CLÍNICAS DE GASTROENTEROLOGÍA DE MÉXICO

PERMANYER

Check for updates

REVIEW ARTICLE

Irritable bowel syndrome and small intestinal bacterial overgrowth

Alicia S. Villar-Chávez[1] and Daniel Ruiz-Romero[2]*

[1]Gastroenterology Service, Hospital Ángeles Acoxpa; [2]Gastroenterology Service, Hospital Médica Sur. Mexico City, Mexico

Abstract

Some authors support the hypothesis that small intestinal bacterial overgrowth (SIBO) is the primary event or cause, but others indicate that it is a consequence, of irritable bowel syndrome (IBS). It is known that SIBO is one of the manifestations of intestinal dysbiosis and, therefore, a cause of symptoms in IBS, and various studies have shown that this entity is highly prevalent in patients with IBS; therefore, it has not been possible to differentiate between the two entities by symptomatology. The prevalence of SIBO in patients with IBS is documented in a wide range, the variation of which is due to the different criteria to define a positive test and the methodology used (28-84% with lactulose breath test, 2-31% with glucose and 2-6% with culture). Rifaximin as the treatment of choice for both IBS without constipation and SIBO, which is a broad-spectrum non-systemic antibiotic that generates little or no resistance.

Keywords: Small intestinal bacterial overgrowth. Irritable bowel syndrome. Diagnostic tests.

Síndrome de intestino irritable y sobrecrecimiento bacteriano de intestino delgado

Resumen

Algunos autores respaldan la hipótesis de que el sobrecrecimiento bacteriano de intestino delgado (SIBO) es el evento primario o causa del síndrome de intestino irritable (SII), pero otros indican que es consecuencia de este. Se conoce que el SIBO es una de las manifestaciones de la disbiosis intestinal y, por lo tanto, causa de síntomas en el SII, además de que en diversos estudios se ha demostrado que esta situación es altamente prevalente en los pacientes con SII y por ello no se han podido diferenciar por sintomatología ambas afecciones. La prevalencia de SIBO en los pacientes con SII se documenta en un intervalo amplio, cuya variación se debe a los diversos criterios para definir una prueba positiva y a la metodología empleada (28-84% con prueba de aliento con lactulosa, 2-31% con glucosa y 2-6% con cultivo). El tratamiento de elección tanto en el SII sin estreñimiento como en el SIBO es la rifaximina, un antibiótico no sistémico de amplio espectro que genera poca o nula resistencia.

Palabras clave: Sobrecrecimiento bacteriano de intestino delgado. Síndrome de intestino irritable. Pruebas diagnósticas.

***Correspondence:**
Alicia S. Villar-Chávez
E-mail: dravillarchavez@gmail.com

Date of reception: 01-04-2025
Date of acceptance: 30-04-2025
DOI: 10.24875/CGME.M25000007

Avaliable online: 17-09-2025
Clín. Gastroenterol. Méx. (Eng). 2025;1(1):54-62
www.clinicasgastroenterologiademexico.com

Small intestinal bacterial overgrowth: cause or consequence of irritable bowel syndrome?

The correlation between the etiopathogenesis of small intestinal bacterial overgrowth (SIBO) and irritable bowel syndrome (IBS) has not yet been satisfactorily clarified. Some authors support the hypothesis that SIBO is the primary event or cause, while others indicate that it is a consequence of IBS. It is well known that SIBO is one manifestation of intestinal dysbiosis and therefore a cause of IBS symptoms, and several studies have demonstrated that this condition is highly prevalent in patients with IBS[1].

The diagnosis of IBS is based on clinical symptoms, while the diagnosis of SIBO is based on a spectrum of symptoms such as diarrhea, malabsorption, bloating, abdominal pain, or nutritional deficiencies, together with objective evidence of an increased bacterial concentration of ≥ 10^3 colony-forming units (CFU) per milliliter in culture of aspirates from the third and fourth duodenal portions or the jejunum, this method being considered the diagnostic gold standard[2]. Noninvasive tests can also be used, such as breath testing for hydrogen (H_2) and methane (CH_4), which are produced exclusively by microbial metabolism and exhaled in the breath[3].

In patients with IBS, positive H_2 breath tests have been associated with diarrhea-predominant (IBS-D) and mixed (IBS-M) subtypes[4], while a positive CH_4 breath test has been associated with constipation-predominant IBS (IBS-C)[1,2]. Of note, recent SIBO guidelines have reclassified a positive CH_4 breath test as intestinal methanogen overgrowth (IMO), since methanogenesis is likely not limited to the small intestine[2].

Over the past decades, several studies have explored the relationship between SIBO and IBS, as small-intestinal bacteria have been implicated in the clinical manifestations of IBS. In a 2020 meta-analysis of 25 case-control studies with 3,192 patients with IBS and 3,320 controls, the prevalence of SIBO in IBS was 31% (95% CI, 29.4-32.6), with an odds ratio of 3.7 vs controls (95% CI, 2.3-6.0; p = 0.001)[5]. Higher rates of SIBO were also found in IBS patients in studies that used breath testing compared to small bowel aspirate cultures (35.5% vs 13.9%, respectively)[5].

Few studies have attempted to characterize the small-intestinal microbiome in subjects with SIBO and IBS. In the REIMAGINE study, duodenal aspirates were analyzed on MacConkey and blood agar plates, and aspirate DNA was studied with 16S rRNA and shotgun sequencing to define SIBO. A total of 385 subjects with bacterial concentrations < 10^3 CFU/mL on MacConkey agar and 98 subjects with ≥ 10^3 CFU/mL, ≥ 10^3 to < 10^5 CFU/mL (n = 66), and ≥ 10^5 CFU/mL (n = 32) were included. Duodenal alpha microbial diversity progressively decreased, while the relative abundance of *Escherichia, Shigella*, and *Klebsiella* increased in subjects with ≥ 10^3 to < 10^5 CFU/mL and ≥ 10^5 CFU/mL. Furthermore, breath testing documented increased H_2 and hydrogen sulfide (H_2S) production in subjects with ≥ 10^3 CFU/mL, with these gas increases associated with diarrhea symptoms. Shotgun sequencing (n = 38) identified 2 main strains of *Escherichia coli* as well as 2 species of *Klebsiella*, representing 40.2% of all duodenal bacteria in subjects with ≥ 10^3 CFU/mL, correlating with symptoms of diarrhea, abdominal bloating, and abdominal pain. It was concluded that an increase of ≥ 10^3 CFU/mL is the optimal cutoff for defining SIBO[6]. This bacterial overgrowth was also observed in a study conducted in Greece including 320 patients with SIBO and IBS, where duodenal aspirates obtained by endoscopy diagnosed SIBO in 62 subjects (19.4%); of these, 42 had IBS (67.7%), and 37.5% of IBS patients had SIBO. *E. coli*, *Enterococcus* spp., and *Klebsiella pneumoniae* were the most frequent isolates in patients with SIBO[7].

Intestinal microbiota of patients with IBS has also been evaluated using 16S rRNA sequencing, showing significantly greater bacterial diversity than healthy controls and SIBO patients. It was characterized by a higher proportion of Firmicutes and a decrease in Bacteroidetes at the phylum level and a predominance of histamine-producing *Klebsiella* and *Mitsuokella*, with increased *Marvinbryantia* and *Thalassospira*, both with potential impact on intestinal motility (which promotes SIBO). These findings support the hypothesis that SIBO is due to IBS[8,9].

As previously mentioned, SIBO comprises a subset of intestinal dysbiosis, making it important to analyze how this mechanism contributes to IBS. Studies have shown that infections (infectious gastroenteritis and diverticulitis) are associated with the development of IBS, termed post-infectious IBS (PI-IBS)[10,11]. In a systematic review, approximately 10% of patients with enteritis developed PI-IBS during the following year, and its prevalence appears to increase over time[11]. The mechanism explaining PI-IBS is multifactorial and includes changes after infectious enteritis, such as persistent low-grade inflammation, increased intestinal permeability, elevated lymphocytes and enterochromaffin cells, and autoimmunity triggered by antibodies against

the bacterial cytolethal distending toxin B, as well as reduced vinculin expression—all generated by intestinal dysbiosis, ultimately leading to IBS symptoms[1,11].

Lu et al.[12] tried to dichotomize IBS from SIBO based on the fecal microbiome and clinical presentation. Their study included IBS patients (n = 74), SIBO patients (n = 78) diagnosed by lactulose breath testing, and healthy controls (n = 80). The IBS group showed greater severity of abdominal pain and diarrhea episodes, associated with higher levels of *Lachnoclostridium*, *Escherichia-Shigella*, and *Enterobacter* vs the SIBO group. The authors concluded that these 2 conditions could be differentiated by microbiome features. However, the study had limitations, such as not diagnosing SIBO through aspirate culture and the fact that the fecal microbiome does not represent bacterial overgrowth in the small intestine. Therefore, further studies are needed to determine whether SIBO is a condition separate from IBS[12]. Based on the above, it is currently concluded that SIBO and IBS remain a dilemma.

Clinical overlap between irritable bowel syndrome and small intestinal bacterial overgrowth

It has been known for 20 years that dysbiosis is involved in the clinical manifestations of both IBS and SIBO, and therefore, based on symptoms alone, the two conditions cannot be differentiated. Because of this, several studies have explored their overlap, remembering that dysbiosis includes both qualitative alterations of the intestinal microbiota and quantitative changes (SIBO)[13,14].

In both SIBO and IBS, bacterial fermentation of dietary substrates in the intestinal lumen produces various gases such as H_2, CH_4, and CO_2, which generate symptoms such as bloating, flatulence, abdominal pain, and distension. CH_4 is known to slow intestinal transit, resulting in constipation. However, these gases may also be produced in the colon of patients without SIBO in cases of carbohydrate malabsorption. SIBO is more frequently associated with diarrhea and with IBS-D, although a minority of SIBO patients may also present with constipation[13].

The mechanism of diarrhea in patients with SIBO, IBS, or both is explained by bile salt deconjugation, the enterotoxic effect of bacterial metabolites, increased intestinal permeability, and low-grade inflammation resulting from immune activation in the small intestinal mucosa. Secondary disaccharidase deficiency (e.g., lactase) is well recognized in patients with SIBO and IBS, leading to poor digestion of carbohydrates such as lactulose, sucrose, and sorbitol. Furthermore, carbohydrate fermentation leads to the generation of short-chain fatty acids (SCFAs), such as acetic acid, propionic acid, and butyric acid. Although SCFAs are beneficial for the colon by providing nutrients to colonocytes, conserving energy, and aiding in water and electrolyte absorption, in the small intestine they inhibit nutrient absorption and jejunal motility (ileal brake) via the release of peptide YY, neurotensin, and glucagon-like peptide 1, thereby promoting SIBO. Lipopolysaccharides derived from gram-negative bacteria can also affect GI motility[13].

On the other hand, increased numbers of enterochromaffin cells in the colonic and rectal mucosa of patients with IBS and SIBO have been involved in symptom generation, due to immune activation in response to bacterial overgrowth. This results in greater recruitment of intraepithelial lymphocytes, mast cells, and enterochromaffin cells. Additionally, host immune mediators may activate the enteric nervous system and alter gastrointestinal motility and visceral hypersensitivity, which are the main pathophysiological mechanisms of IBS[13,15].

Excessive growth of H_2S-reducing bacteria may also play an important role in IBS and SIBO, as H_2S derived from bacteria has been associated with visceral hypersensitivity and diarrhea in IBS. Thus, measuring H_2S in breath tests could be considered a potential noninvasive biomarker for diagnosing SIBO in IBS-D patients. Importantly, patient-reported symptoms such as diarrhea, malabsorption, bloating, or abdominal pain are not predictive of a positive SIBO test[16].

Breath tests (lactulose or glucose)

Breath tests for diagnosing SIBO, measuring H_2, CH_4, and H_2S in exhaled air, have become popular because of their low cost, accessibility, noninvasive nature, and rapid administration.

The basic principle of breath testing is that the substrates lactulose or glucose—nonabsorbable carbohydrates—are metabolized by small intestinal bacteria, absorbed into the bloodstream, and excreted in the patient's breath[3].

The North American consensus defines a positive breath test for SIBO as an increase of ≥ 20 parts per million (ppm) of H_2 above baseline within 90 minutes, using 75 g of glucose or 10 g of lactulose as substrate, and ≥ 10 ppm of CH_4 at any time during the test is considered positive for methanogen overgrowth. These

substrates are diluted in 200 mL of water, and exhaled air samples are collected every 15 minutes. Requirements include fasting for 8-12 hours, avoidance of antibiotics in the last 4 weeks, no colonoscopy preparation in the previous 2 weeks, and no prokinetics or laxatives for 1 week. Additionally, patients should avoid complex carbohydrates and refrain from smoking the day prior to the test, and oral hygiene should be performed on the test day[3].

The use of lactulose breath testing is justified because this substrate passes through areas of relatively low bacterial density in the stomach and small intestine (approximately 10^1-10^5 CFU in the duodenum, 10^3-10^5 CFU in the jejunum, and 10^6 CFU in the ileum, mainly aerobes) before reaching the cecum, where it is exposed to numerous bacteria including anaerobes (approximately 10^{12} aerobes and anaerobes), which rapidly ferment lactulose to produce H_2, CH_4, and H_2S. This production is the only source of these gases, which quickly diffuse into the bloodstream and can be easily captured in exhaled breath samples. Lactulose breath testing was originally developed to measure mean orocecal transit time. When applied to SIBO diagnosis, it was proposed that bacterial overgrowth in the small intestine results in an early rise of H_2 gases, since the time from ingestion of lactulose to fermentation is shortened (occurring in the small intestine rather than in the cecum)[14].

Glucose breath testing has been proposed as an alternative to lactulose for diagnosing SIBO. Conceptually, the advantage is that glucose is absorbed in the proximal small intestine via Na^+/glucose cotransporters and therefore is less likely to escape to the cecum with rapid transit times, reducing the false positives observed with lactulose breath testing[14].

In a systematic review and meta-analysis comparing the sensitivity and specificity of breath tests with the reference standard (jejunal aspirate culture) for diagnosing SIBO, including 14 studies, the sensitivity of lactulose breath testing was 42% and glucose breath testing was 54.5%, while the specificity was 70.6% for lactulose and 83.2% for glucose[17].

A recent meta-analysis evaluated the prevalence of SIBO in IBS subjects and the probability of SIBO in IBS vs healthy controls using different tests (lactulose and glucose breath tests, jejunal aspirate culture, or multiple tests). It found that 36.7% (95% CI, 24.2-44.6) had a positive SIBO test. IBS patients were 2.6 times (95% CI, 1.3-6.9) and 8.3 times (95% CI, 3.0-15.9) more likely to have a positive SIBO test vs controls using glucose breath testing and jejunal aspirate culture, respectively. No difference in SIBO prevalence was found when using lactulose breath testing between IBS patients and controls (relative risk [RR], 1.613; 95% CI, 0.934-2.785; p = 0.086). IBS-D patients were more likely to have a positive glucose breath test vs other subtypes. Considering these findings, the reference diagnostic method (quantitative proximal small bowel aspirate culture) and glucose breath testing showed higher SIBO prevalence in IBS patients vs healthy controls, suggesting glucose breath testing may be preferable to lactulose for diagnosing SIBO[18].

False positives and negatives in the diagnosis of SIBO

Direct aspirate and culture of intestinal contents is considered the reference method for diagnosing SIBO. Currently, the diagnosis is considered positive when there is a bacterial concentration ≥ 10^3 CFU/mL in aspirate cultures from the third and fourth portions of the duodenum or the jejunum. However, this method has limitations, being invasive, costly, time-consuming, and with potential contamination from oropharyngeal microbiota during the procedure, leading to false positives. Since bacteria may be distributed in different areas—SIBO may affect more distal regions of the small intestine, or bacteria may be localized focally and not detected with a single aspirate, or distal areas may not be accessible with standard instruments—this may result in false negatives. Moreover, the air insufflated during endoscopy can compromise anaerobic bacterial survival. Of note, culturing anaerobic microorganisms requires complex microbiological techniques, and many are not cultivable with standard methods, with growth achieved in only about 30% of cases. Despite these inconsistencies, bacterial culture is still generally accepted as the best diagnostic method for SIBO, but aseptic precautions and appropriate technique are key to diagnostic yield[19].

On the other hand, breath tests are the most widely used modalities for diagnosing SIBO and IMO. Their advantage is that they allow personalization of antibiotic therapy and prediction of treatment response; however, they are limited by their indirect measurement method and variability in orocecal transit time. Like any clinical test, breath tests have inherent strengths and limitations, and results must be interpreted in the context of clinical presentation and host factors that may produce false positives or negatives[20] (Table 1).

Both lactulose and glucose substrates have unique advantages and disadvantages, and there is no

Table 1. Diagnostic tests for bacterial overgrowth

Small bowel aspirate culture	Breath tests (lactulose or glucose)
– Invasive and costly method – Potential contamination with oropharyngeal microbiota → false positives – Bacteria may be patchy and located in distal small bowel → high risk of false negatives – Improper sampling – Anaerobic organism culture requires complex microbiological technique and transport → false negatives	– Safe, simple, and noninvasive test – Requires special preparation – False-positive results in smokers and in chronic obstructive pulmonary disease – False-negative results if patient has taken antibiotics within the last 4 weeks, or prokinetics and laxatives within 1 week – Glucose may fail to detect bacterial overgrowth in distal small bowel → false negatives – Glucose test discouraged in diabetic patients – Lactulose may shorten orocecal transit time – Rapid or slow orocecal transit may lead to false positives or false negatives, respectively – Lactulose is metabolized in the cecum → possible false positives – False negatives may occur due to low hydrogen levels in exhaled air when there is an excess of methanogens and hydrogenotrophic bacteria – Conditions affecting substrate delivery to the small intestine (gastroparesis, gastric outlet obstruction, achalasia, enterocutaneous fistula) may yield false negatives – Wide variation in interpretation and diagnosis depending on cutoffs and substrates used

Modified from Lim et al[20].

consensus on which is preferred. Lactulose, a synthetic disaccharide that is neither digested nor absorbed, has the theoretical advantage of sampling the entire small intestine and potentially identifying distal SIBO. Glucose, a monosaccharide rapidly absorbed in the proximal small intestine, is considered a more specific test because it is less likely to result in false positives from colonic fermentation. However, in distal SIBO, glucose may yield false negatives, as it is absorbed proximally and may not reach the site of SIBO. Conversely, lactulose may be preferred in diabetic patients, as it carries no risk of hyperglycemia[20].

The main criticism of glucose and lactulose breath testing is whether an increase in H_2 reflects colonic rather than small-intestinal fermentation. Studies have shown that glucose breath testing may also reach the cecum, and false-positive rates are observed in approximately 10% of cases with normal anatomy, and even more with prior surgery, such as partial gastrectomy[21]. Rapid orocecal transit can result in false positives, while slow transit can yield false negatives; additionally, lactulose can inherently shorten orocecal transit time and is metabolized in the cecum, potentially leading to a higher rate of false positives[20].

False negatives in lactulose and glucose breath tests may also be observed in conditions affecting substrate delivery to the small intestine, such as gastroparesis, gastric outlet obstruction, achalasia, or enterocutaneous fistula. Flat-line H_2 results during breath testing may actually represent an overabundance of hydrogenotrophic bacteria or excessive methanogenic microorganisms, which consume H_2 to produce CH_4[20].

One major strength of breath testing is its ability to diagnose IMO. Breath testing is currently one of the most widely accessible methods in hospitals and laboratories for identifying IMO. Since IMO is attributed to overgrowth of methanogenic archaea (anaerobic microorganisms of the domain *Archaea*), it is a clinical condition distinct from SIBO. As previously noted, the North American consensus defines IMO as an increase of $CH_4 \geq 10$ ppm at any time during a breath test. Unlike SIBO breath testing, IMO is not affected by orocecal transit time. Importantly, CH_4 slows intestinal transit and is therefore associated with constipation and IBS-C. Additionally, CH_4 levels do not fluctuate, correlate directly with constipation severity, and have therapeutic implications, as archaeal species are resistant to most antibiotics[3,20].

Who should be tested for SIBO?

Diagnosing SIBO is challenging, as symptoms are nonspecific and non-predictive; therefore, diagnostic testing should not be ordered based solely on clinical presentation. This was supported by a study in which mean total symptom scores were similar regardless of whether patients tested positive or negative on duodenal aspirate and breath testing ($p = 0.9$)[22].

Since SIBO diagnosis requires specialized testing (e.g., microbial culture or breath testing), and due to variability in patient populations and diagnostic methods used in studies, determining who should undergo diagnostic testing is difficult. Nonetheless, SIBO is correlated with several clinical conditions (Table 2), and it must be

considered that prevalence in these groups is variable (range, 2–92%). Interestingly, up to 13% of healthy individuals have also tested positive for SIBO using either breath testing or small-bowel aspirate cultures[19].

Thus, it is important to consider testing in patients with conditions strongly associated with SIBO, such as motility disorders, gastrointestinal surgery, chronic pancreatitis, or scleroderma. Proton pump inhibitor (PPI) use is also considered an independent risk factor, observed in up to 50% of subjects with unexplained gastrointestinal symptoms[23-25].

Motility disorders are likely the main contributor to SIBO in older adults and in the general population. Chronic pancreatitis is another multifactorial cause, through reduced intestinal motility due to both the inflammatory process and narcotic use, as well as intestinal obstruction. Stasis and recirculation of intestinal contents due to fistulas, enterostomies, and anastomoses also predispose to SIBO, explaining its association with Crohn's disease, radiation enteropathy, and reconstructive GI surgery.

SIBO and increased intestinal permeability, through systemic effects of bacterial endotoxin, have also been implicated in the pathogenesis of metabolic dysfunction-associated steatotic liver disease (MASLD)[26]. In cirrhotic patients, several risk factors for SIBO exist, among which prolonged phase II of the migrating motor complex is one of the most relevant. Chronic alcohol use is linked to smooth muscle myopathy and neuropathy due to direct toxic damage, and higher prevalence of diabetes mellitus has also been reported in these patients[27].

Prevalence of SIBO in IBS patients varies widely depending on the criteria and methodology used: 28-84% with lactulose breath testing, 2-31% with glucose, and 2-6% with culture[25]. A significantly higher percentage of IBS patients with SIBO have motility disorders vs IBS patients without SIBO (86% vs 39%, p = 0.02)[28].

In a case-control study, a significantly higher proportion of colectomy patients had SIBO vs patients with GI complaints without colectomy (62% vs 32%, p = 0.0005)[29].

In conclusion, diagnostic testing for SIBO should be considered in patients with symptoms and clinical conditions strongly associated with SIBO, remembering that it is often secondary, and unless the underlying problem is addressed and controlled, recurrence is highly likely.

Rifaximin: when to use it?

Given the multifactorial pathophysiological mechanism of IBS, symptom control and subtype-targeted therapy have been proposed based on underlying mechanisms. In IBS-D and IBS-M, some treatments such as antibiotics and probiotics are aimed at modulating the intestinal microbiota, potentially correcting dysbiosis. However, the use of conventional antibiotics such as neomycin, metronidazole, or ciprofloxacin is limited due to risks of *Clostridioides difficile* infection, antibiotic resistance, and adverse events such as ototoxicity, neuropathy, or nephrotoxicity[30].

Rifaximin (RFX), a non-systemic, broad-spectrum antibiotic with minimal resistance potential, is the treatment of choice for both IBS without constipation and SIBO. Its alpha-polymorphic form allows minimal absorption (systemic absorption ~0.4%), enabling local intestinal action. One mechanism of action involves modulation of the intestinal microbiota, making it a potential "eubiotic," as it reduces bacterial counts while increasing beneficial species such as *Bifidobacteria*, *Lactobacilli*, and *Faecalibacterium prausnitzii*. Additionally, RFX has an immunomodulatory effect by reducing pro-inflammatory cytokines (interleukin-6 and tumor necrosis factor-α)[30].

RFX has been evaluated in 3 phase III clinical trials in IBS-D and IBS-M, known as TARGET 1, 2, and 3 (Targeted Nonsystemic Antibiotic Rifaximin Gut-Selective Evaluation of Treatment for IBS-D). In TARGET 1 and 2, involving 1,260 patients with IBS without constipation, 40.7% of patients on a 2-week regimen of RFX 550 mg 3 times daily experienced global IBS symptom improvement during at least 2 of the first 4 weeks post-treatment vs 31.7% in the placebo group. Abdominal bloating improved too (40.2% vs 30.3%), along with stool consistency and abdominal pain, with a number needed to treat (NNT) of 10.2. As expected, RFX was well tolerated, with an adverse event profile similar to placebo, and the response was maintained for up to 10 weeks after treatment[31].

TARGET 3 evaluated the safety and efficacy profile of repeat RFX therapy (550 mg 3 times daily for 2 weeks) in IBS-D patients who initially responded during at least 2 of the first 4 weeks post-treatment and experienced recurrence during an 18-week observation period. Among 1,074 IBS-D patients, 382 (35.6%) did not relapse within 22 weeks post-treatment, while 636 did (mean, 4 weeks) and were randomized to RFX (n = 328) or placebo (n = 308) for 2 retreatment cycles, 10 weeks apart. Response rates during the first retreatment were significantly higher with RFX vs placebo (38.1% vs 31.5%; p = 0.03), as was abdominal pain improvement (50.6% vs 42.2%; p = 0.018). Prevention of recurrence (13.2% vs 7.1%; p = 0.007) and sustained responses for abdominal pain and stool consistency

Table 2. Prevalence of small intestinal bacterial overgrowth in associated diseases

Abnormalities	Prevalence
GI motility disorders or GI wall damage	
Celiac disease	9-67%
Connective tissue diseases (e.g., scleroderma)	43-55%
Crohn's disease	25-88%
Ulcerative colitis	81%
Diabetes mellitus	8-44%
Hypothyroidism	54%
Nonspecific motility disorders	76%
Radiation enteropathy	26%
Neuromuscular diseases	
Muscular dystrophy	65%
Parkinson's disease	54%
Surgical	
Abdominal surgery	82%
Bilateral truncal vagotomy	93%
Gastrectomy	63-78%
Ileocecal valve resection	32%
Roux-en-Y reconstruction	86%
Miscellaneous	
Chronic fatigue syndrome	81%
Chronic pancreatitis	34-92%
Acid secretion–inhibiting drugs	26-75%
Advanced chronic renal failure	36%
Fibromyalgia	93%
Irritable bowel syndrome	2-84%
Immunodeficiency syndrome	30-50%
Liver cirrhosis	17-41%
Obesity	17-41%
Parenteral nutrition	70%
Rosacea	46%

Modified from Grace et al[24].

(17.1% vs 11.7%; p = 0.04) were also superior in the RFX group. Adverse events were similar between groups. In the second retreatment, response remained greater for RFX (37% vs 29%; p = 0.04)[32].

A systematic review and meta-analysis assessed symptomatic response rates to antibiotics in SIBO patients and to antibiotics in IBS patients with or without SIBO. Six studies including 196 patients were analyzed, comparing antibiotics vs placebo or no antibiotic. Significantly more patients improved with antibiotics (RR, 2.46; 95% CI, 1.33-4.55; p = 0.004). Another analysis compared symptomatic response rates in IBS patients with (n = 172) and without SIBO (n = 94), showing response rates of 51.2% vs 23.4%, respectively. IBS patients with SIBO were significantly more likely to respond to antibiotics (RR, 2.07; 95% CI, 1.40-3.08; p = 0.0003)[33].

As shown in systematic reviews, the efficacy of RFX is dose-dependent. The recommended regimen is RFX 550 mg every 8 hours for 14 days for SIBO with or without IBS[34], while in IMO, the combination of neomycin 500 mg twice daily plus RFX 550 mg every 8 hours for 14 days is used[35].

Are we overdiagnosing SIBO in IBS patients?

As previously mentioned, intestinal dysbiosis, which is considered part of the SIBO spectrum, is one of the causes of symptoms in patients with IBS. Between 4% and 78% of patients with IBS and 1% to 40% of controls have SIBO; such variations in prevalence may result from analysis of different populations, diverse diagnostic criteria for IBS, and—most importantly—different diagnostic methods. Although quantitative culture of jejunal aspirate is considered the reference method for diagnosing SIBO, noninvasive H_2 breath tests have become popular. While the glucose H_2 breath test is highly specific, its sensitivity is low; in contrast, the early-peak criteria in the lactulose H_2 breath test are highly nonspecific, as they may represent arrival to the colon, which can be modified by the osmotic effect of lactulose or by an inherently rapid transit in IBS patients, as well as by the timing used to measure intestinal transit, which is often shorter than 90 minutes. Therefore, it must be considered that breath tests are not perfect, and their interpretation may vary depending on the operator, the substrate, and the appropriate dose[17].

Furthermore, the accessibility of breath testing has led to its use in patients with a wide range of GI symptoms, often without typical SIBO risk factors. This is important because small-intestinal bacterial density varies between individuals, and many healthy subjects test "positive" for SIBO by breath tests or aspirate culture, influenced by diet and other factors, without symptoms. This raises questions about the specificity of these tests[14].

Recently, at-home breath test devices for gas monitoring during and after meals have been promoted, though their results are not validated. With the SIBO–IBS hypothesis spreading on social media, test numbers may increase, raising concerns: high rates of testing and false positives without clinical foundation may harm patients, leading to confusion, anxiety, and potential loss of trust in healthcare. Importantly, positive tests may drive overuse of antibiotics, sometimes empirically prescribed without diagnostic confirmation, for which no scientific evidence exists[14].

Critical analysis of increased diagnoses and need for clearer guidelines to avoid excessive use of antibiotics

SIBO has been recognized for over a century in patients with predisposing conditions causing intestinal stasis, such as small-bowel surgery or chronic diseases such as scleroderma and is associated with diarrhea and malabsorption. Over 20 years ago, it was hypothesized that small-intestinal bacterial overgrowth could also explain symptoms without malabsorption in IBS and other disorders of gut-brain interaction (DGBIs). This SIBO–IBS hypothesis highlighted the importance of the microbiota-host relationship as a potential mechanism in IBS.

However, after 2 decades, this hypothesis remains unproven and has led to unintended consequences, including widespread use of unreliable breath tests and imprudent antibiotic use[14].

We begin by analyzing the lactulose breath test, which is primarily a measure of intestinal transit and has very low sensitivity and specificity for diagnosing SIBO, with the fundamental underlying flaw in this test being the wide variation in orocecal transit time. It is known that orocecal transit time is shorter than the proposed diagnostic threshold of 90 minutes for a rise in H_2 as a diagnostic marker of SIBO, and it is even shorter in patients with IBS-D compared with asymptomatic subjects. On the other hand, the glucose breath test has better diagnostic performance if the pretest probability is high, as is found in conditions underlying classic SIBO, but it also has a high rate of false positives in disorders of gut-brain interaction (DGBI). Therefore, more studies are needed in DGBI to better understand the impact of bacterial communities, their metabolites, and diet-host interactions in the small intestine and colon on DGBI symptoms, and move away from the sole focus on absolute bacterial counts[14]. A real-world study with more than 1,000 patients showed that the test positivity rate in patients with DGBI was less than 2%[36].

What is crucial for the clinician is to know whether the results of diagnostic tests will impact clinical care and predict prognosis or therapeutic response. Regarding SIBO in IBS, the specific question is: will a positive breath test predict the response to antibiotic therapy? There is wide variability in SIBO eradication rates or normalization of breath tests, ranging from 7% to 100%, with similarly variable rates of symptomatic response. Unfortunately, the literature on any form of therapy for SIBO, regardless of etiology, is limited, and interpretation is affected by variations in study populations, study design (choice of antibiotic, dose, duration of therapy, and follow-up), and clinical outcomes. Furthermore, many studies are observational or adopted an open-label design, few were placebo-controlled, and head-to-head comparisons of different antibiotic regimens are scarce[14].

The role of SIBO in IBS remains controversial, and a recent systematic review of case-control studies concluded that although the literature suggests an association, the overall quality of evidence is low[5].

Regarding clinical practice guidelines, recommendations on the use of breath testing in the diagnosis of IBS differ. The British and Canadian guidelines discourage breath testing in IBS[37,38], whereas the American guidelines make no recommendation either for or against their use[39].

In the TARGET trials, which led to FDA approval of rifaximin (RFX) for the treatment of non-constipation IBS[31], only 98 of the 1,260 study participants underwent a lactulose breath test[40]. Among responders in this small subgroup, 59.7% had a positive baseline breath test. While 48% of these patients were considered overall responders to a 2-week course of RFX at 550 mg 3 times daily, breath test normalization occurred in only 29%. Unsurprisingly, the posttreatment breath test result did not predict response to RFX: 76.5% of those with normalized breath tests were considered responders vs 56% of those who did not normalize. In summary, the correlation between antibiotic eradication of SIBO, breath test normalization, and symptomatic response is far from consistent or clear.

We know that a proportion of IBS patients will experience symptom improvement with antibiotic therapy; however, when including randomized clinical trials such as the TARGET studies, the therapeutic gain is only about 10% over placebo[31].

The challenges of applying the SIBO concept to disorders of DGBI should not minimize the diagnosis of SIBO in “classic” conditions associated with gastrointestinal dysmotility, such as scleroderma, small bowel stasis secondary to surgery, and ileocecal valve resection, in which associated signs of malabsorption are present. In this context, the pretest probability for a glucose breath test is higher, thereby improving diagnostic accuracy. Whether one chooses to treat directly with antibiotics or to perform a breath test first to guide therapy will depend on several factors, including test availability, cost, and both patient and physician preference.

Funding

The authors declared no funding for this study.

Conflicts of interest

The authors declared no conflicts of interest whatsoever.

Ethical considerations

H**uman and animal protection.** The authors declare that no experiments on humans or animals were conducted for this study.

Confidentiality, informed consent, and ethical approval. The study does not involve patient data and does not require ethical approval. SAGER guidelines do not apply.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the preparation of this manuscript.

References

1. Takakura W, Pimentel M. Small intestinal bacterial overgrowth and irritable bowel syndrome - an update. Front Psychiatry. 2020;11:664.
2. Pimentel M, Saad RJ, Long MD, Rao SSC. ACG Clinical Guideline: small intestinal bacterial overgrowth. Am J Gastroenterol. 2020; 115:165-78.
3. Rezaie A, Buresi M, Lembo A, Lin H, McCallum R, Rao S, et al. Hydrogen and methane-based breath testing in gastrointestinal disorders: the North American Consensus. Am J Gastroenterol. 2017; 112:775-84.
4. Chen B, Kim JJ, Zhang Y, Du L, Dai N. Prevalence and predictors of small intestinal bacterial overgrowth in irritable bowel syndrome: a systematic review and meta-analysis. J Gastroenterol. 2018;53:807-18.
5. Shah A, Talley NJ, Jones M, Kendall BJ, Koloski N, Walker MM, et al. Intestinal bacterial overgrowth in irritable bowel syndrome: a systematic review and meta-analysis of case-control studies. Am J Gastroenterol. 2020;115:190-201.
6. Leite G, Rezaie A, Mathur R, Barlow GM, Rashid M, Hosseini A, et al.; REIMAGINE Study Group. Defining small intestinal bacterial overgrowth by culture and high throughput sequencing. Clin Gastroenterol Hepatol. 2024;22:259-70.
7. Pyleris E, Giamarellos-Bourboulis EJ, Tzivras D, Koussoulas V, Barbatzas C, Pimentel M. 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.
8. Pittayanon R, Lau JT, Yuan Y, Leontiadis GI, Tse F, Surette M, et al. Gut microbiota in patients with irritable bowel syndrome — a systematic review. Gastroenterology. 2019;157:97-108.
9. Marasco G, Savarino EV, Barbara G. The IBS and SIBO dilemma: here we go again. Dig Liver Dis. 2024;56:2025-6.
10. Cohen E, Fuller G, Bolus R, Modi R, Vu M, Shahedi K, et al. Increased risk for irritable bowel syndrome after acute diverticulitis. Clin Gastroenterol Hepatol. 2013;11:1614-9.
11. Klem F, Wadhwa A, Prokop LJ, Sundt WJ, Farrugia G, Camilleri M, et al. Prevalence, risk factors, and outcomes of irritable bowel syndrome after infectious enteritis: a systematic review and meta-analysis. Gastroenterology. 2017;152:1042-54.
12. Lu S, Chen Y, Guo H, Liu Z, Du Y, Duan L. Differences in clinical manifestations and the fecal microbiome between irritable bowel syndrome and small intestinal bacterial overgrowth. Dig Liver Dis. 2024; 56:2027-37.
13. Ghoshal UC, Shukla R, Ghoshal U. Small intestinal bacterial overgrowth and irritable bowel syndrome: a bridge between functional organic dichotomy. Gut Liver. 2017;11:196-208.
14. Kashyap P, Moayyedi P, Quigley EMM, Simren M, Vanner S. Critical appraisal of the SIBO hypothesis and breath testing: a clinical practice update endorsed by the European Society of Neurogastroenterology and Motility (ESNM) and the American Neurogastroenterology and Motility Society (ANMS). Neurogastroenterol Motil. 2024;36:e14817.
15. Ford AC, Talley NJ. Mucosal inflammation as a potential etiological factor in irritable bowel syndrome: a systematic review. J Gastroenterol. 2011;46:421-31.
16. Banik GD, De A, Som S. Hydrogen sulphide in exhaled breath: a potential biomarker for small intestinal bacterial overgrowth in IBS. J Breath Res. 2016;10:026010.
17. Losurdo G, Leandro G, Ierardi E, Perri F, Barone M, Principi M, et al. Breath tests for the non-invasive diagnosis of small intestinal bacterial overgrowth: a systematic review with meta-analysis. J Neurogastroenterol Motil. 2020;26:16-28.
18. Ghoshal UC, Nehra A, Mathur A, Rai S. A meta-analysis on small intestinal bacterial overgrowth in patients with different subtypes of irritable bowel syndrome. J Gastroenterol Hepatol. 2020;35:922-31.
19. Rao SSC, Bhagatwala J. Small intestinal bacterial overgrowth: clinical features and therapeutic management. Clin Transl Gastroenterol. 2019; 10:e00078.
20. Lim J, Rezaie A. Pros and cons of breath testing for small intestinal bacterial overgrowth and intestinal methanogen overgrowth. Gastroenterol Hepatol (N Y). 2023;19:140-6.
21. Erdogan A, Rao SS, Gulley D. Small intestinal bacterial overgrowth: duodenal aspiration vs glucose breath test. Neurogastroenterol Motil. 2015;27:481-9.
22. Lin EC, Massey BT. Scintigraphy demonstrates high rate of false-positive results from glucose breath tests for small bowel bacterial overgrowth. Clin Gastroenterol Hepatol. 2016;14:203-8.
23. Jacobs C, Coss Adame E, Attaluri A. 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.
24. Grace E, Shaw C, Whelan K. Review article: small intestinal bacterial overgrowth — prevalence, clinical features, current and developing diagnostic tests, and treatment. Aliment Pharmacol Ther. 2013;38:674-88.
25. Schmulson M, Bielsa MV, Carmona Sánchez R. Microbiota, infecciones gastrointestinales, inflamación de bajo grado y antibioticoterapia en el síndrome de intestino irritable. Una revisión basada en evidencias. Rev Gastroenterol Mex. 2014;79:96-134.
26. Quigley EM, Abu Shanab A. Small intestinal bacterial overgrowth. Infect Dis Clin North Am. 2010;24:943-59.
27. Ghosh G, Jesudian AB. Small intestinal bacterial overgrowth in patients with cirrhosis. J Clin Exp Hepatol. 2019;9:257-67.
28. Posserud I, Stotzer PO, Björnsson ES. Small intestinal bacterial overgrowth in patients with irritable bowel syndrome. Gut. 2007;56:802-8.
29. Rao SSC, Tan G, Abdulla H. Does colectomy predispose to small intestinal bacterial (SIBO) and fungal overgrowth (SIFO)? Clin Transl Gastroenterol. 2018;9:146.
30. Chang C. Short-course therapy for diarrhea-predominant irritable bowel syndrome: understanding the mechanism, impact on gut microbiota, and safety and tolerability of rifaximin. Clin Exp Gastroenterol. 2018;11:335-45.
31. Pimentel M, Lembo A, Chey WD. Rifaximin therapy for patients with irritable bowel syndrome without constipation. N Engl J Med. 2011;364:22-32.
32. Lembo A, Pimentel M, Rao SS. Repeat treatment with rifaximin is safe and effective in patients with diarrhea-predominant irritable bowel syndrome. Gastroenterology. 2016;151:1113-21.
33. Takakura W, Rezaie A, Chey WD, Wang J, Pimentel M. Symptomatic response to antibiotics in patients with small intestinal bacterial overgrowth: a systematic review and meta-analysis. J Neurogastroenterol Motil. 2024;30:7-16.
34. Wang J, Zhang L, Hou X. Efficacy of rifaximin in treating with small intestine bacterial overgrowth: a systematic review and meta-analysis. Expert Rev Gastroenterol Hepatol. 2021;15:1385-99.
35. Pimentel M, Chang C, Chua KS, Mirocha J, DiBaise J, Rao S, et al. Antibiotic treatment of constipation-predominant irritable bowel syndrome. Dig Dis Sci. 2014;59:1278-85.
36. Dervin H, Zarate-Lopez N, Sweis R. Low prevalence of positive hydrogen breath tests in patients with functional gastrointestinal conditions and hypermobile Ehlers-Danlos syndrome. Neurogastroenterol Motil. 2023;35:e14570.
37. Vasant DH, Paine PA, Black CJ. British Society of Gastroenterology guidelines on the management of irritable bowel syndrome. Gut. 2021;70:1214-40.
38. Moayyedi P, Andrews CN, MacQueen G. Canadian Association of Gastroenterology clinical practice guideline for the management of irritable bowel syndrome (IBS). J Can Assoc Gastroenterol. 2019;2:6-29.
39. Lacy BE, Pimentel M, Brenner DM. ACG clinical guideline: management of irritable bowel syndrome. Am J Gastroenterol. 2021;116:17-44.
40. Rezaie A, Heimanson Z, McCallum R, Pimentel M. Lactulose breath testing as a predictor of response to rifaximin in patients with irritable bowel syndrome with diarrhea. Am J Gastroenterol. 2019;114: 1886-93.