Small Intestinal Bacterial Overgrowth: Clinical Features and Therapeutic Management

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Small intestinal bacterial overgrowth (SIBO) is a common, yet underrecognized, problem. Its prevalence is unknown because SIBO requires diagnostic testing. Although abdominal bloating, gas, distension, and diarrhea are common symptoms, they do not predict positive diagnosis. Predisposing factors include proton-pump inhibitors, opioids, gastric bypass, colectomy, and dysmotility. Small bowel aspirate/culture with growth of 10^3–10^5 cfu/mL is generally accepted as the "best diagnostic method," but it is invasive. Glucose or lactulose breath testing is noninvasive but an indirect method that requires further standardization and validation for SIBO. Treatment, usually with antibiotics, aims to provide symptom relief through eradication of bacteria in the small intestine. Limited numbers of controlled studies have shown systemic antibiotics (norfloxacin and metronidazole) to be efficacious. However, 15 studies have shown rifaximin, a nonsystemic antibiotic, to be effective against SIBO and well tolerated. Through improved awareness and scientific rigor, the SIBO landscape is poised for transformation.

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INTRODUCTION

The adult gastrointestinal (GI) tract has the largest microbial population in the human body (1); the predominant site is the colon, containing 38 trillion bacteria (2). Culture-independent methods, such as next-generation sequencing, show low concentration of distinct bacterial populations in the duodenum of healthy individuals, in contrast with bacterial populations that inhabit the mouth (3). Bacterial concentrations increase progressively along the small intestine (4,5).

Small intestinal bacterial overgrowth (SIBO) is characterized by the presence of an abnormal amount of bacteria in the small intestine together with a constellation of GI symptoms. The purpose of this article is to provide an up-to-date review of SIBO, including symptom patterns, predisposing risk factors, prevalence, specialized diagnostic testing, and potential therapeutic interventions, and to describe gaps in our knowledge and unmet needs.

METHODS

A PubMed search was performed on June 8, 2018, to identify English-language publications of clinical trials pertaining to SIBO in adults since 1985 using the search terms "small bowel bacterial overgrowth," "small intestinal bacterial overgrowth," "SIBO," "epidemiology," "diagnosis," "treatment," "antibiotic (e.g., ciprofloxacin, cotrimoxazole, and metronidazole)," "rifaximin," or "probiotic." Clinical studies of rifaximin ($n = 15$), systemic antibiotics ($n = 6$), and probiotics ($n = 3$) in SIBO were included, whereas studies of combination therapies, for example, rifaximin with another antibiotic and/or other combination of systemic antibiotics or probiotics, were excluded from this review. A total of 23 references on predisposing factors and 4 on diagnostic testing for SIBO were included. Although we recognize that SIBO occurs in a wide spectrum of diseases discussed below, most literature on this topic has focused on patients presenting with either unexplained symptoms or symptoms of irritable bowel syndrome (IBS). Our review primarily focuses on these patients, as they are most commonly encountered in gastroenterology clinics, but other conditions are appropriately referenced wherever necessary.

CLINICAL FEATURES, PREVALENCE, AND PATHOETIOLOGY

Symptoms of SIBO are nonspecific and include abdominal pain, belching, bloating, diarrhea, distension, flatulence, and indigestion that overlap and vary in frequency, duration, and severity. Typically, over two-thirds of patients report the aforementioned symptoms (6,7). Diagnosis of SIBO is challenging, as illustrated by 1 study in which mean total symptom scores were similar regardless of whether patients tested positive or negative with duodenal aspirate and breath testing ($P = 0.9$) (6). Because a SIBO diagnosis requires specialized testing (e.g., microbial culture and breath testing), and owing to variability in patient populations and methods used to establish a diagnosis across studies (8), prevalence has been difficult to estimate. However, SIBO appears to be more prevalent in women and in older individuals (9).

Several factors are associated with or predispose patients to SIBO, including small intestinal dysmotility (10). A study using duodenal aspirate/culture demonstrated that patients with small intestinal dysmotility were at increased risk of SIBO (>10^3 colony-forming units [cfu]/mL threshold, odds ratio [OR], 3.6; $P = 0.0003$; >10^5 cfu/mL threshold, OR, 2.7; $P = 0.005$) (7).

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Indeed, a significantly greater percentage of patients with IBS and SIBO were considered to have dysmotility vs patients with IBS without SIBO (86% vs 39%, respectively; $P = 0.02$) (11). Besides IBS, conditions that have been associated with SIBO include inflammatory bowel disease, dyspepsia, rosacea, restless legs syndrome, small bowel diverticula, pancreatitis, hypothyroidism, Parkinson's disease, diabetes, coronary artery disease, and abdominal surgery (e.g., hysterectomy, gastrectomy, cholecystectomy, and colectomy). However, the prevalence of SIBO in patients with these associated conditions is highly variable (range, 4%–79%) (11–16). In a 2018 case-control study, a significantly greater percentage of patients who underwent colectomy had SIBO compared with patients with long-standing GI complaints without colectomy (62% vs 32%, respectively; $P = 0.0005$) (17).

Some studies have suggested an association between SIBO and use of proton-pump inhibitors (PPIs) (7,18,19); however, others have not (9,20). PPIs may predispose patients to bacterial overgrowth by decreasing gastric acid (21). An initial study reported that 56% of 25 patients with peptic ulcers who received omeprazole had SIBO compared with none of 15 controls referred for diagnostic endoscopy ($P = 0.0003$). Subsequent studies have confirmed the association of SIBO with PPIs (18,19), including a retrospective study ($n = 1{,}263$ duodenal aspirates), showing that PPI use was significantly greater in patients with positive duodenal culture results compared with negative culture results (52.6% vs 30.2%, respectively; $P < 0.0001$) (18). Results of a 2017 meta-analysis of 19 studies ($N = 7{,}055$) confirmed a higher risk of SIBO with PPI use (OR, 1.7; 95% confidence interval [CI], 1.2–2.4) (22). A recent study demonstrated that probiotic bacteria may colonize the small bowel and predispose patients to SIBO and brain fogginess (23). Thus, numerous factors predispose an individual to the development of SIBO (Table 1) (7,9,11–19,23–34). Interestingly, up to 13% of healthy individuals have also tested positive for SIBO, based on the results of breath testing or small bowel aspirate and culture (26,35–41).

Table 1. Predisposing factors for SIBO

Category	Factor
Demographics	Female sex (9)
	Age (9)
Medication use	PPIs (7,18,19)
	Opioids (23)
GI conditions	Dyspepsia (24)
	IBD (9,25)
	IBS (11–14)
	Intestinal dysmotility (7)
	Small bowel diverticula (9)
	Systemic sclerosis (33)
Other conditions	Abdominal surgery (i.e., hysterectomy, gastrectomy, cholecystectomy, colectomy, and Roux-en-Y gastric bypass) (17,26,34)
	Coronary artery disease (16)
	Diabetes (27)
	Hypothyroidism (28)
	Pancreatitis (9,29)
	Parkinson's disease (30)
	Restless legs syndrome (31)
	Rosacea (32)

GI, gastrointestinal; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; PPI, proton-pump inhibitor; SIBO, small intestinal bacterial overgrowth.

DIAGNOSIS OF SIBO

Small bowel culture is widely accepted as the "best diagnostic method" for establishing a diagnosis of SIBO (9); a threshold of $\geq 10^3$ cfu/mL is recommended as a positive test result for SIBO, especially when performing duodenal aspirate and culture, because of very low bacterial counts in this more acidic environment (6–8). However, some investigators have suggested a higher threshold of $\geq 10^5$ cfu/mL based on traditional microbiological standards for bacterial infection and for jejunal culture (11–13,42,43). In culture-based diagnostic testing, aseptic technique is critical to minimize cross-contamination from outside the duodenum (6), and standardized methods are needed (8). To this end, aspiration of duodenal juice by endoscopic suction and collection in a container may be fraught with contamination (18). One study described the use of a double-lumen catheter for collection of small bowel aspirate to prevent oropharyngeal cross-contamination of the sample (12), but this device is not commercially available. For more than 2 decades, we have successfully used a 6F Liguory catheter (COOK Medical, Bloomington, IN) with multiple side holes at its tip (Figure 1) for collection of small bowel aspirate. The catheter assembly and aspiration kit is first prepared by wearing sterile gloves before the procedure (Figure 1). Next, a sterilized upper endoscope, kept in a sterile wrap and flushed with sterile water before intubation, is passed into the second/third portion of the duodenum using minimal air insufflation. Thereafter, the staff change to another set of sterile gloves to prevent contamination during specimen collection. The endoscopist then passes the Liguory catheter through the biopsy channel of the scope, using the short overtube to prevent biopsy valve contamination. The technician is usually seated for gravity-assisted suction and flow and gently aspirates fluid by repeated suction using a 5-mL sterile syringe connected to a 3-way stopcock. If the lumen is dry, the liver may be gently massaged to facilitate the flow of bile into the duodenum. Typically, within approximately 2–5 minutes, 3 mL of bile-stained duodenal juice is successfully aspirated (Figure 1) (17). The syringe is capped with a sterile cap, and the specimen is placed in a biohazard bag and immediately sent to the microbiology laboratory for aerobic and anaerobic cultures (6,7,44).

Care is taken not to aspirate oral secretions or stomach juices before securing the scope in the duodenum and passing the catheter. In the microbiology laboratory, after vortexing the sample, the following agar plates are inoculated using a 0.001 calibrated loop: blood, chocolate, MacConkey, Columbia nalidixic acid with blood, anaerobic blood, phenyl ethyl alcohol, Remel Anaerobic LPV Blood (Thermo Fisher Scientific, Waltham, MA), which contains paromomycin and vancomycin, inhibitory mold, and mycobiotic. Agar plates are then struck for the colony count. The blood and chocolate agars are held at 37 °C in carbon dioxide for 5 days. MacConkey and Columbia nalidixic

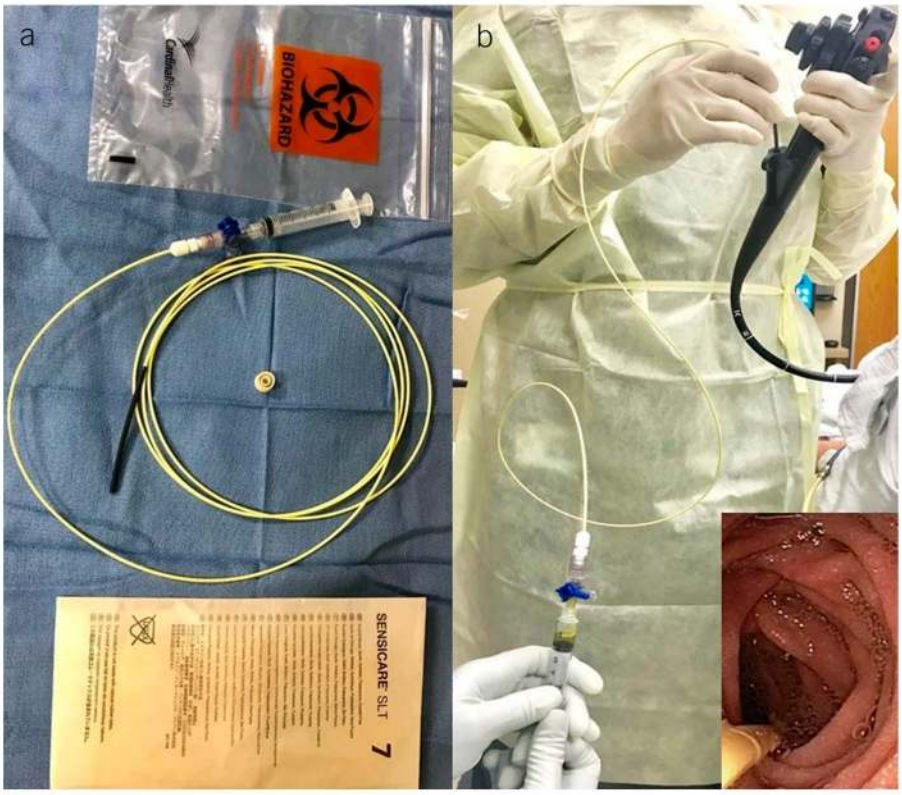

Figure 1. Description of the procedure for duodenal aspiration, specimen collection, and handling: The technician flushes the scope with sterile water and prepares a sterile field. A Liguory catheter with a stopcock is assembled (**a**). The scope is passed into the second/third portion of the duodenum with minimal air insufflation and suctioning. The endoscopist and the technician wear sterile gloves and advance the Liguory catheter through the biopsy channel. The technician performs gravity-assisted aspiration by holding the syringe at a height lower than the patient to aid fluid flow. Using gentle suction, ~3 mL of duodenal fluid is collected and immediately transferred to the microbiology laboratory (**b**).

acid plates are held in oxygen for 48 hours before being discarded. Anaerobic media are incubated under anaerobic conditions for 5 days. Any bacterial growth ≥1,000 cfu/mL is identified and reported out using colony count numeration. The organisms (i.e., *Neisseria* sp, Gram-positive bacilli resembling diphtheroids/coryneforms, *Lactobacillus* species, *Streptococcus* viridans group, *Staphylococcus* coagulase negative, and *Rothia* sp.) are identified based on gram stain, colonial morphology, or spot tests. Wherever appropriate, antibiotic susceptibility panels are performed and reported (17).

The limitations of small bowel culture include its invasive nature, cost, potential inability to detect bacterial strains that are difficult to grow under standard culture conditions, detection of proximal SIBO only, and potential for sample contamination (6,8).

Breath testing is a safe and noninvasive diagnostic method for SIBO. However, there is currently no standard methodology for breath testing (8). During a breath test, patients ingest a carbohydrate substrate that is metabolized when exposed to GI microbes, leading to the production of hydrogen and methane. Some of these gases are absorbed from the GI tract into the blood stream and finally exhaled through the lungs, and therefore, analysis of breath samples after carbohydrate ingestion provides an indirect measure of detecting SIBO (45). Glucose and lactulose are commonly used as breath test substrates for detecting SIBO (Table 2) (6,8,46).

In 2017, the North American consensus regarding breath testing (8) provided updates to previously published statements by expert groups from Germany and Italy in 2005 and 2009, respectively (47,48). The consensus recommends that patients avoid treatment with antibiotics for 4 weeks and promotility agents and laxatives for at least 1 week before breath testing (8). Furthermore, a strict bland diet, including avoidance of fermentable foods (e.g., complex carbohydrates), is recommended for the day before administration of the breath test. Patients should also fast 8–12 hours before the breath test, avoid smoking the day of the breath test, and minimize physical exertion during the breath test (8).

The North American consensus for breath testing recommends administering 75 g of glucose or 10 g of lactulose, taken with or followed by 1 cup of water; breath testing should measure hydrogen, methane, and carbon dioxide (see Table 2 for test characteristics) (8). An increase in hydrogen concentrations of ≥20 ppm from baseline within 90 minutes (8) (Figure 2a,b) (49) and an increase from baseline in methane concentrations of ≥10 ppm within 2 hours are considered diagnostic of SIBO (Figure 2a,c) (8,49). When using lactulose as a substrate, an initial duodenal peak from bacterial overgrowth in the small intestine followed by a second hydrogen peak from colonic bacterial fermentation has been observed (50), although both hydrogen peaks are not required for the diagnosis of SIBO (8). In addition, the first peak must occur within 90 minutes of substrate administration

Table 2. Diagnostic tests for SIBO

Diagnostic test	Substrate and characteristic	Testing protocol	Test interpretation[a]	Diagnostic performance	Limitations
Breath test					
Glucose[8,46]	Monosaccharide • Absorbed in the proximal small intestine	75 g of glucose in 250 mL of water Breath samples are collected at baseline and every 15 min for 90–120 min and measured for hydrogen and methane	Rise in hydrogen ≥20 ppm from baseline Or Rise in methane ≥10 ppm from baseline Or Rise in hydrogen and methane combined ≥15 ppm from baseline	Sensitivity: 20%–93% Specificity: 30%–86%	A negative test excludes proximal SIBO, but not distal SIBO Not suitable for patients with diabetes
Lactulose[8,46]	Disaccharide • Nonabsorbable • Reaches the colon • Used to measure orocecal transit in some cases	10 g of lactulose Breath samples are collected at baseline and every 15 min for 180–240 min for hydrogen	Interpretation of the test results requires reliable differentiation of the colonic peak from the small intestine peak[b] Positive test: increase from baseline ≥20 ppm H_2 by 90 min	Sensitivity: 31%–68% Specificity: 44%–100%	May accelerate gut transit, giving the false-negative results May cause bloating Interpretation difficult if only 1 peak in hydrogen concentration
Fructose[8]	Monosaccharide • Absorbed in the proximal small intestine • Suitable for patients with diabetes	25 g of fructose in 250 mL of water Breath samples are collected at baseline and every 15 min for 180 min and measured for hydrogen and methane	Rise in hydrogen ≥20 ppm above baseline Or Rise in methane ≥10 ppm above baseline Or Rise in hydrogen and methane combined ≥15 ppm from baseline	Sensitivity: 25%–71% Specificity: 42%–92%	Observation based on the single study Cannot differentiate between SIBO and fructose intolerance in patients with diabetes
Small bowel aspirates/ culture					
Duodenal[6,8]	Upper endoscopy performed to obtain samples from the third or fourth portion of the duodenum	3–5 mL of duodenal liquid aspirated using an aseptic technique (e.g., sterile gloves) Samples sent to the laboratory immediately after collection	Positive test: ≥10^3 cfu/mL 65.5% agreement between GBT and duodenal aspirate/culture	Currently, the most widely accepted best diagnostic method for SIBO	Testing is invasive, time intensive, and expensive
Jejunal[8]	Upper endoscopy performed to obtain samples from the proximal jejunum	≥2 mL of jejunal liquid aspirated Samples sent to the laboratory in sterile fashion immediately	Positive test: ≥10^3 cfu/mL	Currently, the most widely accepted best diagnostic method for SIBO	Testing is invasive, time intensive, and expensive

[a]Glucose dose of 50 g with rise in hydrogen >12 ppm from baseline is also considered positive.
[b]North American consensus no longer considers 2 peaks on a lactulose breath test a requirement for establishing a diagnosis of SIBO (8).
The table created with data from 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 (8); Erdogan A, Rao SS, Gulley D, et al. Small intestinal bacterial overgrowth: Duodenal aspiration vs glucose breath test. *Neurogastroenterol Motil* 2015;27:481–9 (6); and 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;97:1113–26 (46).
GBT, glucose breath test; SIBO, small intestinal bacterial overgrowth.

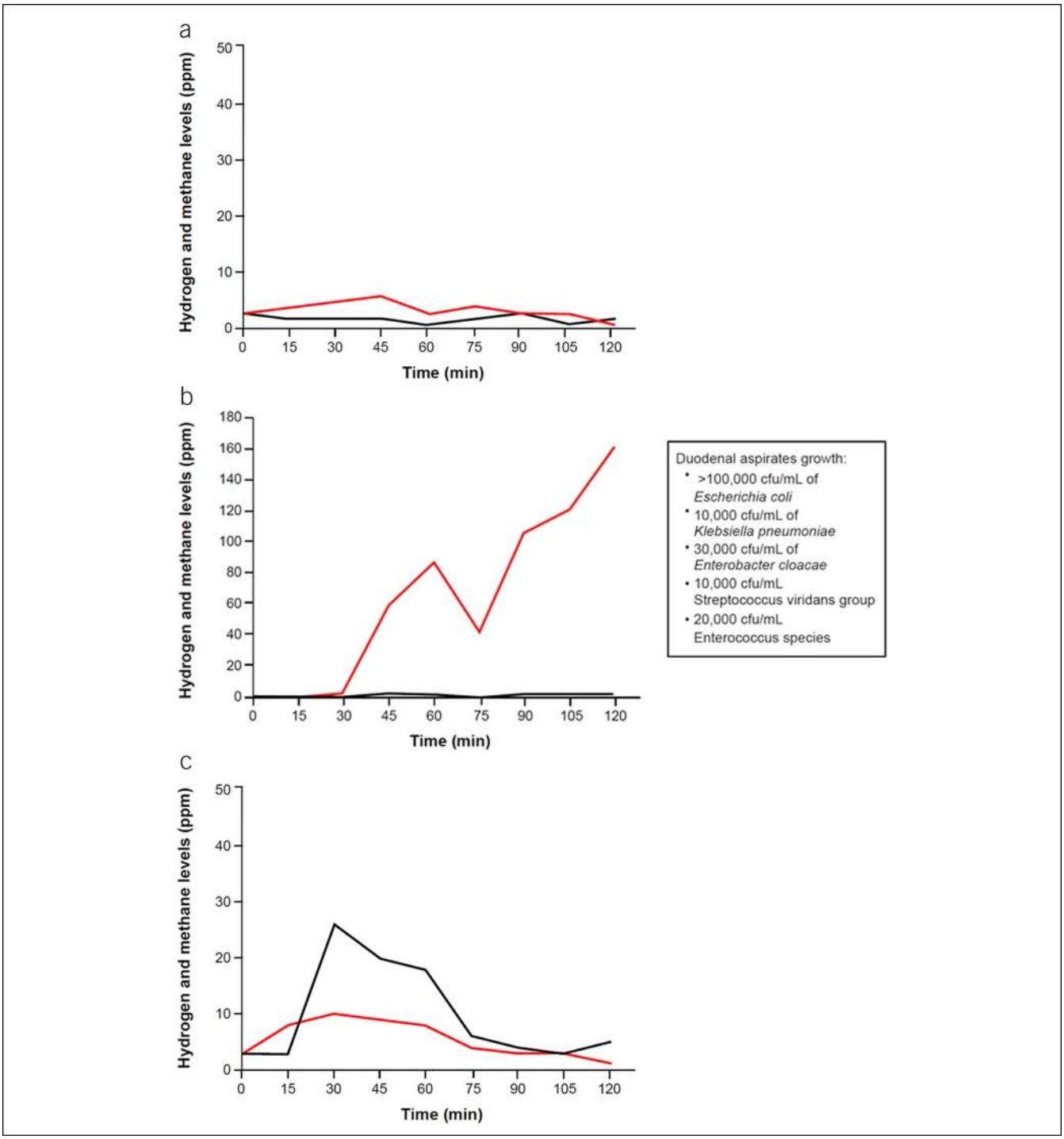

Figure 2. Typical example of breath test results: Shown are a negative breath test result (**a**), a positive hydrogen breath test showing hydrogen concentration rising >20 ppm from baseline (**b**), and a positive breath test showing methane concentration rising >10 ppm from baseline (**c**). Red lines show hydrogen concentrations, and black lines show methane concentrations. Duodenal aspirates and culture results are shown in the text inset of (**b**).

for the test to be considered positive (Table 2) (8). Although lactulose breath testing has higher sensitivity than glucose, scintigraphic studies have shown that the rise in breath hydrogen coincides with the arrival of lactulose in the cecum, raising concerns for a false-positive result; by contrast, the glucose breath test (GBT) has good specificity but low sensitivity, as it detects only proximal SIBO because glucose is completely absorbed in the proximal jejunum (Table 2) (8,46). A study from Lin and Massey (51) demonstrated that rapid transit of glucose into the cecum may provide a false-positive breath test within 90 minutes, possibly because of colonic fermentation, based on GBT combined with nuclear scintigraphy. Although possible, the likelihood of glucose reaching the cecum is low, as glucose is usually completely absorbed in the proximal small bowel. On the other hand,

lactulose invariably will reach the cecum, as it is a nonabsorbable disaccharide (52). Arguably, scintigraphy is an imperfect test to localize the cecum. Small bowel loops or diverticula overlying the cecal region could be erroneously reported as a tracer filling this area. Also, the head of the meal may have reached the cecum, but the bulk of the meal could remain in the small intestine undergoing fermentation from SIBO, and both sources of fermentation could produce a rise in breath hydrogen or methane. Consequently, better substrates, better localization methods, and further validation are needed to settle this dilemma.

Microbial culture and breath testing used to diagnose SIBO do not always produce similar findings (6,12). In 1 study, duodenal aspirate culture (i.e., $\geq 10^3$ cfu/mL) and GBT (i.e., increase from baseline of both hydrogen and methane $\geq$20 ppm, of hydrogen $\geq$20 ppm, or of methane $\geq$15 ppm) agreed on the diagnosis of SIBO in 65.5% of 139 patients with GI-related symptoms (i.e., abdominal discomfort, gas, bloating, and diarrhea) considered related to SIBO (6). Another study found that although 39% of 18 patients were positive for SIBO with GBT, these results correlated poorly with jejunal culture results, suggesting that further validation is required. Therefore, 1 testing method may not definitively diagnose SIBO, and additional testing may be necessary when SIBO is suspected (6).

The North American consensus recommended a cutoff of $\geq 10^3$ cfu/mL when using culture methods for the diagnosis of SIBO (8). Although additional validation studies are warranted to standardize breath testing including optimal cutoff thresholds (8), new approaches of breath testing have been investigated. A 2017 study reported the results of administering glucose through endoscope rather than oral ingestion in patients with a negative oral GBT (53). The results showed an increased yield for the diagnosis of SIBO, implying that endoscopic administration of glucose may facilitate detection of distal SIBO. This requires further validation with combined scintigraphy to reassure that the rise is not from colonic fermentation. A novel, orally ingested capsule technology that can measure *in vivo* hydrogen and carbon dioxide after ingestion of a carbohydrate meal is currently under development and may provide a better alternative to current breath hydrogen measurement techniques (54). Also, another novel oral diagnostic capsule, a smart capsule bacterial detection system, has been developed and tested *ex vivo* (55). This system can detect bacteria and, in a noninvasive manner, provides bacterial concentration; however, further clinical trials and validation are needed to assess the use of the smart capsule bacterial detection system for SIBO diagnosis (55).

TREATMENT OF SIBO

The goal of treatment for patients with SIBO is symptom relief by eradicating overgrowth of bacteria. This is typically achieved by treatment with antibiotics. However, some patients may remain symptomatic despite treatment, suggesting that other underlying conditions (e.g., dysmotility and PPI use) may potentially be the cause of symptoms and/or the bacteria may be antibiotic resistant (56). Hence, effective treatment includes eradication of bacteria, treatment of predisposing conditions, and prevention of SIBO. To date, no drugs have received regulatory approval in the United States or Europe specifically for the treatment of SIBO. However, the following treatments have been studied in patients with SIBO.

Rifaximin, a nonsystemic antibiotic, is currently the most studied agent for patients with SIBO, with numerous studies demonstrating its efficacy (e.g., eradication of SIBO), although the dose and duration of treatment, SIBO diagnostic methods and definitions, and patient populations vary among studies (Table 3) (15,18,25,28,30,57–66). A systematic review and meta-analysis of rifaximin (dose range: 600–1,600 mg/d; duration of treatment: 5–28 days) reported that SIBO was eradicated (determined by glucose or lactulose breath testing) in 70.8% of patients (26 studies; 95% CI, 61.4–78.2) (67). Adverse events (AEs) were uncommon and occurred in 4.6% of 815 patients from 17 studies reporting safety (67). In the meta-analysis (67), patients discontinued rifaximin treatment because of an AE (5% of 120 patients) in only 1 study (68). *Clostridium difficile* infection was reported in 1 patient receiving rifaximin 1,200 mg/d for 4 weeks; however, detailed information was lacking (59,67).

Systemic antibiotics

Studies of systemic antibiotics (e.g., ciprofloxacin, norfloxacin, and metronidazole) also reported eradication of SIBO as determined by either the breath test or bacterial culture (Table 4) (43,69–73). However, the sample sizes are small, and the methodologies used and populations evaluated differ across studies. A meta-analysis of 10 prospective clinical studies of nonsystemic antibiotics in patients with SIBO reported higher rates for breath test normalization with an antibiotic vs placebo (51.1% vs 9.8%, respectively; effectiveness ratio, 2.6; 95% CI, 1.3–5.0; $P = 0.03$) (56). Normalization of the breath test occurred in 49.5% of the pooled population ($n = 325$) treated with a nonsystemic antibiotic, rifaximin. The response rate varied widely (21.7%–85.0%), possibly because of rifaximin dosing and the timing of the breath test. Normalization of the breath test with metronidazole, a systemic agent ($n = 86$), was observed in 51.2% of patients (56). Finally, 70% of patients with SIBO and brain fogginess who received different antibiotics reported significant improvement of SIBO symptoms ($P = 0.005$), and 85% achieved complete resolution of brain fogginess ($P = 0.05$) (23).

Probiotics

Probiotics are believed to have beneficial effects on the gut microbiota. However, few clinical studies have examined this option (Table 4) (74–76); furthermore, these studies lack consistency not only in the formulations used but also in the duration of treatment, populations assessed, and methods of diagnosing SIBO (74,75). In a safety study, probiotics were not associated with AEs (76). More recently, a 2017 meta-analysis of 18 studies reported that probiotics were associated with significantly increased clearance of SIBO compared with nonprobiotic therapy (6 studies; relative risk, 1.6; 95% CI, 1.2–2.2), although probiotics were not found to be efficacious for the prevention of SIBO (77). Furthermore, probiotics may inadvertently colonize the small bowel, causing both SIBO and D-lactic acidosis, as well as brain fogginess (23). Some experts consider these findings to be controversial (78).

Nonpharmacologic and dietary therapies

Several nonpharmacologic treatments have been proposed because of the cost and potential adverse effects of antibiotics and probiotics. One such approach is an elemental diet, which contains predigested micronutrients that are mostly absorbed within the proximal small bowel, thus limiting the delivery of nutrients to bacteria in the distal portion of the small intestine (79). In a retrospective review, 124 patients with SIBO received an elemental diet for 14 days; patients without normalization of breath

Table 3. Summary of clinical studies of rifaximin

Study and design	Location and population	Method used to diagnose SIBO	Pts with SIBO	Treatment	Efficacy
Bae et al.[57] Retrospective study	South Korea Pts with IBS-D or IBS-M ($N = 192$)	LBT (10 g of lactulose/15 mL of water; BT result at baseline ≥20 ppm, or an increase from baseline >20 ppm H_2 or $CH_4 \leq 90$ min)	100%	Rifaximin 1,200 mg/d ($N = 192$) for 4 wk (initial tx); LBT repeated every 4 wk until normalization with maintenance tx (max, 12 wk)	102 pts had normalized LBT results after receiving rifaximin for 4 wk ($n = 36$), 8 wk ($n = 43$), or 12 wk ($n = 23$) Rifaximin significantly improved symptom scores in pts receiving rifaximin for 4, 8, and 12 wk ($P < 0.05$, for all comparisons)
Franco et al.[18] Retrospective review	United States Pts undergoing upper endoscopy ($N = 1,263$) for diarrhea ($n = 480$), gas-related symptoms ($n = 419$), diffuse/upper abdominal pain ($n = 397$), dyspepsia/GERD ($n = 199$), and/or nausea/vomiting ($n = 174$)	Bacterial culture ($>10^5$ cfu/mL)	30.4%	Antibiotic use in pts with positive culture results: 67.4% Rifaximin: 73.4% Ciprofloxacin: 6.9% Metronidazole: 5% (dosage not provided)	Overall, significant symptom improvement in pts receiving antibiotics (53.1%) vs no antibiotics (24.6%; $P < 0.0001$) In pts with a positive culture result, clinical improvement in pts receiving antibiotics (53%) vs no antibiotics (46.5%; $P =$ NS)
Greco et al.[25] Prospective study	Italy Pts with CD ($N = 68$)	GBT (75 g of glucose/150 mL of water; BT result indicating an increase from baseline ≥12 ppm H_2 and/or $CH_4 \leq 180$ min, in ≥3 samples taken every 30 min)	26.5%	Pts with SIBO received ciprofloxacin 500 mg/d ($n = 9$), metronidazole 750 mg/d ($n = 4$), or rifaximin 1,200 mg/d ($n = 2$) for 1 mo, followed by probiotics containing *Lactobacillus casei* DG Tx (≥7,595 billion living cells/100 g) for 2 mo	Normalization of GBT 1 mo after tx with probiotic, 86.7%
Boltin et al.[58] Prospective study	Israel Pts with bloating and flatulence (non-IBS)	LBT (15 g of lactulose/400 mL of water; BT result indicating an increase from baseline >10 ppm $H_2 \leq 90$ min)	41.5%	Rifaximin 1,200 mg/d for 10 d ($n = 19$)	Normalization of LBT, 42.1%
Chedid et al.[59] Retrospective, OL, SC	Pts with SIBO based on the positive LBT result	LBT (10 g of lactulose/30 mL of water; BT result at baseline >10 ppm for H_2 or >7 ppm for CH_4 if pts were compliant with tx, or an increase from baseline ≥20 ppm H_2 or ≥12 ppm CH_4 excretion ≤90 min)	100%	Rifaximin 400 mg t.i.d. ($n = 67$) vs herbal therapy b.i.d. ($n = 37$; Dysbiocide and FC-Cidal [Biotics Research Laboratories, Rosenberg, TX] or Candibactin-AR and Candibactin-BR [Metagenics, Aliso Viejo, CA]) for 4 wk Rifaximin nonresponders ($n = 41$) received herbal therapy ($n = 14$) or triple antibiotic (clindamycin 300 mg t.i.d., metronidazole 250 mg t.i.d., and neomycin 500 mg t.i.d.; $n = 10$) for 4 wk	Negative LBT results with rifaximin (34%) vs herbal therapy (46%; $P = 0.2$) Herbal therapy vs rifaximin: OR, 1.8; CI, 0.8–4.4; $P = 0.2$ Retreatment of rifaximin nonresponders: Negative LBT results with herbal therapy (57.1%) vs antibiotics (60%; $P > 0.99$)
Fasano et al.[30] Prospective study	Italy Pts with Parkinson's disease ($N = 33$)	LBT or GBT (50 g of glucose/250 mL of water; BT result indicating an increase from baseline >12 ppm $H_2 \leq 120$ min)	54.5%	Rifaximin 400 mg t.i.d. for 7 d ($n = 18$)	77.8% of pts with SIBO had resolution of SIBO 1 mo after tx

Table 3. (*continued*)

Study and design	Location and population	Method used to diagnose SIBO	Pts with SIBO	Treatment	Efficacy
Moraru et al.[60] Prospective study	Romania Pts with IBS ($N = 72$)	GBT (50 g of glucose/250 mL of water; BT result indicating an increase from baseline >20 ppm H_2 < 120 min)	11.1%	Rifaximin 400 mg t.i.d. for 14 d ($n = 8$ with SIBO)	7 of 8 pts (87.5%) with SIBO underwent GBT and had resolution of SIBO and little to complete improvement (range, no improvement to complete improvement) of IBS symptoms 1 wk after the end of tx Of the 7 pts, 1 pt (14.2%) with SIBO received a second 2-wk course of rifaximin and had resolution of SIBO with repeat rifaximin tx
Rosania et al.[61] R	Italy Pts with SIBO ($N = 40$)	LBT GBT (BT result [i.e., 2 H_2 peaks, with the first peak an increase from baseline of ≥10 ppm and a second, larger peak at ~60 min for both tests])	100%	Rifaximin 400 mg/d for 7 d, followed by probiotic (*L. casei* DG 24 milliards/d) for 7 d, vs rifaximin 400 mg/d for 7 d, followed by prebiotic (fructooligosaccharides 2.5 g/d) for 7 d	Rifaximin/probiotic significantly improved symptoms from baseline to 6 mo: diffuse abdominal pain ($P < 0.001$), left iliac area pain ($P < 0.002$), abdominal distension ($P < 0.002$), flatulence ($P < 0.001$), and nausea ($P < 0.01$) Rifaximin/prebiotic significantly improved symptoms from baseline to 6 mo: diffuse abdominal pain ($P < 0.02$), left iliac area pain ($P < 0.005$), abdominal distension ($P < 0.001$), and flatulence ($P < 0.001$)
Lauritano et al.[62] Prospective, PG, R	Italy Pts with GI symptoms ≥6 mo ($N = 142$)	GBT (50 g of glucose; BT result indicating an increase from baseline >12 ppm H_2 ≤ 120 min)	NA	Rifaximin 400 mg t.i.d. ($n = 71$) vs metronidazole 250 mg t.i.d. ($n = 71$)	GBT normalization with rifaximin (63.4%) vs metronidazole (43.7%) 1 mo after tx Rifaximin vs metronidazole: OR, 1.5; 95% CI, 1.1–4.4; $P < 0.05$
Lauritano et al.[28] Prospective study	Italy Pts with overt hypothyroidism ($n = 50$) vs healthy individuals ($n = 40$)	GBT (50 g of glucose; BT result indicating an increase from baseline >12 ppm H_2 ≤ 120 min)	54% (pts) 5% (healthy individuals)	Rifaximin 400 mg t.i.d. for 7 d Only pts with positive GBT received rifaximin ($n = 27$)	70.4% of pts with SIBO had eradication of SIBO 1 mo after the end of tx Abdominal discomfort, bloating, and flatulence significantly improved after 1 mo ($P < 0.01$)
Majewski and McCallum[15] Study design not described	United States Pts with IBS ($N = 204$)	GBT (50 g of glucose/150 mL of water; BT result indicating [1] for baseline measurement <10 ppm, then >20 ppm H_2 or CH_4, or [2] for baseline measurement >10 ppm, then an increase from baseline >12 ppm H_2 or CH_4 ≤ 90 min)	46%	Rifaximin 200 mg q.i.d. for 4 wk Pts with positive GBT received rifaximin ($n = 8$ of 204)	GBT results after rifaximin tx ($n = 8$): 75% of pts had normal GBT and 12.5% of pts had normal GBT by hydrogen, not methane Overall symptom score improved in 87.5% of pts

Table 3. (*continued*)

Study and design	Location and population	Method used to diagnose SIBO	Pts with SIBO	Treatment	Efficacy
Scarpellini et al.[63] Prospective, PG, R	Italy Pts with positive GBT results, including pts with IBS ($N = 80$)	GBT (50 g of glucose/200 mL of water; BT result indicating an increase from baseline >12 ppm H_2 and/or >100% $CH_4 \leq 120$ min)	100% IBS: 79%	Rifaximin 1,200 mg/d or 1,600 mg/d for 7 d	GBT normalization 1 mo after the end of tx: rifaximin 1,600 mg/d (80%) vs 1,200 mg/d (58%; $P < 0.05$; OR, 1.8; 95% CI, 1.1–8.0)
Lauritano et al.[64] Prospective, PG, R	Italy Pts with positive GBT results ($N = 90$)	GBT (50 g of glucose; BT result indicating an increase from baseline >12 ppm H_2 ≤ 120 min)	100%	Rifaximin 600 mg/d, 800 mg/d, or 1,200 mg/d for 7 d	GBT normalization 1 mo after the end of tx: rifaximin 600 mg/d (16.7%), 800 mg/d (26.7%), and 1,200 mg/d (60%) Rifaximin 1,200 mg/d vs 600 mg/d: OR, 7.5; 95% CI, 2.2–25.1; $P < 0.001$; rifaximin 1,200 mg/d vs 800 mg/d: OR, 4.1; 95% CI, 1.4–12.3; $P < 0.01$; and rifaximin 600 mg/d vs 800 mg/d: OR, 1.8; 95% CI, 0.5–6.4; P = NS
Di Stefano et al.[65] DB, R, C	Italy Pts with SIBO ($N = 26$)	GBT[a] (50 g of glucose; BT result indicating an increase from baseline >12 ppm H_2 ≤ 120 min; or in the fasted state, increase from baseline >12 ppm H_2)	100%	Rifaximin 400 mg t.i.d. ($n = 10$) vs chlortetracycline 333 mg t.i.d. ($n = 11$) for 7 d	Rifaximin, but not chlortetracycline, significantly improved fasting, peak, and total hydrogen excretion from baseline ($P < 0.03$, $P < 0.01$, and $P < 0.05$, respectively)
Corazza et al.[66] Prospective study	Italy Pts with SIBO ($N = 12$)	LBT (10 g of 50% lactulose solution; BT result indicating an increase from baseline >10 ppm H_2, ≥20 min before the colonic peak. Samples collected for 180 min)	100%	Rifaximin 400 mg b.i.d. or t.i.d. for 5 d ($n = 6$ in each group)	66.7% of pts in each group with eradication of SIBO 1 d after the end of tx Symptoms (i.e., abdominal distension, abdominal pain, and no. of bowel movements) improved from baseline in 83.3% of pts

[a]SIBO could also be diagnosed if any of the following were present: malabsorption or other predisposing conditions (i.e., autoimmune atrophic gastritis, chronic nonspecific diarrhea after travel to the tropical region, diabetic neuropathy, ileocolonic anastomosis, jejunoileal bypass, radiation enteritis, small bowel diverticula, small bowel obstruction, subtotal gastrectomy with gastrojejunostomy, and systemic sclerosis) (65).
b.i.d., twice a day; BT, breath test; C, controlled; CD, Crohn's disease; cfu, colony-forming unit; DB, double blind; GBT, glucose breath test; GERD, gastroesophageal reflux disease; GI, gastrointestinal; IBS, irritable bowel syndrome; IBS-D, diarrhea-predominant IBS; IBS-M, mixed IBS; LBT, lactulose breath test; NA, not applicable; NS, not specified; OL, open label; OR, odds ratio; PG, parallel group; pt(s), patient(s); q.i.d., 4 times a day; R, randomized; SC, single center; SIBO, small intestinal bacterial overgrowth; t.i.d., 3 times a day; tx, treatment.

testing continued the diet for an additional 7 days (80). The cumulative symptomatic response rate for an elemental diet was 85% (79/93 patients) (80). A total of 14 patients (12%) were unable to tolerate the diet (80). At 1-month follow-up ($n = 63$ patients), 28/36 patients with improved IBS symptoms had a normalized breath test result (80). However, these diets are generally not palatable and difficult to adhere to and require a motivated patient (79).

A diet low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols has been shown to be beneficial in IBS (81). This may be due to decreasing the exposure of small intestinal bacteria exposure to carbohydrate and its fermentation products, thereby stifling bacterial growth or altering luminal fluid transport and/or colonic gas production. However, there is a lack of sound data to suggest that a low fermentable oligosaccharides, disaccharides, monosaccharides, and polyol diet is beneficial for patients with SIBO.

Recurrent SIBO

Approximately 44% of patients with SIBO may experience a relapse of symptoms within 9 months of initial treatment (82). For these patients, the most effective way to achieve eradication is by first identifying the appropriate organism(s) and providing targeted antibiotic therapy (i.e., "the right drug for the right bug"

Table 4. Summary of clinical studies of systemic antibiotics or probiotics

Study and design	Location and population	Method used to diagnose SIBO	Pts with SIBO	Treatment	Efficacy for eradication of SIBO	AEs
Ghoshal et al.[43] Prospective, DB, R, PBO-C, SC	India Pts with IBS ($N = 80$)	Bacterial culture ($\geq 10^5$ cfu/mL) and GBT (100 g of glucose/200 mL of water; BT result indicating an increase from baseline >12 ppm H_2)	19%	Norfloxacin 400 mg b.i.d. vs PBO for 10 d Pts with SIBO: Norfloxacin ($n = 8$) vs PBO ($n = 7$) Pts without SIBO: Norfloxacin ($n = 32$) vs PBO ($n = 33$)	Norfloxacin eliminated SIBO in 100% of 4 pts who had a repeat test for SIBO 1 mo after tx	Tx well tolerated
Khalighi et al.[69] Prospective, R, DB, SC	Iran Pts with SIBO ($N = 30$)	BT (BT result indicating an increase from baseline >20 ppm H_2)	100%	Broad-spectrum antibiotics for 3 wk, then minocycline 100 mg b.i.d. for 15 d, followed by probiotic (*Bacillus coagulans* and fructooligosaccharides) b.i.d. for 15 d ($n = 15$) vs minocycline 100 mg b.i.d. for 15 d ($n = 15$), then no tx for 6 mo	HBT results negative with antibiotic plus probiotic (93.3%) vs antibiotic (66.7%; $P = 0.2$)	NR
Sajjad et al.[70] C	United Kingdom Pts with NASH ($n = 12$) vs healthy individuals ($n = 11$)	GBT (75 g of glucose/250 mL of water; increase from baseline >20 ppm $H_2 \leq 120$ min)	NR	Ciprofloxacin 500 mg b.i.d. for 5 d	GBT positive result at baseline and 4–7 d after tx: NASH: 50% vs 8.3%, respectively ($P = 0.025$); healthy individuals: 9.1% vs 9.1%	NR
Castiglione et al.[71] R	Italy Pts with CD ($N = 145$)	LBT (10 g of lactulose/100 mL of water; peak >20 ppm occurring 15 min before the colonic peak ≤180 min); or in the fasted state, H_2 and/or CH_4 > 12–15 ppm; If positive LBT, then GBT (50 g of glucose/100 mL of water; increase from baseline >12 ppm $H_2 \leq 120$ min)	20%	Metronidazole 250 mg t.i.d. or ciprofloxacin 500 mg b.i.d. for 10 d	GBT normalization 1 wk after the end of tx: metronidazole (86.7%) vs ciprofloxacin (100%; $P =$ NS)	Tx well tolerated; 1 pt receiving metronidazole discontinued due to nausea
Madrid et al.[72] R, PBO-C	Chile Pts with liver cirrhosis ($N = 34$)	LBT (12 g of lactulose/300 mL of water; baseline >20 ppm H_2 and ≥100 ppm $H_2 \leq 60$ min)	—	Norfloxacin 400 mg b.i.d. and neomycin 500 mg t.i.d. for alternating 15-d periods ($n = 12$), cisapride 10 mg t.i.d. ($n = 12$), or PBO t.i.d. ($n = 10$) for 6 mo	Patients positive for SIBO in norfloxacin and neomycin, cisapride, and PBO groups: baseline: 67%, 42%, and 40%, respectively; 3 mo: 50%, 25%, and 60%; 6 mo: 17%, 8%, and 60%	NR

Table 4. (*continued*)

Study and design	Location and population	Method used to diagnose SIBO	Pts with SIBO	Treatment	Efficacy for eradication of SIBO	AEs
Attar et al.[73] R, DB, CO	France Pts with chronic diarrhea (i.e., >3 stools/d for >3 mo), predisposition to SIBO, and positive GBT result ($N = 20$)	GBT (50 g of glucose; increase from baseline >10 ppm H_2 < 120 min)	—	Norfloxacin 800 mg/d, amoxicillin-clavulanic acid 1,500 mg/d, *S. boulardii* 1,500 mg/d, or PBO for 7 d	GBT normalized in 30% and 50% of 10 pts receiving norfloxacin and amoxicillin-clavulanic acid, respectively, at the end of tx; no change from baseline with PBO and *S. boulardii*	NR
Probiotics						
Yao et al.[89] DB, R, PBO-C, OL	Australia Pts with IBS ($N = 56$)	LBT (15 g of lactulose/100 mL of solution, including 100 mg of ^{13}C sodium acetate tracer; increase ≥10 ppm H_2 at ≥2 consecutive time points <90 min)	100%	Probiotic (Yakult; contains 6.5×10^9 cfu *L. casei* strain Shirota; $n = 28$) vs PBO ($n = 28$) for 6 wk, then OL probiotic for 6 wk ($n = 45$)	Loss of early rise in breath hydrogen after lactulose with probiotic (43%) vs PBO (54%) in the DB phase OL phase: probiotic (33%) vs DB PBO (33%)	DB phase: 37% vs 32% (e.g., UTI, URTI, gastroenteritis, musculoskeletal pain, sinusitis, anxiety, and depression) OL phase: 24%
Kwak et al.[74] R, PBO-C	South Korea Pts with chronic liver disease ($N = 52$; $n = 50$ completed study)	LBT (10 g of lactulose/250 mL of water; baseline ≥20 ppm H_2 or increase >20 ppm H_2 < 90 min)	26%	Probiotic (Duolac Gold; contains 5×10^9 total viable cells: *Bifidobacterium bifidum*, *Bifidobacterium lactis*, *Bifidobacterium longum*, *Lactobacillus acidophilus*, *Lactobacillus acidophilus rhamnosus*, and *Streptococcus thermophilus*; $n = 25$) vs PBO ($n = 25$) b.i.d. for 4 wk	Improvement in SIBO (by LBT) with probiotic (24%) vs PBO (0%; $P < 0.05$)	NR
Lunia et al.[76] OL, R	India Pts with cirrhosis and no previous history of HE ($N = 160$)	GBT (100 g of glucose/200 mL of water; increase from baseline >12 ppm H_2 < 180 min)	36.9%	Probiotic (VSL#3, Sigma-Tau Pharmaceuticals, Gaithersburg, MD; $n = 86$) vs PBO ($n = 74$) t.i.d.	Significant decrease from baseline in pts with SIBO (by GBT) receiving probiotic at 3 mo (38.4% vs 17.7%; $P = 0.006$), but not PBO (35.1% vs 33.9%; $P = 0.9$)	No AEs observed
Stotzer et al.[75] DB, CO	Sweden Pts with SIBO ($N = 17$; $n = 14$ completed study)	Achieve ≥2 criteria: Bacterial culture (>10^5 cfu/mL) GBT (50 g of glucose/250 mL of water; increase from baseline >12 ppm H_2 < 120 min) Tx response (GBT and symptoms)	100%	Probiotic (*Lactobacillus fermentum* KLD 1–3 × 10^{11} bacteria) vs PBO b.i.d. for 4 wk, followed by a 4-wk washout period, then cross-over to PBO or probiotic for 4 wk	No significant difference between probiotic and PBO regarding GBT, stool frequency, or symptom score	NR

AE, adverse event; b.i.d., twice a day; BT, breath test; C, controlled; CD, Crohn's disease; cfu, colony-forming unit; CO, cross-over; DB, double blind; GBT, glucose breath test; HBT, hydrogen breath test; HE, hepatic encephalopathy; IBS, irritable bowel syndrome; LBT, lactulose breath test; NASH, nonalcoholic steatohepatitis; NR, not reported; NS, not specified; OL, open label; PBO, placebo; PBO-C, placebo-controlled; pt(s), patient(s); R, randomized; SC, single center; SIBO, small intestinal bacterial overgrowth; t.i.d., 3 times a day; tx, treatment; URTI, upper respiratory tract infection; UTI, urinary tract infection.

approach). This is best achieved by small bowel aspiration, culture, and sensitivity. Another strategy is to identify and correct any underlying condition(s), such as avoiding medications that delay gut transit, reduce PPI and opioid use, and improve glycemic control, and adhesiolysis or correction of blind loops (7,83). Prokinetic agents improve motility and could enhance antegrade clearance of bacteria (72). Hence, a trial of prokinetic agents such as cisapride, tegaserod, erythromycin, and prucalopride may be considered, but there are no data to support their use, and some of these agents are not universally available or have risks (72,84,85). Some factors are not reversible, such as radiation enteritis, systemic sclerosis, postgastric resection, and surgical resection of the ileocecal valve (83,86). In such patients, some experts recommend cyclical monthly low-dose antibiotic therapy using 2 or 3 antibiotics (83,86). However, these approaches merit controlled trials.

Treatment failures

Approximately 30%–40% of patients may not have resolution of SIBO symptoms with antibiotic trials as shown in Table 4. In such cases, other overlapping or alternate diagnosis should be considered, such as disaccharide deficiency or food intolerances (87,88). For example, a patient with SIBO and lactose intolerance could present with symptoms of gas, bloating, and diarrhea; antibiotics will only confer partial resolution of symptoms. In addition, the patient will require a lactose-free diet. Therefore, a comprehensive assessment of symptoms with appropriate diagnostic tests and careful exclusion of other conditions is important in a patient with risk factors or in those with suboptimal response to therapy. Rigorous controlled studies are needed to guide clinical management. Moreover, other overlapping conditions such as pancreatic exocrine insufficiency, bile acid malabsorption, hormonal oversecretion, medications, functional bloating, hypersensitivity, and factitious symptoms should all be considered as possible causes.

CONCLUSIONS

SIBO causes nonspecific GI symptoms and is associated with other GI and non-GI conditions. Because of the broad range of symptoms experienced by these patients, symptoms alone cannot be used to establish a SIBO diagnosis. Consequently, diagnostic testing is required. Although inconsistencies exist, bacterial culture of small bowel aspirates is generally accepted as the best diagnostic method for the diagnosis of SIBO, but aseptic precautions and proper technique is key. Although a perfect breath test for SIBO is currently lacking, the 2017 North American consensus document offers clinical direction regarding choice of substrate, testing methodology, and interpretation of results, which requires further refining as new evidence emerges (8). Breath testing is considered a safe and noninvasive diagnostic tool for SIBO, although gaps in knowledge regarding the optimal method(s) of performing and interpreting the breath test remain.

Therapies shown to be efficacious and well tolerated for patients with SIBO include the nonsystemic antibiotic rifaximin and systemic antibiotics. However, given the differences across study populations, diagnostic tests and interpretation, and dosing and duration of antibiotic therapy, large well-designed randomized clinical trials with appropriate patient selection and well-defined symptoms and objective criteria are warranted to guide effective management of SIBO.

CONFLICTS OF INTEREST

Guarantor of the article: Satish S. C. Rao, MD, PhD, is the guarantor of the narrative review and assumes responsibility for the decision to publish.

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