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PERSPECTIVES IN CLINICAL GASTROENTEROLOGY AND HEPATOLOGY

Breath Testing for Small Intestinal Bacterial Overgrowth: Maximizing Test Accuracy

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This article has an accompanying continuing medical education activity on page e119. Learning Objective–At the end of this activity, the successful learner will be able to understand measures to improve the diagnostic accuracy of breath testing for suspected small intestinal bacterial overgrowth.

The diagnosis of small intestinal bacterial overgrowth (SIBO) has increased considerably owing to a growing recognition of its association with common bowel symptoms including chronic diarrhea, bloating, abdominal distention, and the irritable bowel syndrome. Ideally, an accurate and objective diagnosis of SIBO should be established before initiating antibiotic treatment. Unfortunately, no perfect test exists for the diagnosis of SIBO. The current gold standard, small-bowel aspiration and quantitative culture, is limited by its high cost, invasive nature, lack of standardization, sampling error, and need for dedicated infrastructure. Although not without shortcomings, hydrogen breath testing provides the simplest noninvasive and widely available diagnostic modality for suspected SIBO. Carbohydrates such as lactulose and glucose are the most widely used substrates in hydrogen breath testing, with glucose arguably providing greater testing accuracy. Lactose, fructose, and sorbitol should not be used as substrates in the assessment of suspected SIBO. The measurement of methane in addition to hydrogen can increase the sensitivity of breath testing for SIBO. Diagnostic accuracy of hydrogen breath testing in SIBO can be maximized by careful patient selection for testing, proper test preparation, and standardization of test performance as well as test interpretation.

Keywords: Small Intestinal Bacterial Overgrowth; Hydrogen Breath Test; SIBO; Glucose Hydrogen Breath Test; Lactulose Hydrogen Breath Test.

The concept of small intestinal bacterial overgrowth (SIBO) was first suggested in 1939 by Barker and Hummel[1] who observed the development of macrocytic anemia in patients with intestinal stricture. Over time, our understanding of SIBO has evolved with a growing knowledge of the gut microbiota and its bidirectional interaction with immune function, digestion, metabolism and brain-gut communication. Traditionally defined as an excessive concentration of bacteria in the small intestine based on culture of a jejunal aspirate, SIBO more recently was defined by measurable changes in exhaled gases produced by the bacterial metabolism of orally ingested carbohydrates or bile salts. Not only can SIBO complicate the illness experience of patients with a range of systemic diseases and structural abnormalities of the gastrointestinal (GI) tract, but it is now recognized for its role in a variety of common GI symptoms including bloating, flatulence, diarrhea, abdominal cramping, nausea, and weight loss. The presentation of SIBO can range from a variety of nonspecific GI and/or constitutional symptoms, to complications of malabsorption including weight loss, steatorrhea, and a wide range of nutritional deficiencies such as B12, vitamin A, vitamin D, and vitamin E deficiency. The diverse clinical and nutritional consequences of untreated SIBO can lead to megaloblastic anemia, peripheral neuropathy, night blindness, and osteoporosis.[2] Indeed, the number of clinical conditions associated with SIBO continues to grow, now including common GI syndromes such as the irritable bowel syndrome.[3,4] It is oftentimes clinically challenging to distinguish SIBO from other organic and functional etiologies for commonly reported symptoms such as diarrhea, bloating, cramping, excessive flatulence, and nausea. Furthermore, the treatment of SIBO requires the use of oral antibiotics, which can lead to a wide variety of potential adverse effects. For instance, the indiscriminant use of systemic antibiotics in the outpatient setting represents one of the most common reasons for the rapidly growing incidence of multidrug resistant strains of bacteria such as *Clostridium difficile*, *Staphylococcus aureus*, and *enterococcus*.[5,6] Therefore, the ability to make an accurate diagnosis of SIBO is clinically meaningful given the potential adverse consequences of empiric treatment with systemically absorbed antibiotics. In this review, we discuss the currently available

Abbreviations used in this paper: **GBT, glucose breath test; GI, gastrointestinal; LBT, lactulose breath test; ppm, parts per million; SIBO, small intestinal bacterial overgrowth.**

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means by which to diagnose SIBO with a focus on the strengths and weaknesses of breath testing.

Pathophysiology of Small Intestinal Bacterial Overgrowth

Several key mechanisms play a role in preventing bacteria overgrowth in the proximal gut including gastric acid; the migrating motor complex; integrity of the intestinal mucosa; the gut immune system; enzymatic activities of intestinal, pancreatic, and biliary secretions; direct effects of commensal bacterial within the small bowel; and the physical barrier created by the ileocecal valve.[7] A number of conditions capable of adversely affecting one or more of these protective mechanisms have been associated with an increased risk for SIBO (Table 1). This includes developmental and acquired anatomic abnormalities of the proximal gut such as small-bowel diverticulosis, strictures, fistula, and mucosal inflammation associated with inflammatory bowel disease.[8] Surgical alterations of the GI tract affecting small-bowel motility, impairing gastric acid production, or allowing migration of colonic bacteria into the small bowel such as fundoplication, gastric resection, gastric bypass, small-bowel resection, and ileocecal valve resection have been associated with SIBO.[9–13] Advancing age can affect motility, pancreaticobiliary secretion, and absorption, increasing the risk for SIBO.[8] Specific diseases associated with SIBO include diabetes,[14,15] scleroderma,[16,17] celiac disease,[18–20] amyloidosis,[21] hypothyroidism,[22] gastroparesis,[23] intestinal pseudo-obstruction,[24] cirrhotic liver disease,[25] chronic pancreatitis,[26] immune deficiency syndromes,[27] and chronic renal disease.[28] Use of certain medications also may increase the risk of SIBO. For example, narcotic analgesics that alter GI motility increase the risk of SIBO.[8] Although SIBO is prevalent in achlorhydria,[29,30] an association with chronic proton pump inhibitor treatment remains controversial.[31,32]

Table 1. Conditions Associated With SIBO

Developmental and acquired anatomic abnormalities
Small-bowel diverticulosis
Small-bowel strictures
Small-bowel fistula
Small-bowel Crohn's disease
Surgical alterations of the GI tract
Gastric fundoplication
Gastric resection
Gastric bypass
Small-bowel resection
Ileocecal valve resection
GI motility disorders
Gastroparesis
Small-bowel pseudo-obstruction
Colonic inertia
Other GI disorders
Celiac disease
Chronic pancreatitis
Achlorhydria
Cirrhosis
Systemic disorders
Diabetes mellitus
Scleroderma
Amyloidosis
Hypothyroidism
Immune deficiency syndrome
Chronic renal disease
Miscellaneous conditions
Advanced age
Chronic narcotic use
Chronic PPI use?

Diagnostic Studies for Small Intestinal Bacterial Overgrowth

Small-Bowel Aspiration and Quantitative Culture

Small-bowel aspiration for quantitative culture traditionally has been regarded as the gold standard for the diagnosis of SIBO. Because it is imperative not to contaminate the sample, aspiration is performed either through an endoscopically or fluoroscopically confirmed guidewire-placed sterile catheter.[33,34] It is also important that the specimen be transferred promptly to the appropriate laboratory for culturing under aerobic and anaerobic conditions. However, small bowel culturing methodology is variable as reported in a systematic review of 50 published studies from 1996 to 2007.[35] Considerable heterogeneity exists in methodology including: device placement for fluid aspiration, location and quantity of the aspirate, technique in sample handing and culture, and interpretation of culture results. There also is a general lack of validation against controls because this was only performed in 3 of the studies. Furthermore, there is a lack of standardization regarding the definition of a positive culture with studies using more than 10^4 cfu/mL to more than 10^7 cfu/mL to define SIBO. However, it should be noted that most experts have accepted a bacterial count of 10^5 cfu/mL or more to be diagnostic of SIBO.[7,36,37] Overall, there are considerable limitations with small-bowel aspiration for quantitative culture including its cost, invasive nature, time commitment, potential for sample contamination, lack of adequate validation, accuracy of culturing, and the potential for missing distal small-bowel bacterial overgrowth. From a practical standpoint, groups that choose aspiration and quantitative culture should appreciate that the threshold that defines "abnormal" in the duodenum is almost certainly different than the current standard established for the jejunum. The good news is that the application of the current threshold of more than 10^5 CFU/mL aspirate is likely to be quite specific. However, given that normal bacterial concentrations in the duodenum are lower than the jejunum, this threshold may be too high and is likely to be insensitive for SIBO.[14]

Perhaps more importantly, quantitative culture can identify only a small proportion of the organisms that reside in an aspirated sample. At present, we do not know if quantitative, qualitative, or both types of assessments are important to SIBO. For example, an interesting question is whether quantitative culture identifies the bacterial strains responsible for a patient's illness experience. In other words, are the bacteria identified the cause or effect of the underlying pathophysiologic abnormalities that cause a patient's illness experience?

Breath Testing

In contrast to small bowel aspiration for quantitative culture, breath testing provides a more readily available, safe, inexpensive, and noninvasive alternative to jejunal aspiration culture for the diagnosis of SIBO. Furthermore, it may represent a more inclusive definition of SIBO (when lactulose is used as substrate) because it is likely to include cases of distal small-bowel bacterial overgrowth and pathologic bacterial strains not identified by culturing techniques.[37] By measuring exhaled gases produced by bacterial fermentation of various orally ingested substrates, the bacterial load within the small bowel can be assessed indirectly. The measured gases can include labeled carbon dioxide (CO_2), hydrogen, and methane. For the labeled CO_2 studies, the orally ingested substrates include ^{14}C-glycocholate, ^{13}C-glycocholate, ^{14}C-xylose, or ^{13}C-xylose.[38] For hydrogen and methane breath testing, the substrates include glucose or lactulose. Other simple sugars such as lactose, fructose, and sorbitol are available, but are not used for the assessment of SIBO. The measurement of methane gas has been advocated to improve the diagnostic yield of breath testing, although there is no consensus on its role in the diagnostic assessment of SIBO.[39]

Although there are clear advantages to the simplicity of breath testing, it is important to realize this testing modality can be subject to misinterpretation or overinterpretation.[40–42] In most instances, breath testing is unable to distinguish small bowel from colonic metabolism of the substrates. This is particularly problematic for the substrates glycocholic acid, d-xylose, sorbitol, and lactulose because they are not, or incompletely, absorbed in the small bowel. A variety of clinical conditions accelerating small-bowel transit can be equally problematic on the diagnostic accuracy of breath testing regardless of the substrate. Similar to jejunal culturing, a general lack of standardization for test preparation, test performance, and, most importantly, test interpretation has made it challenging to define the true diagnostic accuracy of breath testing.

Carbon Dioxide Breath Testing

Initial breath testing relied on the recovery and measurement of labeled CO_2.[43] This methodology required interval breath sampling of labeled CO_2 for variable periods of time, ranging from 4 to 24 hours.[43,44] Testing used either the radioactive isotope of carbon, ^{14}C,[45] or the nonradioactive ^{13}C isotope.[46] One of the greatest challenges with CO_2 breath testing was correcting for the endogenous CO_2 production, which differed considerably in the various disease states adversely affecting test accuracy. Furthermore, the process of conjugating substrates with labeled carbon added to the cost and limited availability. For these reasons, CO_2 breath testing has been abandoned in clinical practice.

^{14}C-Glycocholate Breath Test

The first reported breath tests for the evaluation of suspected SIBO used glycocholic acid labeled with ^{14}C.[47] The principle underlying the use of glycocholic acid was that under normal circumstances, bile acids readily were absorbed in the ileum.[42] Any unabsorbed glycocholic acid was subject to metabolism, either by bacteria in the proximal small bowel before ileal absorption, or in the colon in the event of glycocholate malabsorption. This bacterial catabolism resulted in the production of labeled glycine, which then was converted to labeled CO_2. The labeled CO_2 then was absorbed rapidly into the bloodstream, and excreted by the lungs. A subsequent increase in labeled CO_2 in expired breath within 6 hours was interpreted as a positive study. Limitations included an inability to distinguish small bowel from colonic bacterial deconjugation of the glycocholic acid and decreased accuracy with underlying rapid small-bowel transit.[42] Not surprisingly, a wide variation in performance characteristics of this modality existed with a reported sensitivity of 33% to 100% and a specificity of 76% to 86%.[48–50] A compounding concern is the theoretical risk of long-term radiation exposure with the ^{14}C-labeled substrates. Given the potential for incorporation of ^{14}C into tissue and its half-life of 5730 years, this concern was addressed by a study of 18 adults assessing the long-term biokinetics and dosimetry of ^{14}C-glycocholic acid and ^{14}C-xylose, concluding that the exposure was equivalent to 3 weeks of natural radiation from the environment.[51] For these reasons, this diagnostic modality for SIBO has been largely abandoned.

^{13}C/^{14}C D-Xylose

D-xylose is a poorly absorbed 5-carbon monosaccharide found in plants. D-xylose labeled with either ^{13}C or ^{14}C was ingested orally, and metabolized by gut bacteria yielding labeled CO_2 measured in the breath.[52] However, D-xylose is variably absorbed and metabolized, which can blur the baseline breath CO_2 measurements, making it more difficult to measure labeled CO_2 production in the setting of SIBO.[53] Furthermore, D-xylose may be a poor metabolic substrate for common coliform bacteria including *Escherichia coli*, enterococci, and clostridia,

thereby increasing the risk of false-negative results.[53] The specificity may be affected adversely in cases of rapid intestinal transit resulting in colonic metabolism of D-xylose.[53] Not surprisingly, the performance of this test has varied widely, with sensitivity ranging from 14% to 95% and a specificity ranging from 40% to 94%.[45,48,54–57] Although still available, D-xylose is used primarily for the assessment of intestinal malabsorption.[58–60]

Hydrogen and Methane Breath Testing

Hydrogen breath testing was introduced as an alternative to CO_2 breath testing for SIBO.[61] Hydrogen breath testing is based on the principle that bacterial metabolism (fermentation) of nonabsorbed carbohydrates is the sole source of hydrogen and methane in exhaled breath.[62,63] After the oral ingestion of various substrates, hydrogen can be measured in exhaled breath using gas chromatography and reported as a concentration in parts per million (ppm).[64] Methane can be measured in a similar manner to hydrogen. The addition of methane to hydrogen measurement is thought to improve the diagnostic accuracy of these breath tests by capturing the 20% to 30% of the general population who produce methane as a main byproduct of carbohydrate fermentation.[65] Methanogenic bacteria comprise a group of microorganisms that rely on the production of methane from hydrogen and carbon dioxide for their sole source of energy.[66] Because methane is not used in human beings it must be excreted, either as flatus (80%) or in the breath (20%), after its absorption into the circulation through the intestinal mucosa.[66] Although methanogenic bacteria are believed to exist in the majority of human beings, only those with a critical concentration of such bacteria produce measurable levels of methane in the breath owing to its primary excretion in flatus.[66] Based on these points, it is reasonable to suggest that an increase in breath methane excretion after substrate ingestion is indicative of SIBO. However, it must be said that the specifics in regards to the timing and magnitude of increase in breath methane excretion that constitutes SIBO remains largely unvalidated.[39] Most centers, including ours, have adopted thresholds for methane that are very similar to those applied to breath hydrogen excretion. Lactulose and glucose are the most frequently used substrates, each having distinct advantages and disadvantages. The obvious technical advantages of hydrogen and methane breath testing compared with CO_2 breath testing includes the elimination of labeled substrates, absence of a need to correct for endogenous gas production, and lower cost.

Methodologic Issues in Hydrogen and Methane Breath Testing

The performance characteristics of hydrogen and methane breath testing are variable. Much of this variability stems from a general lack of standardization for test preparation, test performance, and test interpretation. In an attempt to address this issue, the Rome Consensus Conference Expert Group recently published recommendations on patient preparation and test performance for hydrogen and methane breath testing.[39] A modified summary of their recommendations can be found in Table 2.

Table 2. Recommendations for the Preparation and Performance of Breath Testing

Preparation
Avoidance of antibiotics for 4 weeks before testing
Avoidance of bismuth for 2–4 weeks before testing
Avoidance of probiotics for 2–4 weeks before testing
Avoidance of prokinetics for 3 half-lives before testing
Avoidance of colonic purging within 4 weeks of testing
Consumption of a diet free of nonabsorbable carbohydrates (pasta, bread, fiber cereal, beans) the evening before testing
Overnight fast before testing
Avoid cigarette smoking before and during testing
Consider mouthwash with chlorhexidine solution before substrate ingestion
Test performance
All stationary gas chromatographs have proven accuracy
The Haldane–Priestly, Y-piece, or 2-bag system should be used for breath sample collection
Breath sample should be obtained after a maximal inspiration, 15-second period of apnea, and prolonged expiration
Breath sample analysis should be performed within 6 hours of collection unless stored at −20°C
Avoidance of vigorous physical exertion during testing

There is controversy regarding an increased baseline breath hydrogen level. This can occur as a consequence of poor oral hygiene; ongoing bacterial fermentation of poorly absorbed carbohydrates in the stomach, small intestine, or colon; or recent smoking. This can be minimized by avoiding a diet rich in poorly absorbed carbohydrates on the day before testing, an overnight fast, and using an oral chlorhexidine rinse as well as avoiding smoking before breath testing. Test cancelation has been recommended for a baseline breath hydrogen level higher than 16 ppm.[40] It has been argued that this finding may represent ongoing fermentation by bacteria in the small bowel, and a basal breath hydrogen level of 20 ppm or higher is indicative of SIBO.[67] To some extent, both recommendations can be correct depending on the specific clinical scenario. For example, a patient with an increased fasting breath hydrogen level who consumed a large amount of pasta the evening before or who smoked a cigarette before their test should be rescheduled. On the other hand, in our laboratory, a patient predisposed to SIBO (ie, scleroderma or diabetes mellitus) who properly prepared for the test but had an increased fasting breath hydrogen level would still undergo breath testing with interpretation of the results in the usual manner.

Lactulose Breath Test

Lactulose is a synthetic, nonabsorbable disaccharide consisting of fructose and galactose, which is used clinically as an osmotic laxative. Lactulose passes intact through the normal small intestine to the cecum where it is metabolized by colonic bacteria to short-chain fatty acids and gases including hydrogen and/or methane, which are absorbed systemically and ultimately excreted in exhaled breath. These characteristics explain the rationale upon which the lactulose breath test (LBT) was developed as a means of assessing orocecal transit time.[68]

The use of the LBT in SIBO was first reported in 1979.[61] In an individual with SIBO, the proximally displaced bacteria theoretically should lead to an early increase in breath hydrogen excretion. In the classic description of this test, a second increase in breath hydrogen excretion should occur as a consequence of lactulose fermentation in the cecum. Unfortunately, this classic "double-peak" pattern of breath hydrogen or methane excretion is more the exception than the rule. Much more commonly, a single broad peak is seen. The typical protocol entails the oral ingestion of 10 g lactulose in 200 mL water. Breath samples then are collected at 15-minute intervals for 120 to 240 minutes. A variety of end points have been used to define a positive test, including a fasting hydrogen level greater than 20 ppm, the presence of a double peak with hydrogen levels, early increase (within 90 minutes) greater than 20 ppm, or a sustained increase by greater than 10 ppm over baseline hydrogen levels (Table 3). Unlike glucose, which is avidly absorbed in the proximal small bowel, it has been argued that lactulose is more suited to identify SIBO because of its exposure to the entire small intestine. Unfortunately, there are a number of significant problems with concluding that a positive LBT represents SIBO. Chief among the concerns is that an early increase in breath hydrogen or methane excretion may be the result of rapid orocecal transit, which is more likely in patients with diarrhea.[69,70] Further, because lactulose is an osmotic laxative, it likely accelerates orocecal transit time.[71] As has been pointed out, there is no universally recognized or validated standard for a positive study. In addition, studies evaluating breath tests are difficult to interpret given the lack of a reliable and reproducible gold standard for SIBO. Not surprisingly, the accuracy of the LBT is quite variable with a sensitivity in clinical trials ranging from 17% to 68%, and a specificity ranging from 44% to 86% (Table 4).[57,70,72,73]

Glucose Breath Test

Glucose is a monosaccharide that is completely absorbed in the proximal small intestine under normal physiologic conditions. However, in the presence of SIBO, glucose is fermented by bacteria before it can be absorbed in the proximal intestine. The glucose breath test (GBT) was introduced in 1976 in the assessment of SIBO.[74] In an individual with SIBO, the proximally displaced bacteria theoretically should lead to the fermentation of glucose and a resultant increase in breath hydrogen excretion. In the classic description of this test, a single peak in the hydrogen concentration after the ingestion of glucose is indicative of SIBO. Similar to the LBT, there is no widely agreed upon standard for the performance or interpretation of the GBT. Most investigators have recommended a glucose dose ranging from 50 to 100 g, a breath sampling period ranging from 120 to 240 min, and the definition of a positive result ranging from an increase in hydrogen from 10 to 12 ppm compared with baseline. The GBT protocol recommended by the Rome Consensus Conference Expert Group consists of a glucose dose of 50 g in 250 mL of water, with breath samples collected every 15 minutes for a total of 120 minutes, and a positive test defined as an increase in hydrogen levels by 12 ppm or more from baseline[39] (Table 3). It generally is recommended that the increase in hydrogen level be sustained for a least 2 consecutive readings. The accuracy of GBT also has varied considerably in clinical trials, with sensitivity ranging from 20% to 93% and specificity ranging from 30% to 86% (Table 4).[45,48,57,72,73,75,76] Because glucose is completely absorbed in the proximal small intestine and does not reach the distal jejunum and ileum, it is conceivable that patients who have distal SIBO might be missed by the GBT. Poor

Table 3. Glucose and Lactulose Breath Test Methodology for SIBO

	Test dose	Sampling duration, *min*	Sampling interval	Measured gas, *ppm*	Definition of a positive study
Glucose	50 g in 250 mL	120	Every 15 min	Hydrogen or methane	Increase by 12 ppm or more over baseline (ideally for 2 consecutive measurements) Baseline greater than 20 ppm (controversial, possibly representing improper test preparation)
Lactulose	10 g in 200 mL	120–240	Every 15 min	Hydrogen or methane	Baseline level >20 ppm, or Presence of a double peak, or Early increase (within 90 min) >20 ppm, or Sustained increase by >10 ppm more than baseline level

accuracy also has been reported in the elderly and cirrhotic patients.[48,75,76] There also have been reports of false-positive results in the setting of rapid small-bowel transit resulting in the delivery of unabsorbed glucose to the colon.[77]

How Do the Lactulose and Glucose Breath Tests Compare?

In their consensus document, the expert working group identified 11 cross-validation clinical trials that compared hydrogen breath tests and jejunal aspirate culture, showing a median sensitivity and specificity of 62.5% and 81.8% for GBT vs 52.5% and 85.7% for the LBT, respectively.[39] From these values, the positive predictive value and negative predictive value were calculated to be 80% and 65.5% for GBT vs 61.5% and 53.6% for the LBT, respectively, yielding a diagnostic accuracy of 71.7 for GBT vs 55.1 for the LBT. Based on these results, the expert working group concluded that the GBT is the most accurate of the breath testing modalities for the diagnosis of suspected SIBO.[39]

A recent study from India compared the performance of the LBT with the GBT in 325 individuals (175 meeting Rome II criteria for irritable bowel syndrome with diarrhea and 150 age- and sex-matched controls).[78] A positive GBT was significantly more likely in diarrhea-predominant irritable bowel syndrome patients compared with controls (6% vs 0.7%; $P < .01$), whereas there was no difference in the likelihood of a positive LBT. By using the GBT as the gold standard in this study, Rana et al[78] reported a sensitivity of 64%, a specificity of 68%, a positive predictive value of 12%, and a negative predictive value of 97% of LBT in SIBO.

The existing literature and an understanding of the physiology of substrate absorption allows us to make the following statements. Because orally administered glucose is avidly absorbed by the human small intestine and does not normally reach the distal small intestine or colon, a positive GBT likely represents SIBO affecting the stomach or proximal small bowel. However, a negative GBT cannot exclude SIBO affecting the distal small bowel. From a practical standpoint, this means that the GBT favors specificity over sensitivity. On the other hand, because ingested lactulose is nonabsorbed, it theoretically should be able to detect bacterial fermentation anywhere along the length of the small intestine. Unfortunately, in the absence of SIBO, lactulose always reaches the colon, where it is fermented by resident bacteria. So, from a practical standpoint, the LBT favors sensitivity over specificity. Therefore, providers who choose the LBT have accepted the higher rate of false-positive test results and the consequent overtreating of their patients for SIBO. Those choosing the GBT have accepted the opposite calculus: the possibility of a higher rate of false-negative results, which could cause some affected patients to not be treated for SIBO.

Testing for Small Intestinal Bacterial Overgrowth in Clinical Practice

The ideal approach to a suspected case of SIBO would be confirmation of the diagnosis before the initiation of antibiotic treatment. Based on the available evidence, we recommend hydrogen breath testing using glucose as the substrate, and measuring methane along with hydrogen to improve the sensitivity of testing. Lactulose also may be considered as a substrate, although the clinician should be aware of the practical implications of this choice. If breath testing is not available, small-bowel aspiration for quantitative culture is a reasonable consideration. However, this methodology may prove to be logistically challenging if not performed with any regularity. In the event there is no testing readily available, a trial of empiric antibiotic therapy may be considered. Given the limitations, cost, and lack of availability of the current tests, it is entirely appropriate to choose this strategy in circumstances where the pretest probability is high (clear predisposing condition and appropriate clinical presentation). However, when more diagnostic precision is desired, as is often the case in day-to-day clinical practice, objective testing can provide a level of reassurance/confidence

Table 4. Performance Characteristics of Glucose and Lactulose for SIBO

	Sensitivity	Specificity	Practical points	Treatment implications
GBT	20%–93%	30%–86%	Only samples proximal small bowel, possibly missing distal SIBO Positive test likely represents SIBO False-positive results can occur with rapid small-bowel transit Accuracy may be decreased in the elderly and cirrhotic patients	Greater diagnostic certainty may lead to underdiagnosis and undertreatment of patients with SIBO
LBT	17%–68%	44%–86%	Samples entire small bowel but a positive test cannot distinguish between SIBO and rapid orocecal transit Lactulose accelerates orocecal transit The classic double peak is frequently not seen on testing	Identifies most patients with SIBO but likely leads to treatment in patients who do not have SIBO

that makes the provider and patient more comfortable with the prospect of repeated courses of antibiotic therapy. This is particularly true in an age of growing concerns over the emergence of multidrug resistant "superbugs."[5,6] In the event there is not a clear response in symptoms to treatment or the need for re-treatment arises, every effort should be made to pursue some form of objective testing to confirm the diagnosis of SIBO. We recommend referral for hydrogen breath testing or to a center with experience in small-bowel aspiration for quantitative culture.

Concluding Remarks

There remains a need for a gold standard test for SIBO. The invasive nature of testing, lack of standardization, sampling error, the need for dedicated infrastructure, and high cost cast doubt on the legitimacy of small-bowel aspiration and quantitative culture as a gold standard. Breath testing provides a solution to some of the practical issues that detract from aspiration and quantitative culture, but suffers from its own limitations. Proper patient selection, test preparation, standardized test performance, and measurement of methane improves the diagnostic accuracy of hydrogen breath testing.

Given the imperfect nature of the current tests, more work is desperately needed to better understand the role of the microbiota in the development of GI symptoms. The use of sophisticated molecular techniques to define the human microbiome in health and disease should accelerate our ability to address this issue. Another important question is whether viruses and fungi play a role in what we currently refer to as SIBO. Expanding the science will help us to understand whether future tests should focus on quantitative and/or qualitative changes in the luminal or mucosal microbiota.

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Conflicts of interest
The authors disclose no conflicts.