver Physiol 2006;290:G1089–95.
86. Jahng J, Jung IS, Choi EJ, et al. The effects of methane and hydrogen gases produced by enteric bacteria on ileal motility and colonic transit time. Neurogastroenterol Motil 2012;24:185–90, e92.
87. Park YM, Lee YJ, Hussain Z, et al. The effects and mechanism of action of methane on ileal motor function. Neurogastroenterol Motil 2017;29:e13077.
88. Woese CR, Kandler O, Wheelis ML. Towards a natural system of organisms: Proposal for the domains archaea, bacteria, and eucarya. Proc Natl Acad Sci USA 1990;87:4576–9.
89. Miller TL, Wolin MJ. Enumeration of *Methanobrevibacter smithii* in human feces. Arch Microbiol 1982;131:14–8.
90. Kim G, Deepinder F, Morales W, et al. *Methanobrevibacter smithii* is the predominant methanogen in patients with constipation-predominant IBS and methane on breath. Dig Dis Sci 2012;57:3213–8.
91. Gatta L, Scarpignato C. Systematic review with meta-analysis: Rifaximin is effective and safe for the treatment of small intestine bacterial overgrowth. Aliment Pharmacol Ther 2017;45:604–16.
92. Deng L, Liu Y, Zhang D, et al. Prevalence and treatment of small intestinal bacterial overgrowth in postoperative patients with colorectal cancer. Mol Clin Oncol 2016;4:883–7.
93. Zhang Y, Feng Y, Cao B, et al. Effects of SIBO and rifaximin therapy on MHE caused by hepatic cirrhosis. Int J Clin Exp Med 2015;8:2954–7.
94. Castiglione F, Rispo A, Di Girolamo E, et al. Antibiotic treatment of small bowel bacterial overgrowth in patients with Crohn's disease. Aliment Pharmacol Ther 2003;18:1107–12.
95. Sajjad A, Mottershead M, Syn WK, et al. Ciprofloxacin suppresses bacterial overgrowth, increases fasting insulin but does not correct low acylated ghrelin concentration in non-alcoholic steatohepatitis. Aliment Pharmacol Ther 2005;22:291–9.
96. Lisowska A, Pogorzelski A, Oracz G, et al. Oral antibiotic therapy improves fat absorption in cystic fibrosis patients with small intestine bacterial overgrowth. J Cyst Fibros 2011;10:418–21.
97. Lewis SJ, Potts LF, Malhotra R, et al. Small bowel bacterial overgrowth in subjects living in residential care homes. Age Ageing 1999;28:181–5.
98. Ghoshal UC, Srivastava D, Misra A, et al. A proof-of-concept study showing antibiotics to be more effective in irritable bowel syndrome with than without small-intestinal bacterial overgrowth: A randomized, double-blind, placebo-controlled trial. Eur J Gastroenterol Hepatol 2016;28:281–9.
99. Attar A, Flourié B, Rambaud JC, et al. Antibiotic efficacy in small intestinal bacterial overgrowth-related chronic diarrhea: A crossover, randomized trial. Gastroenterology 1999;117:794–7.
100. Shindo K, Machida M, Fukumura M, et al. Omeprazole induces altered bile acid metabolism. Gut 1998;42:266–71.
101. Tahan S, Melli LCFL, Mello CS, et al. Effectiveness of trimethoprim-sulfamethoxazole and metronidazole in the treatment of small intestinal bacterial overgrowth in children living in a slum. J Pediatr Gastroenterol Nutr 2013;57:316–8.
102. Lauritano EC, Gabrielli M, Scarpellini E, et al. Small intestinal bacterial overgrowth recurrence after antibiotic therapy. Am J Gastroenterol 2008;103:2031–5.
103. Marie I, Ducrotté P, Denis P, et al. Small intestinal bacterial overgrowth in systemic sclerosis. Rheumatology (Oxford) 2009;48:1314–9.
104. Pimentel M, Chow EJ, Lin HC. Normalization of lactulose breath testing correlates with symptom improvement in irritable bowel syndrome: A double-blind, randomized, placebo-controlled study. Am J Gastroenterol 2003;98:412–9.
105. Low K, Hwang L, Hua J, et al. A combination of rifaximin and neomycin is most effective in treating irritable bowel syndrome patients with methane on lactulose breath test. J Clin Gastroenterol 2010;44:547–50.
106. Dionne J, Ford AC, Yuan Y, et al. A systematic review and meta-analysis evaluating the efficacy of a gluten-free diet and a low FODMAPs diet in treating symptoms of irritable bowel syndrome. Am J Gastroenterol 2018;113:1290–300.
107. Ong DK, Mitchell SB, Barrett JS, et al. Manipulation of dietary short chain carbohydrates alters the pattern of gas production and genesis of symptoms in irritable bowel syndrome. J Gastroenterol Hepatol 2010;25:1366–73.
108. McIntosh K, Reed DE, Schneider T, et al. FODMAPs alter symptoms and the metabolome of patients with IBS: A randomised controlled trial. Gut 2017;66:1241–51.
109. Husebye E, Hellström PM, Sundler F, et al. Influence of microbial species on small intestinal myoelectric activity and transit in germ-free rats. Am J Physiol Gastrointest Liver Physiol 2001;280:G368–80.
110. Kumar K, Saadi M, Ramsey FV, et al. Effect of *Bifidobacterium infantis* 35624 (Align) on the lactulose breath test for small intestinal bacterial overgrowth. Dig Dis Sci 2018;63:989–95.
111. Leventogiannis K, Gkolfakis P, Spithakis G, et al. Effect of a preparation of four probiotics on symptoms of patients with irritable bowel syndrome: Association with intestinal bacterial overgrowth. Probiotics Antimicrob Proteins 2019;11:627–34.

112. Zhong C, Qu C, Wang B, et al. Probiotics for preventing and treating small intestinal bacterial overgrowth: A meta-analysis and systematic review of current evidence. J Clin Gastroenterol 2017;51:300–11.
113. Allegretti JR, Kassam Z, Chan WW. Small intestinal bacterial overgrowth: Should screening be included in the pre-fecal microbiota transplantation evaluation? Dig Dis Sci 2018;63:193–7.
114. U.S. Food and Drug Administration. Important safety alert regarding use of fecal microbiota for transplantation and risk of serious adverse reactions due to transmission of multi-drug resistant organisms. 2019 (https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/important-safety-alert-regarding-use-fecal-microbiota-transplantation-and-risk-serious-adverse). Accessed June 28, 2019.
115. Chang BW, Rezaie A. Irritable bowel syndrome-like symptoms following fecal microbiota transplantation: A possible donor-dependent complication. Am J Gastroenterol 2017;112:186–7.