How to Test and Treat Small Intestinal Bacterial Overgrowth: an Evidence-Based Approach

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Abstract Small intestinal bacterial overgrowth (SIBO) is characterized by an excessive amount of bacteria in the small intestine and a constellation of symptoms that include bloating, pain, gas, and diarrhea. Although known for many decades, there is a lack of consensus and clarity regarding the natural history and methods for its diagnosis. Several tests have been proposed, including the glucose breath test, lactulose breath test, small intestinal aspiration and culture, and others. However, there is a lack of standardization of these tests and their interpretation. Treatment of SIBO remains empirical; generally, broad spectrum antibiotics are recommended for 2 weeks (amoxicillin, rifaximin, ciprofloxacin, etc.) but evidence for their use is fair. Clearly, there is a strong need to develop a systematic approach for the management of SIBO and to perform multicenter clinical trials for the treatment of SIBO. In this review, we will discuss the current evidence for the diagnosis and treatment of SIBO, which includes (1) elimination/modification of the underlying causes, (2) induction of remission (antibiotics and elemental diet), and (3) maintenance of remission (promotility drugs, dietary modifications, repeat or cyclical antibiotics).

Keywords Small intestinal bacterial overgrowth (SIBO) • Glucose breath test • Lactulose breath test • Small intestinal aspiration and culture • Antibiotics • Elemental diet • Promotility drugs

Introduction

Small intestinal bacterial overgrowth (SIBO) is defined by the presence of abnormal and excessive numbers of bacteria in the small intestine [1] associated with a myriad of symptoms including bloating, flatulence, abdominal pain, nausea, dyspepsia, fatigue, diarrhea, and constipation [2]. Malabsorption, weight loss, anemia, and deficiency of vitamins and iron are less frequent but more serious manifestations of SIBO [3].

Multiple independent risk factors have been identified for SIBO including [4]: (1) anatomical abnormalities such as small intestinal diverticulosis; (2) postsurgical structural changes such as ileocecal valve resection, gastric bypass, and Roux-en-Y; (3) medications that slow the gut motility such as narcotics, anticholinergics, and anti-diarrheals; (4) hypo- or achlorhydria due to surgery, autoimmune gastritis, or proton pump inhibitors [5••, 6]; and (5) small bowel dysmotility irrespective of the cause (e.g., inflammatory bowel disease, celiac disease, radiation enteritis, small bowel adhesions, and systemic diseases associated with dysmotility such as scleroderma, diabetes, and amyloidosis) [5••, 7].

In addition, SIBO has been associated with multiple conditions including irritable bowel syndrome [8], rosacea [9], hepatic encephalopathy [11, 12], obesity [13], gastroparesis [14], Parkinson’s disease [15], fibromyalgia [16], chronic
pancreatitis [17], end-stage renal disease [18], and inflammatory bowel diseases [19].

Despite the high prevalence and importance of SIBO, there is a lack of consensus and clarity regarding the optimal method for the diagnosis of this condition. Moreover, there is a strong need to develop an evidence-based approach for the management of SIBO including well-designed clinical trials for its treatment of SIBO. In this review, we will discuss the current methods for diagnosis of SIBO followed by a systematic approach for the treatment of this condition.

**Diagnosis of SIBO**

Numerous methods have been proposed and tested for the diagnosis of SIBO [20, 21]. The most common diagnostic tests include assessment of clinical symptom profiles, empirical treatments, breath tests, and small intestinal aspiration and culture.

**Clinical Symptoms**

Several studies have assessed the clinical utility and predictive value of symptoms associated with SIBO. These studies have concluded that symptoms are non-specific and as such cannot be used to accurately diagnose SIBO.

In one study, Jacobs et al. [5] assessed 168 subjects with SIBO (n = 38), small intestinal fungal overgrowth (SIFO, n = 24), mixed SIFO/SIBO (n = 32), or no overgrowth proven by aerobic/anaerobic/fungal small bowel cultures (n = 74). There was no difference in the intensity, frequency, and duration of abdominal pain, bloating, fullness, belching, indigestion, nausea, vomiting diarrhea, and gas.

Recently, in a retrospective study, Baker et al. [22] assessed the symptom profiles of 5045 patients who underwent glucose breath testing. Those with a positive breath test (n = 1680) had similar prevalence of heartburn, regurgitation, chest pain, nausea, abdominal pain, bloating, gas, diarrhea, and constipation when compared to those with a negative test. These findings emphasize the inaccuracy of patients’ symptom profile in the diagnosis of SIBO among those patients with or without SIBO.

**Clinical Response to Empirical Treatment with Antibiotics**

Symptomatic response to antibiotics has been proposed as a clinical tool for the diagnosis of SIBO [21]. However, given the non-specific nature of symptoms(s), the inability to predict which antibiotic may be effective against which constellation of symptoms or organisms, the potential for misuse of antibiotics and development of drug resistance, and the recent increase in the incidence of *Clostridium difficile* colitis, empiric therapy with antibiotics may pose unjustified risks to the patients. Also, there is no consensus or an objective method of identifying symptom response to antibiotics. Hence, this approach is not recommended.

**Breath Testing**

Quantification of hydrogen and methane gas in breath samples remains the most inexpensive, non-invasive, and widely available test for the diagnosis of SIBO [21]. Human cells are not capable of producing methane or hydrogen gas [23]. The presence of these gases in the human breath signifies the metabolism of carbohydrate residues by gut, their absorption from the gut, and expiration through lungs. Based on this principle, when lactulose or glucose is given to a patient with presumed SIBO, the changes in hydrogen and methane concentrations in sequential breath samples will indicate the presence of SIBO (Fig. 1) [24]. Gas production in SIBO patients is clearly variable and depends on the concentration and the types of colonizing bacteria in the small bowel, as well as the availability of carbohydrate residue and the absorptive capacity of the small bowel. Current commercially available gas chromatography equipment is unable to detect hydrogen sulfide, which is another important gas produced by gut microbiome, and its assessment may enhance the yield of breath tests.

In the absence of a universally acceptable gold-standard test and cutoffs for an increase in hydrogen or methane concentration above baseline for a diagnosis of SIBO, exact determination of the test characteristics of breath testing is difficult to assess. In a systematic review, Khosini et al. [21] found 11 studies that have attempted to validate the accuracy of lactulose breath testing for SIBO. The sensitivity ranged from 31 to 68 % and specificity ranged from 44 to 100 %. The sensitivity of glucose breath testing has varied from 20 to 93 % and specificity from 30 to 86 %. Multiple patterns of hydrogen and methane production have also been described in the literature, such as flat line (non-methane fixed-hydrogen production), hydrogen-predominant, methane-predominant, and mixed hydrogen/methane bacterial overgrowth [25]. However, hydrogen-predominant overgrowth and methane-predominant bacterial overgrowth are the two patterns that have been more widely studied. Although patients with either pattern share similar symptoms such as bloating...
and abdominal distension, those with excessive methane production are five times more likely to have constipation [26]. Moreover, the severity of constipation directly correlates with the methane level [27] and the choice of antibiotics for the treatment of SIBO differs between these two groups.

There is also a great degree of heterogeneity in defining a positive breath test, underlining the need for large-scale validation studies and expert consensus reviews [28]. In one recent study that compared glucose breath hydrogen testing with duodenal aspiration/culture, a cutoff value of ≥20 ppm hydrogen above baseline had a sensitivity and specificity of 77 and 66 %, respectively [28, 29].

Small Bowel Aspiration/Culture for Identifying SIBO

Although not fully validated, currently, the accepted gold standard for diagnosis of SIBO is the aspiration of small bowel fluid, followed by culture and bacterial count [5, 14, 28]. As opposed to breath testing, small bowel aspiration is time-consuming, costly, and invasive, often requiring endoscopy with sedation, although fluoroscopic-assisted small bowel tube placement has been described [24]. Proximal small bowel culture may be falsely negative as it can miss overgrowth of bacteria in the mid and distal small bowel, which is beyond the reach of a regular endoscope [4]. Moreover, given the current sample collection techniques, contamination with oral and esophageal flora may lead to false-positive results [5], although use of aseptic technique could minimize this [5, 28, 29].

Historically, a bacterial concentration ≥10⁵ colony forming units (CFU)/mL has been used for identifying any bacterial infection including a diagnosis of SIBO. However, this cutoff is debatable, especially in the context of SIBO, and has not been well validated [5, 28]. A systematic review of literature on the diagnosis of SIBO found that healthy controls have ≤10³ CFU/mL, and concentrations ≥10⁵ CFU are mostly seen in patients with Billroth II patients [21]. Currently, a bacterial concentration of ≥10³ CFU/mL is generally considered significant [5, 6]. In a recent comparative study, duodenal culture was positive in 62/139 (45 %) patients whereas glucose breath test was positive in 38/139 (27 %) patients. The sensitivity and specificity of GBT were 42 and 84 %, respectively [28].

Further research regarding bacterial concentrations in various small bowel segments in healthy subjects using sterile and anaerobic techniques is urgently needed. Moreover, these studies should consider integrating deep sequencing techniques for further assessment of bacterial diversity in SIBO patients [9, 10].
Treatment

Treatment of SIBO is comprised of three broad strategies: (1) induction of remission, (2) maintenance of remission, and (3) treatment/modification of the underlying cause of SIBO (Fig. 2).

Induction of Remission

Antibiotics are the mainstay of therapy for SIBO. However, given the limited qualitative and quantitative assessment of the bacteria that are causing the symptoms, the choice, dosing, and duration of antibiotic therapy have not been fully understood.

A systematic review found 23 trials in the literature that addressed the role of antibiotics in SIBO [21]. The majority of these trials were uncontrolled, and 17 studies included less than 20 subjects. Study endpoints were variable, with investigator-defined clinical response being the most common primary endpoint which ranged from 35 to 100 %. While the most common antibiotics were clindamycin, metronidazole, neomycin, rifaximin, and tetracycline, other antimicrobial compounds such as ampicillin, amoxicillin, chloramphenicol, ciprofloxacin, erythromycin, and trimethoprim/sulfamethoxazole have been used in smaller numbers of subjects. The duration of therapy has varied from 5 days to 1 month, and the frequency of repeat therapy has ranged from none to monthly and for 4–6 months. In a meta-analysis of 10 placebo-controlled trials, antibiotics were shown to be superior to placebo with a combined normalization rate of 51 % (95 % confidence interval (CI), 47–56 %) for antibiotics compared with 10 % (95 % CI, 5–18 %) for placebo [30].

In an uncontrolled open-label trial, Pimentel et al. [31] assessed 157 IBS patients with hydrogen-predominant bacterial overgrowth diagnosed by lactulose breath test. All patients underwent treatment with neomycin, ciprofloxacin, metronidazole, or doxycycline as per discretion of managing physicians and patients’ preference. Of 157 subjects, 47 had a follow-up breath testing 7–10 days after antibiotic therapy. There was significant improvement in symptoms of diarrhea and abdominal pain in those who showed eradication of bacterial overgrowth on the repeat breath testing (n = 22, 47 %).

In a double-blind randomized placebo-controlled study [32], 111 IBS patients (84 % had a positive lactulose breath test) were randomized to neomycin 500 mg twice daily or placebo for a total of 10 days. Clinical response was defined as a 50 % reduction in a composite score calculated from the three symptoms of abdominal pain, diarrhea, and constipation each on a scale of 0–5. In subjects with abnormal breath test, 21 of 46 (46 %) receiving neomycin had a clinical response,

![Image](https://example.com/image.png)

**Fig. 2** A high-resolution solid-state catheter with 36 pressure sensors (Given Imaging Inc.) was used to measure intraluminal pressures from lower esophageal sphincter to proximal jejunum in a 22-year-old patient with myogenic chronic intestinal pseudo-obstruction (CIPO). During the first 4 h of the fasting phase, patient only had a 2-min MMC-like contraction compatible with his known diagnosis of myogenic CIPO. One hour after oral administration of prucalopride 2 mg, patient had a 3-min MMC-like contraction originating from proximal duodenum (a). Subsequently, 50 mg of intravenous erythromycin was administered which after 10 min, led to a 6-min-long MMC phase III contraction originating from antrum (b).
compared with seven of 47 (15 %) in the placebo group \((P<0.01)\). Only one out of 43 patients with an abnormal breath test who received placebo had a normal breath test at the end of the study. No severe adverse events were reported.

Rifaximin is one of the most extensively studied antibiotics in functional bowel disorders. It has been approved by Food and Drug Association (FDA) for traveler’s diarrhea, hepatic encephalopathy, and IBS with diarrhea. In the largest study that specifically addressed the effect of rifaximin on SIBO, Lauritano et al. [33] randomized 142 SIBO patients diagnosed by glucose breath test to rifaximin 400 mg thrice daily or metronidazole 250 mg thrice daily for 7 days. After 1 month, breath test normalized in 63 % of patients in the rifaximin group versus 44 % in the metronidazole group \((P<0.05)\). The number of dropouts was significantly greater in the metronidazole group. Clinical response was not reported in this study.

TARGET 1, 2 [34], and 3 [35] assessed the efficacy and safety of rifaximin in large number of IBS patients without constipation; however, the presence or absence of SIBO was not fully assessed in these studies. TARGET 1 and 2 were two identically designed double-blind placebo-controlled trials that randomized 1258 IBS patients without constipation to placebo or rifaximin 550 mg twice daily for 14 days. By week 4, more patients in the treatment arm had achieved a relief from global IBS symptoms as compared to placebo \((40.7 \text{ vs. } 31.7 \%, P<0.001)\). Adequate relief from bloating was also achieved more frequently in the rifaximin group \((40.2 \text{ vs. } 30.3 \%, P<0.001)\). In addition, significantly more patients in the rifaximin arm had a positive response as assessed by daily ratings of IBS symptoms, bloating, abdominal pain, and stool consistency. Adverse events were similar in both groups, and there were no cases of \textit{Clostridium difficile} infection (CDI).

TARGET 3 was designed to assess the efficacy and safety of repeated courses of rifaximin in IBS-D patients whose symptoms recurred after an open-label course of rifaximin. Of 2579 patients who received open-label rifaximin, 1074 patients showed a clinical response within 4 weeks of therapy and were followed up for a maximum of 18 weeks for signs and symptoms of relapse. Of the initial responders, 636 relapsed and were randomized to receive rifaximin 550 mg or placebo twice daily for 2 weeks with a 4-week follow-up post-therapy. Subsequently, patients received a second blinded treatment with placebo or rifaximin and were followed for four more weeks. Based on FDA guidelines, response was defined as \(\geq 30 \%\) decrease in mean abdominal pain score from baseline and \(\geq 50 \%\) decrease in the stool consistency score of type 6/7 from baseline in a given week for at least 2 weeks of a month. In the open-label phase of the study, 46 % of patients had a response while 72 % had improvement on at least one component of response (i.e., abdominal pain or stool consistency). Significantly, more patients had a clinical response \((32.5 \%)\) after the first round of repeat treatment with rifaximin as compared to placebo \((25.0 \%)\). Similar pattern was observed in the second repeat treatment phase. Adverse events were similar among both groups. There was one case of CDI in the treatment arm during maintenance phase; however, this patient was being treated with a cephalosporin for urinary tract infection.

While the exact mechanism of action of rifaximin in IBS is unknown, given the high prevalence of SIBO in IBS patients [6, 36], the safety profile of rifaximin, and the size and quality of TARGET trials, we suggest that a similar regimen may be useful for induction of remission in SIBO although this merits a further assessment in a randomized controlled trial.

When there is excess methane production, rifaximin alone may not have the expected efficacy. \textit{Methanobrevibacter smithii} is an archaeon that is responsible for methane production in humans and is resistant to many antibiotics. In a retrospective study, Low et al. [37] observed that methane-producing subjects receiving either neomycin or rifaximin did not have a substantial benefit. However, a combination of neomycin and rifaximin appeared to decrease methane production in greater than 80 % of subjects with similar outcome in constipation-related symptoms.

There has been only one randomized controlled trial that addressed the effect of antibiotics on methane productivity. Pimentel et al. [38••] randomized 31 patients with C-IBS and methane levels \(>3\) ppm to neomycin \((500 \text{ mg twice daily})\) plus placebo or neomycin plus rifaximin \((550 \text{ mg thrice daily})\) for 14 days and followed patients for 4 weeks after antibiotic therapy. Constipation severity, bloating, and straining were significantly less in the rifaximin plus neomycin group as compared to the neomycin-alone group. Abdominal pain was not different between the groups. The main determinant of clinical response in the neomycin plus rifaximin group was a decrease in methane production to below 3 ppm, which occurred in two thirds of patients. Similar rates of adverse events were seen in the two groups. Based on this, we advocate 2 weeks of therapy with neomycin and rifaximin for treatment of patients with methane-predominant bacterial overgrowth. Although antibiotic trials have not been performed in this population; anecdotally, neomycin alone, metronidazole \((500 \text{ mg thrice daily})\), or amoxicillin-clavulanic acid may be considered. It should be noted that in patients who have a blind loop and SIBO, systemic antibiotic therapy rather than non-absorbable antibiotics such as neomycin and rifaximin should be considered.

Recently, there has been interest in the use of statins as a treatment for methane production in humans. Statins have been shown to inhibit growth and production of methane in several \textit{Methanobrevibacter} isolates, presumably by interfering with mevalonate synthesis needed for isoprenoid lipid synthesis in methanogens [39]. The clinical use of this warrants further study in the treatment of constipation [40].
Therapeutic options for the induction of remission in patients with SIBO with allergies to antibiotics or those who do not respond to optimal doses of antibiotics are very limited. Elemental diets may be an extremely safe and effective alternative to antibiotics. These formulations are believed to be absorbed within the first few feet of small bowel and potentially limiting the delivery of nutrients to the bacteria residing in distal portion of small bowel [41]. In a retrospective study, 124 patients with methane- or hydrogen-predominant SIBO were treated exclusively with elemental diet (Vivonex Plus, Novartis Nutrition Corp., Minneapolis, MN) for at least 2 weeks. If breath test did not normalize by week 2, patients continued the diet for a total of 3 weeks. Fourteen patients could not tolerate the diet and dropped out. By day 15, 80% of subjects normalized their breath test. Of 19 subjects who did not normalize their breath test, only five had a normal breath test by day 22 for a cumulative response of 85%. Patients who normalized their breath test showed 66% improvement in symptoms as opposed to 12% improvement in patients with persistently abnormal breath tests [42]. While the cost and palatability of elemental formulations can be a limiting factor in their use, this strategy may be effective in the induction of remission of SIBO and merits randomized clinical trials.

Herbal Antibiotics

There is a growing interest among patients in the use of complementary and alternative medicine. In a recent non-randomized open-label trial, of 37 breath test-positive SIBO patients who received a mixture of over 10 herbal therapies for 4 weeks, 17 (46%) had a negative lactulose breath test at follow-up, compared to 23/67 (34%) in the rifaximin (400 mg thrice daily) group (P = 0.24). No data was provided regarding clinical response [43]. Although the use of herbal medications with antibiotic properties such as peppermint oil [44] in the treatment of SIBO is intriguing, these compounds need to undergo robust clinical trials for assessment of their efficacy, correct dosing, and safety profiles before widespread clinical use.

Maintenance of Remission

SIBO is a relapsing disease, especially when there are predisposing factors. Lauritano et al. [45] showed that 13, 28, and 44% of SIBO patients experience a relapse of their symptoms and breath test positivity at 3, 6, and 9 months after induction of remission with rifaximin, respectively. Therefore, following induction of remission, one should consider implementing appropriate therapeutic interventions to decrease the chance of recurrence (i.e., maintenance of remission).

Watchful Observation and Retreatment as Needed

Watchful observation is a reasonable option after induction of remission of SIBO, although most experts believe that patients will eventually relapse. In the recent TARGET 3 study of IBS-D patients, 36% of responders in the open phase of the trial did not experience a relapse for at least 22 weeks after treatment with rifaximin. In addition, approximately one third of patients who relapsed after open-label therapy responded to retreatment with rifaximin. Although this study did not address SIBO, clinical experience suggests that SIBO patients are at higher risk of relapse and may require a more rigorous management plan for maintenance of remission.

Use of Promotility Drugs

Motility is an important determinant of gut flow and stasis. It is therefore intuitive that improving motility might have a benefit in maintaining remission in SIBO patients. During the fasting state (i.e., inter-digestive period), every 90–120 min, phase III migrating motor complexes (MMCs) repetitively sweep through the foregut [46]. These so-called housekeeper waves are vital to maintain balanced gut floral populations and to clear residual food particles and secretions from the small bowel [5••, 47]. Patients with IBS-like symptoms have abnormal intensity and frequency of phase III MMCs [48]. In addition, many of the disease states that can lead to SIBO are associated with normal MMC patterns including opioid-induced gut dysmotility, partial obstructive disease, and diabetes [48]. Neuronal and hormonal control of MMCs is complex. Motilin, ghrelin, and serotonin have been shown to induce phase III-like MMCs [49]. Hence, promotility drugs such as motilin receptor agonists (e.g., erythromycin and azithromycin) and 5-HT4 agonists (e.g., tegaserod, cisapride, and prucalopride) can induce phase III MMCs in a fasting state [50] and potentially decrease the recurrence of bacterial overgrowth (Fig. 3).

In an open-label trial [51], 34 cirrhotic patients were randomized to alternating antibiotics, cisapride and placebo for 6 months. At 6 months, cisapride was superior to placebo and non-inferior to antibiotics in normalization of the breath test. In a retrospective study, patients who underwent maintenance of remission with tegaserod experienced less relapse when compared to those who underwent no treatment, and there was a trend towards benefit with erythromycin [52].

Diet Restriction

A low FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides and polyols) diet significantly affects the gut microbiota [53]. However, to date, no study has systematically addressed the role of diet in SIBO patients. Carbohydrate intolerance (e.g., lactose, fructose, and fructan)
is very common among SIBO patients [54], and dietary restrictions can lead to symptomatic improvement. Theoretically, a diet with low fermentable foods can decrease the chance of bacterial overgrowth by creating a less favorable environment.

Table 1  Disease states that lead to SIBO and can be potentially treated or modified

<table>
<thead>
<tr>
<th>Disease states leading to SIBO</th>
<th>Diagnosis</th>
<th>Potential treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gut dysmotility (idiopathic, scleroderma, pseudo-obstruction, post-infectious, and opioid-induced constipation)</td>
<td>-History, transit studies, antroduodenal manometry -Temporal correlation of opioid use and symptoms -Symptomatic response to partial μ-receptor antagonists</td>
<td>-Prokinetics (erythromycin, domperidone, and prucalopride) -Decreasing or stopping the opioids -Partial μ-receptor antagonists (e.g., methylaltrexone [56] and naloxegol [57]) -Prucalopride [58] -Lubiprostone [59]</td>
</tr>
<tr>
<td>Adhesive diseasea</td>
<td>-Sharp bowel angulations on SBFT or enterographic studies -Exploratory laparotomy</td>
<td>-Lysis of adhesions with possible use of bioabsorbable membranes [60]</td>
</tr>
<tr>
<td>Small bowel stricturing disease (Crohn’s disease, NSAIDs, anastomosis narrowing and radiation)</td>
<td>-Enterographic studies -Wireless capsule endoscopy -Enteroscopy</td>
<td>-Enteroscopic dilatation -Surgical repair -NSAIDs avoidance -Treating active CD</td>
</tr>
<tr>
<td>Active inflammation in the small bowel (e.g. CD, celiac disease, radiation enteritis)</td>
<td>-Enterographic studies -Wireless capsule endoscopy -Enteroscopy</td>
<td>-Anti-inflammatory drugs -Strict gluten-free diet</td>
</tr>
<tr>
<td>Small bowel diverticular disease</td>
<td>-Small bowel follow through and enterographic studies</td>
<td>-Promotility drugs -Long-term low-dose antibiotic therapy</td>
</tr>
<tr>
<td>Collagen vascular disease (hypermobility joint syndrome, scleroderma, SLE)</td>
<td>-Clinical history and physical examination -Visceroptosis in standing position on SBFT [61]</td>
<td>-Promotility drugs -Pyridostigmine in patients with concomitant postural orthostatic tachycardia syndrome [62]</td>
</tr>
<tr>
<td>Diabetic enteropathy</td>
<td>-Clinical history</td>
<td>-Promotility drugs -Strict control of blood glucose levels -Avoiding diabetic drugs known to slow gut motility (e.g., GLP1 agonists) [63]</td>
</tr>
</tbody>
</table>

SBFT small bowel follow through, CD Crohn’s disease, POTS postural orthostatic tachycardia syndrome, GLP-1 glucagon-like peptide-1, NSAIDs non-steroidal anti-inflammatory drugs

a Adhesive disease can be seen even in virgin abdomen (e.g., Fitz-Hugh-Curtis disease, endometriosis, and contained or missed appendicitis/ diverticulitis)
luminal environment for overgrown bacteria. In a systematic review, Rao et al. [55] found that a low FODMAP diet improved overall IBS symptoms in 6/6 trials, but the key principle in its success was dependent on dietary education. This was confirmed by a recent multicenter single-blind trial that showed similar rate of improvement in severity of IBS symptoms with FODMAP vs. traditional IBS diet (i.e., regular meal pattern; avoidance of large meals; and reduced intake of fat, fiber, and gas-producing foods).

Overall, it appears that dietary education and avoidance of fermentable foods have favorable effects on symptom control; however, the role of dietary intervention in objective outcomes of induction and maintenance of treatment of SIBO needs further evaluation.

**Treatment of the Underlying Cause of SIBO**

SIBO is often a secondary disease, and unless the underlying problem is addressed and well controlled, the chance of recurrence remains high. However, in the majority of cases, elimination of the underlying cause is not possible. In Table 1, specific strategies are presented that may be helpful in the modification of the underlying cause.

**Role of Probiotics, Prebiotics, and Symbiotics**

The role of probiotics/prebiotics/symbiotics in the management of SIBO remains to be clarified. While the concept of “replacement of bad bacteria with good bacteria” in the treatment of SIBO is intriguing, there is little objective evidence to support this. In a retrospective study of 10 children with abdominal pain and SIBO who were treated with bifidobacterium and lactobacillus strains, four had symptomatic improvement by 15 months [64]. The PLACIDE trial (the largest placebo-controlled randomized study in the field of probiotics to date, with over 3000 subjects) examined the role of bifidobacterium and lactobacillus strains in the prevention of antibiotic-associated diarrhea and *C. difficile* infection. The rates of diarrhea and *C. difficile* infection were similar in the placebo and probiotic arms [65, 66]. However, patients on probiotics experienced significantly more bloating and flatulence.

Until further data is available regarding the benefit and safety of probiotics/prebiotics/symbiotics in the management of SIBO, one should exercise caution with their use in clinical practice.

**Conclusions**

Aspiration and culture of the small bowel contents remain the gold standard for diagnosis of SIBO, but their clinical use is limited by the cost and invasive nature of the test [28••]. Alternatively, glucose or lactulose breath tests are widely available, non-invasive, safe, and useful for diagnosis of SIBO.

Induction of remission for SIBO can be achieved with antibiotics. The choice of antibiotics is dependent on the type of bacteria (aerobic or anaerobic, especially when cultures are performed) as well as the presence of excessive methane on breath test. Elemental diet may be an alternative to antibiotic therapy. Prokinetic drugs, peppermint oil, and dietary carbohydrate restriction may serve as useful adjuncts to the management and maintenance of remission. Where possible, attempts should be made to eliminate or modify the underlying causes of SIBO.

**Compliance with Ethical Standards**

Conflict of Interest  Ali Rezaie reports support from the following sources for teaching, research, and consultation, outside the submitted work: Commonwealth Laboratories, Actavis, and Salix Pharmaceuticals. Mark Pimentel reports support from the following sources for teaching, research, and consultation, outside the submitted work: Commonwealth Laboratories, Salix Pharmaceuticals, Entera Health, Synthetic Biologies, Synthetic Biologies, Micropharma, and Naia Pharmaceuticals. Satish Rao reports support from the following sources for teaching, research, and consultation, outside the submitted work: Forest Laboratories, Hollister, Ironwood Pharmaceuticals, Sucampo Pharmaceuticals, In Control Medical, Vibrant, American Medical Systems, Sun Sweet Corporation, Synergy Pharmaceuticals, Salix Pharmaceuticals, and Ventrus Laboratories.

Human and Animal Rights and Informed Consent  With regard to the authors’ research cited in this paper, all procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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- Of importance
- Of major importance

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