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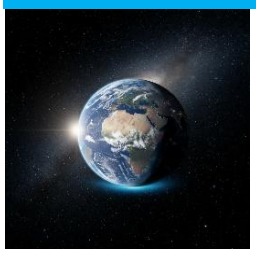

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Abstract

Background:
Small intestinal bacterial overgrowth (SIBO) is a condition characterized by an abnormal alteration and/or increase in bacterial populations within the small intestine, leading to excessive carbohydrate fermentation and gas production. Clinical manifestations are nonspecific and include abdominal pain, bloating, diarrhea, and nutritional deficiencies. Despite increasing clinical recognition, accurate diagnosis remains challenging.

Aim:
To review currently available diagnostic methods for SIBO and evaluate their diagnostic accuracy and limitations.

Material and methods:
This study was conducted as a narrative literature review. A literature search was performed in the PubMed and Scopus databases. Systematic reviews, meta-analyses, original research articles, and clinical guidelines were included. The search was conducted using a combination of keywords including: “Small Intestinal Bacterial Overgrowth”, “SIBO”, “breath test”, “hydrogen breath test”, “methane breath test”, “small bowel aspirate”, “intestinal methanogen overgrowth”, and “SIBO diagnosis”. The literature screening and selection were performed independently by the authors. Studies published in languages other than English were excluded. No time restrictions were applied to the literature search.

Results:
Breath tests, particularly the glucose hydrogen breath test (GHBT) and lactulose hydrogen breath test (LHBT), are widely used due to their non-invasive nature and availability. However, their diagnostic accuracy remains limited. Small bowel aspirate remains the diagnostic gold standard but is invasive and methodologically limited.

Conclusions:
Current diagnostic methods for SIBO have significant limitations. Diagnostic results should therefore always be interpreted within the clinical context, highlighting the need for more accurate and standardized diagnostic approaches.

Key words:
SIBO, small intestinal bacterial overgrowth, breath test, glucose breath test, lactulose breath test, small bowel aspirate

1. Introduction

Small intestinal bacterial overgrowth (SIBO) is defined as a clinical syndrome characterized by an abnormal alteration and/or increase in the bacterial population of the small intestine, resulting in excessive fermentation of carbohydrates that would normally be absorbed, with subsequent gas production. The most common symptoms of SIBO include abdominal pain, bloating, excessive gas, abdominal distension, flatulence, and diarrhea. It may also lead to

complications such as nutritional deficiencies, including deficiencies of vitamin B12, vitamin D, and iron.
Unfortunately, none of these symptoms are specific to SIBO, which can result in significant diagnostic challenges in clinical practice [1].
SIBO is identified in approximately 33.8% of patients presenting with gastrointestinal symptoms who undergo breath testing. Proton pump inhibitor (PPI) therapy has been acknowledged as a significant risk factor for the development of SIBO. The prevalence of SIBO increases with age but appears to be independent of sex or race. SIBO has been reported in 31.0%–36.7% of patients with irritable bowel syndrome (IBS), 25.4% of patients with Crohn's disease, 37.0%–73.4% of patients following bariatric surgery [2], 29% of patients with diabetes mellitus [3], and 41% of patients with gastroparesis [4]. These data underline the broad clinical relevance of SIBO across multiple disorders making accurate diagnosis of SIBO a greater importance.
Currently, several diagnostic methods are available in clinical practice. The most commonly utilized method is breath testing, which is based on the principle that human cells are incapable of producing hydrogen and methane gases. These gases are produced in the small intestine through bacterial fermentation of carbohydrates by altered intestinal microbiota. Once produced, hydrogen and methane diffuse into the bloodstream and are exhaled by the lungs, allowing their measurement in exhaled air. This physiological mechanism has enabled the development of carbohydrate substrate-based breath tests [1,5]. However, despite their broad use, the diagnostic accuracy and clinical validity of breath tests remain highly controversial, with substantial heterogeneity in methodology and interpretation criteria [6,7,8].
Despite the widespread use of breath testing, the current gold standard for diagnosing SIBO remains small bowel aspirate, where the detection of $\geq 10^3$ CFU/ml in a duodenal aspirate generally confirms the diagnosis. However, although this method offers superior diagnostic accuracy, it is associated with significant practical limitations. Collection of small intestinal fluid is typically performed during endoscopy but without any standardized techniques for aseptic collection of aspirate. Sampling of small intestinal aspirate also carries a significant risk of contamination, which may further compromise diagnostic accuracy [1,5,9].
The aim of the present article is to evaluate the available diagnostic approaches for SIBO, with particular emphasis on their diagnostic accuracy, clinical utility, and overall applicability in routine clinical practice

2. Breath tests

Hydrogen and/or methane breath tests are a widely used, inexpensive, non-invasive, and relatively easy to perform and interpret method for the indirect diagnosis of small intestinal bacterial overgrowth (SIBO). Glucose hydrogen breath test (GHBT) and lactulose hydrogen breath test (LHBT) are currently the most commonly used breath tests for this purpose. The test is based on the principle that hydrogen and methane gases are produced solely through bacterial fermentation of carbohydrates that are incompletely absorbed in the small intestine, as human cells are incapable of producing these gases. After ingestion of a carbohydrate load, the sugar is rapidly fermented by intestinal bacteria producing hydrogen, while methanogenic archaea use hydrogen as a substrate for methane production. These gases diffuse into the bloodstream and are subsequently exhaled through the lungs, allowing their evaluation in samples [10,11,12].

Proper patient preparation is essential to minimize false results. Antibiotics should be discontinued at least four weeks prior to testing, while prokinetics and laxatives should also be withheld due to their potential impact on intestinal transit and gas production and lead to false-positive results. On the day before testing, patients should follow a low-carbohydrate diet.

Smoking and physical activity should be avoided on the day of the test. Proper oral hygiene is recommended to reduce early hydrogen peaks related to oral bacterial fermentation. Attention should also be paid to the presence of "hydrogen non-producers," whose intestinal microbiota do not generate hydrogen, potentially resulting in false-negative findings [10,11].

Either glucose or lactulose may be used as a substrate. Glucose is absorbed early in the proximal small bowel—primarily in the duodenum and jejunum—so under normal conditions it rarely reaches the more distal segments of the small intestine, which may result in false-negative results when bacterial overgrowth is limited to distal segments. In lactulose breath testing (LBT), patients typically ingest 10 g of lactulose dissolved in or followed by a cup of water. Unlike glucose, lactulose passes through the small intestine without being absorbed, allowing it to interact with microbial populations present in both the small intestine and the colon. Consequently, a rapid increase in hydrogen levels during the test is generally interpreted as evidence of bacterial fermentation in the small intestine. However, such an early rise may also occur in patients with rapid orocecal transit. In glucose breath testing (GBT), patients usually ingest 75 g of glucose mixed with or followed by one cup of water. A rise in hydrogen of ≥20 ppm above baseline within 90 minutes is generally considered positive for SIBO. Methane levels ≥10 ppm are considered methane-positive and may indicate methanogenic overgrowth caused by microorganisms belonging to the Archaea domain rather than bacteria. Furthermore, SIBO should be excluded prior to performing breath tests for carbohydrate malabsorption in order to avoid false-positive results. A rise in hydrogen of ≥20 ppm above baseline during breath testing has also been used to define carbohydrate maldigestion. [12, 13, 14]

2.1 controversy

Despite widespread use, the diagnostic value of breath testing remains highly controversial. In particular, lactulose breath testing (LBT) may yield false-positive results, as an early rise in exhaled hydrogen may reflect accelerated intestinal transit rather than SIBO. [1,15]

In a systematic review and meta-analysis, the pooled sensitivity of LBT compared with small bowel aspirate was approximately 42%, with a specificity of 70%, and significant heterogeneity across included studies. The analysis also suggested a higher specificity of glucose breath testing compared to lactulose-based testing [5].
The ESNM/ANMS clinical practice update emphasized the limited correlation between breath test results and direct microbiological assessment of small intestinal aspirates, highlighting the potential for overdiagnosis when early hydrogen peaks in LBT are interpreted as diagnostic of SIBO [7].

Although breath tests are non-invasive, widely available, and inexpensive, their clinical utility is limited by methodological shortcomings. Current guidelines emphasize that test interpretation must be performed within the broader clinical context and should not serve as a standalone diagnostic criterion for SIBO [1,3]. Accumulating evidence suggests that lactulose-based testing may contribute to overdiagnosis in selected populations [16].

Notably, studies comparing glucose breath testing with small intestinal aspirate have failed to demonstrate a significant correlation between breath test positivity and actual bacterial counts [17]. Moreover, direct comparison of LBT with duodenal aspirate culture has revealed very poor agreement between the two diagnostic methods, further questioning the reliability of breath testing [18]. In a systematic review and meta-analysis, glucose breath testing demonstrated higher diagnostic performance than lactulose testing, with a pooled sensitivity of

54.5% and specificity of 83.2%, compared with 42.0% sensitivity and 70.6% specificity for lactulose breath testing [5].

Parameter	Glucose Hydrogen Breath Test (GHBT)	Lactulose Hydrogen Breath Test (LHBT
Substrate	Glucose	Lactulose
Dose	75 g glucose dissolved in water	10 g lactulose dissolved in water
Absorption in the intestine	Rapidly absorbed in the proximal small intestine (duodenum and jejunum)	Not absorbed in the small intestine
Potential diagnostic limitations	May produce false-negative results if bacterial overgrowth is limited to distal small intestine	May produce false-positive results due to rapid orocecal transit leading to an early rise in hydrogen levels
Diagnostic performance (meta-analysis)	Sensitivity 54.5%, specificity 83.2%	Sensitivity 42.0%, specificity 70.6%

3. Intestinal Methanogen Overgrowth (IMO)

Intestinal methanogen overgrowth (IMO) represents a distinct entity syndrome and complicates the conventional diagnostic framework of SIBO. In contrast to SIBO, methane is produced by archaea, particularly Methanobrevibacter smithii, rather than bacteria [19]. Patients with IMO demonstrate a higher prevalence and greater severity of constipation, along with a lower prevalence and severity of diarrhea [20]. Currently, there is no established gold standard for the diagnosis of IMO. It is typically defined as methane levels reaching ≥10 ppm at any point during breath testing [21]. Diagnosis relies exclusively on breath tests, as small intestinal aspirate is not used for IMO assessment [22]. Methanogens are present throughout multiple segments of the gastrointestinal tract. Given that conditions favoring their growth are especially prominent in the colon, a positive methane breath test does not allow precise differentiation between small intestinal overgrowth and colonic methanogen abundance [23]. Thus, IMO challenges the traditional small-intestinal framework underlying the concept of SIBO.

4. Small Bowel Aspirate

Small bowel aspirate is currently accepted as the gold standard for the diagnosis of SIBO, as it enables direct quantitative microbiological assessment of bacteria present in the proximal small intestine through culture-based techniques. At present, a bacterial colony count of $\geq 10^3$ CFU/mL obtained from an upper small intestinal sample is considered positive, replacing the previously accepted cutoff of $\geq 10^5$ CFU/mL. In healthy individuals, bacterial concentrations in the small intestine are typically $<10^3$ CFU/mL and concentrations above 10^5 CFU/mL are typically associated with conditions such as gastrectomy. However, there is no standardization of the technique used to perform the test, which may affect the reliability of results. Existing methods differ in terms of the site of aspiration, the volume of fluid collected, handling of the sample, and its subsequent culture techniques. In clinical practice, aspirates are usually obtained during upper endoscopy by advancing a catheter through the biopsy channel of the endoscope into the distal duodenum, where several milliliters of intestinal fluid are aspirated for microbiological analysis. After collection, the specimen should be transported to the microbiology laboratory as soon as possible to allow prompt processing and culture under both

aerobic and anaerobic conditions. Laboratory personnel should be informed to use appropriate culture media, and results should be reported quantitatively as colony counts expressed in CFU/mL rather than as simple positive or negative findings.
[1,14,24]

In clinical practice, aspirates are most commonly obtained from the duodenum, where bacterial counts are physiologically lower than in the jejunum [25]. It should be emphasized that quantitative CFU assessment alone may not reflect microbiological disturbances, and may overlook qualitative alterations in microbial composition, which recent evidence suggests play a key role in the pathogenesis of SIBO [26]. Furthermore, culture-based techniques may not provide a comprehensive picture of the small intestinal microbiota, as not all intestinal microorganisms are capable of growing under standard laboratory conditions [27]. Notably, in a clinical trial, no significant correlation was found between a positive result of duodenal aspirate culture and patient-reported symptoms, including diarrhea, abdominal pain, and bloating [28].

Moreover, bacterial concentration may vary depending on the segment of the small intestine and the patchy distribution of microorganisms may limit the reliability of quantitative assessment of overgrowth based on a single sample [29]. There is also a risk of contamination of the sample with oral flora during endoscopy [29]. Aseptic sample collection is crucial to minimize these limitations [30]. An additional limitation of this method is its invasive nature and high cost [13,31].

In response to these limitations, novel sampling approaches have been developed to ensure greater sterility and reduce contamination risk including the use of modern catheters that are sterile double-lumen catheters [32,33], endoscopic channel plugs [34] and other innovative technical modifications [35]. Nevertheless, despite these efforts, the small bowel aspirate—although widely considered the gold standard—remains a diagnostic method burdened with significant methodological and clinical limitations.

5. Clinical Consequences of Overdiagnosis

The increasing popularity of breath tests, combined with the absence of a reliable diagnostic gold standard, contributes to the concern about SIBO overdiagnosis [36]. This issue carries significant clinical and systemic consequences.

Antibiotic therapy plays a central role in the treatment of SIBO, despite the continued lack of high-quality evidence adequately evaluating the efficacy of antibiotics in this condition; therefore, treatment is often empirical in clinical practice [37].

A meta-analysis including randomized controlled trials demonstrated no statistically significant superiority of rifaximin over placebo or other active comparators in achieving SIBO eradication, despite an overall pooled eradication rate of approximately 60% [38]. Moreover, an additional challenge of antibiotic therapy is the need for repeated treatment due to recurrence of SIBO [39].

Importantly, both initial and repeated courses of antibiotics may be associated with potential risks, including antibiotic resistance, diarrhea, including Clostridioides difficile infection, intolerance, gut microbiota dysbiosis, and increased healthcare-related costs [40].

6. Future directions

Despite the growing number of studies on SIBO diagnostics, standardized diagnostic criteria and tests with high sensitivity and specificity remain lacking [1,14,24].

Recent research has focused on incorporating hydrogen sulfide (H_2S) measurement as an additional marker in breath testing, reflecting the activity of sulfate-reducing bacteria and potentially improving diagnostic accuracy in SIBO [41,42,43]. In this context, the concept of intestinal sulfide overproduction (ISO) has been proposed; however, its relationship with SIBO and IMO requires further validation through studies using breath testing in large clinical cohorts [44].

Advances in molecular diagnostics, particularly the application of Next-Generation Sequencing (NGS) technologies—including 16S rRNA gene sequencing and shotgun metagenomics—offer the potential for a more comprehensive characterization of the small intestinal microbiota beyond mere bacterial quantification. These approaches may overcome limitations of conventional culture-based methods [31,45].

In parallel, the development of smart capsule technologies represents a promising innovation in gastrointestinal diagnostics. These devices are capable of sensing physiological parameters such as pH, temperature, pressure, and gases within the small intestine, and may provide a less invasive alternative to traditional diagnostic strategies [46,47].

7. Conclusions

The diagnosis of small intestinal bacterial overgrowth (SIBO) remains a significant clinical challenge due to the nonspecific nature of its symptoms and the limitations of currently available diagnostic methods. Widely used breath tests, despite their non-invasive nature and broad availability, are characterized by limited sensitivity and specificity, as well as a risk of false-positive results, which may contribute to the overdiagnosis of SIBO. In contrast, small bowel aspirate, traditionally considered the diagnostic gold standard, remains an invasive and costly procedure, further limited by the lack of technical standardization and the risk of sample contamination, which significantly restricts its practical utility in routine clinical practice. Consequently, none of the currently available diagnostic methods allows for a definitive diagnosis when interpreted independently of the clinical context. Therefore, diagnostic results should always be interpreted in conjunction with the patient's clinical presentation, coexisting conditions, and potential predisposing factors for small intestinal microbiota disturbances. At the same time, the growing understanding of the complexity of the small intestinal microbiota, the development of novel diagnostic technologies, and the increasing recognition of concepts such as intestinal methanogen overgrowth (IMO) and intestinal sulfide overproduction (ISO) suggest the need to reconsider and refine the current definitions and diagnostic criteria of SIBO. Future research should focus on the development of more precise and standardized diagnostic tools, as well as on improving the understanding of the pathophysiology of small intestinal microbiota disturbances. Such advances may ultimately improve diagnostic accuracy and support a more rational therapeutic approach in patients with suspected SIBO.

Disclossure:

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