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SIBO: Challenges and Perspectives in Contemporary Gastroenterology

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Abstract

Small Intestinal Bacterial Overgrowth (SIBO) is characterized by an excessive increase in bacteria in an area that normally has a restricted microbiota. This study aims to review the clinical features, diagnostic methods, risk factors, and treatment options for SIBO, with a particular focus on its prevalence in chronic diseases such as irritable bowel syndrome (IBS) and functional diyspepsia, diabetes, and liver diseases. The review highlights the variability in diagnostic methods and the absence of a gold standard, which limits diagnostic accuracy. Among treatment options, antibiotics, probiotics, and herbal therapies (phytotherapy) show potential in symptom management. The need for standardized diagnostic criteria and further research on integrative therapies is emphasized to optimize clinical practice in the treatment of SIBO.

Keywords: Small intestine bacterial overgrowth. SIBO. Gut microbiome. Funcional gastrointestinal diseases. SIBO treatment.

Introduction

The gut microbiota is a complex ecosystem composed of trillions of microorganisms, including bacteria, archaea, viruses, and fungi, which perform essential functions for human health. These functions range from nutrient digestion and the synthesis of vitamins such as K and B to modulating the immune system and protecting against pathogens. However, when the delicate balance of this microbiota is disrupted, especially in the small intestine - an area that normally harbors a controlled number of microorganisms - conditions such as Small Intestinal Bacterial Overgrowth (SIBO) can arise **[1]**.

SIBO is characterized by an abnormal increase in bacteria in the small intestine, which leads to excessive fermentation of carbohydrates, the production of gases such as hydrogen and methane, and changes in intestinal motility. These changes are associated with a wide range of symptoms, such as bloating, pain, diarrhea, or constipation. They can contribute to systemic conditions such as chronic inflammation and increased intestinal permeability. Furthermore, the impact of SIBO extends beyond the physical realm,

significantly affecting patients' quality of life due to the recurrent nature of symptoms and their emotional and social implications [2].

Despite decades of research, the diagnosis and management of SIBO remain challenging. The absence of standardized diagnostic methods and the lack of consensus on specific criteria limit diagnostic accuracy and hinder the development of effective therapeutic strategies. While antibiotics, probiotics, and integrative therapies, such as herbal medicines, show potential in symptom management, treatment often faces high recurrence rates and limitations related to antimicrobial resistance and its impact on the healthy microbiota [2].

Given the growing relevance of SIBO in clinical practice and its association with several chronic conditions, this study aimed to critically review key aspects of this condition, including its epidemiology, clinical associations, diagnostic methods, and therapeutic approaches. By highlighting existing challenges and exploring potential solutions, we hope to contribute to a better understanding of this condition and to improving clinical management.

Development

The prevalence of SIBO varies widely across studies, primarily due to differences in diagnostic methods. Overall, SIBO is estimated to affect approximately 20% of patients with functional gastrointestinal disorders, with rates reaching up to 40% in chronic conditions such as diabetes mellitus and liver disease [3].

SIBO is particularly common in patients with irritable bowel syndrome (IBS), with a prevalence reaching 78% [4], where its presence is correlated with symptom exacerbation. Antibiotic treatment in some of these patients results in symptom improvement, suggesting a strong link between these two conditions. Several risk factors contribute to the development of SIBO. Conditions that alter the stomach's natural barrier to the environment, imposed by its acidic pH, such as prolonged use of proton pump inhibitors (PPIs), and factors that alter intestinal motility, such as abdominal surgery and ileocecal valve dysfunction, significantly increase the risk of bacterial overgrowth in the small intestine. Furthermore, aging and autoimmune diseases are also predisposing factors, especially due to changes in the gut microbiota and immune barriers [5].

The diagnosis and treatment of SIBO represent complex and evolving areas in gastroenterology, due to significant challenges in defining, identifying, and managing this condition. Despite decades of research, SIBO still lacks consensus regarding diagnostic methods and treatment criteria, which limits both clinical practice and the development of optimized therapeutic strategies. This discussion explores the main points raised in this review, focusing on diagnostic challenges, therapeutic approaches, and future research directions [5].

Diagnostic Challenges and the Need for Standardization

Standardization of diagnostic methods for SIBO is crucial because the condition involves a range of gastrointestinal symptoms, the presence and severity of which vary widely. Current approaches include breath tests (with lactulose or glucose) and jejunal aspirate culture [6]. These tests differ not only in methodology but also in the conditions under which they are interpreted, resulting in considerable discrepancies in the detection and prevalence of SIBO across different populations and clinical settings.

This variability stems from several method-specific limitations. Breath tests, for example, measure the production of hydrogen and/or methane exhaled after the ingestion of specific substrates (lactulose or glucose). However, they are subject to influences beyond bacterial overgrowth. In particular, factors such as orocecal transit time and variation in individual microbiota can significantly affect results. This means that a positive SIBO result on a breath test may reflect changes in intestinal motility, rather than the presence of excess bacteria in the small intestine [7]. Furthermore, the different substrates used (lactulose and glucose) generate distinct bacterial fermentation profiles, which can also affect the consistency of results between populations and even between patients at different times [8].

The use of jejunal aspirate culture is considered more specific, as it allows for the direct quantification of bacteria present in the small intestine. However, this technique is invasive, requiring an esophagogastroduodenoscopy, making it less practical and difficult to implement on a large scale. Even when performed, the interpretation of culture results depends on variable cutoffs for the number of colony-forming units (CFU), with thresholds inconsistent between studies and clinical guidelines [9]. In some studies, $\geq 10^3$ CFU/mL is considered indicative of SIBO, while others use higher thresholds, which alters the sensitivity and specificity of the diagnosis and can impact treatment. Furthermore, this approach is limited to detecting cultivable bacteria, overlooking a wide range of microbial diversity that could be present and is identifiable only by molecular methods, such as DNA sequencing [9].

The consequences of this lack of standardization are significant. In clinical practice, uncertain diagnoses

can lead to unnecessary antibiotic prescriptions. This occurs because false positives in SIBO tests, especially respiratory tests, can erroneously indicate the presence of bacterial overgrowth, leading to antibiotics being used in response to treat gastrointestinal symptoms that may not be related to SIBO. The indiscriminate use of antibiotics, in turn, can lead to antimicrobial resistance, harmfully alter the gut microbiota, and lead to side effects that impact the patient's quality of life **[9]**.

Therefore, to advance the management of SIBO and improve clinical outcomes, it is essential to develop diagnostic methods that are not only accurate but also practical for widespread application. The implementation of standardized protocols and the use of new diagnostic technologies, such as high-throughput DNA sequencing, could provide more reliable and detailed data on the gut microbiota. This approach would allow for a more comprehensive view of the microbiome and help more accurately identify the microbial interactions that truly influence gastrointestinal symptoms **[9]**.

Therapeutic Approaches: Efficacy and Limitations

Antibiotics are prescribed for SIBO to reduce the abnormal bacterial load in the small intestine directly. They work by destroying or inhibiting the growth of the bacteria responsible for the overgrowth, which can alleviate symptoms such as bloating, pain, diarrhea, and other discomforts associated with SIBO. In the case of SIBO, the most commonly used antibiotics include **[10]**:

- **Rifaximin:** This broad-spectrum antibiotic acts predominantly in the intestine. Due to its low systemic absorption, rifaximin concentrates in the gastrointestinal tract, reducing side effects and the potential for systemic toxicity. Rifaximin is especially effective for hydrogen-type SIBO, in which there is excessive hydrogen production by bacteria.
- **Neomycin:** Often used in combination with rifaximin for the treatment of methane-type SIBO (where bacteria produce methane, often associated with Methanobrevibacter smithii). This combination has shown greater efficacy for this specific subtype of SIBO, as methane is more associated with constipation than diarrhea, and neomycin may help reduce this effect.
- **Metronidazole and Ciprofloxacin:** Although less specific for SIBO, these antibiotics are sometimes used as an alternative, especially when an anaerobic bacterial infection is suspected. Metronidazole, for example, is effective against anaerobes and can be used in specific situations where SIBO overlaps with other intestinal dysbiosis.
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Despite the benefits, the use of antibiotics in the treatment of SIBO has several important limitations **[11]**:

- **High Recurrence:** One of the main limitations of antibiotic treatment is the high recurrence rate of SIBO. Many patients experience a return of symptoms weeks or months after completing treatment, as antibiotics do not address the underlying causes of bacterial overgrowth, such as impaired intestinal motility or reflux of colonic contents. Studies indicate that SIBO recurrence after treatment can range from 20% to 50% in the first few months, requiring repeated treatments and increased surveillance.
- **Bacterial Resistance:** Repeated antibiotic use, especially in cases of recurrent SIBO, increases the risk of bacterial resistance. Rifaximin, despite its low systemic absorption profile, still poses a risk of bacterial resistance when used repeatedly.
- **Impact on the Gut Microbiota:** Broad-spectrum antibiotics, while effective against bacterial overgrowth, can cause dysfunction in the gut microbiota as a whole. This means that, by reducing the burden of pathogenic bacteria in the small intestine, antibiotics can also negatively affect beneficial bacteria, leading to secondary dysbiosis. This loss of microbial diversity can have adverse effects on long-term gut health and predispose the patient to new microbiological imbalances.

The antibiotic approach to SIBO is an essential tool, but it should be used with caution. Given the high recurrence rate and the risks of resistance and secondary dysbiosis, antibiotic therapy is often most effective when combined with other strategies, such as dietary adjustments and the introduction of probiotics post-treatment, to help restore beneficial gut microbiota. In some cases, complementary therapies, such as the use of herbal remedies with antimicrobial properties, may also be considered to minimize the need for repeated courses of antibiotics **[11,12]**.

In the case of SIBO, the role of probiotics goes beyond replenishing beneficial bacteria. They act in a complex way, helping to control bacterial overgrowth in the small intestine and influencing the intestinal environment in several ways **[11,12]**:

- **Competition with Pathogenic Bacteria and Microenvironmental Regulation:** Probiotics occupy niches in the small intestine, competing

directly with pathogenic bacteria for nutrients and space. Certain strains, such as Lactobacillus rhamnosus and Bifidobacterium breve, produce short-chain fatty acids (SCFAs), such as lactic acid and acetic acid. These SCFAs acidify the intestinal environment, making it less favorable for pathogenic bacteria, which prefer a more neutral pH.

- **Modulation of the Intestinal Immune System:** Probiotics interact with immune cells in the intestinal mucosa, such as macrophages and dendritic cells, promoting a regulatory response that controls inflammation without damaging the intestinal barrier.
- For example, strains such as Lactobacillus acidophilus stimulate the production of anti-inflammatory cytokines (such as IL-10), which help control the inflammation associated with SIBO and may reduce symptoms such as pain and bloating.
- **Production of Antimicrobial Substances (Bacteriocins):** Some probiotic strains produce antibacterial substances, called bacteriocins, that act selectively against pathogens. Lactobacillus plantarum, for example, can produce plantacin, a bacteriocin that inhibits potentially harmful bacteria. This mechanism helps directly control bacterial overgrowth without negatively affecting beneficial bacteria.
- **Strengthening the Intestinal Barrier:** Probiotics help increase the expression of junction proteins, such as occludin and claudin, which are essential for the integrity of the intestinal barrier. Strengthening the intestinal barrier is essential for SIBO, as it prevents bacteria and toxins from entering the systemic circulation and causing systemic inflammation, which can be associated with symptoms such as fatigue and malaise.

Herbal remedies also act as a complement to conventional SIBO treatment. Compounds such as oregano oil, berberine, and garlic extract act to control bacteria and modulate the microbiota through the following mechanisms **[12,13]**:

- **Direct Antimicrobial Activity and Selective Efficacy:** Oregano oil, for example, contains carvacrol and thymol, phenolic compounds that disrupt bacterial cell membranes, leading to their death. The efficacy of these compounds is interesting in the context of SIBO, as they appear to be more selective toward pathogens, partially preserving beneficial bacteria. Berberine, found in plants such as Berberis vulgaris, interferes with bacterial protein synthesis and has been effective against a variety of bacteria, including some resistant to traditional antibiotics **[13-15]**.
- **Reduction of Inflammation and Protection of the Intestinal Mucosa:** Many herbal remedies, such as garlic extract, contain anti-inflammatory and antioxidant compounds, such as allicin. Allicin neutralizes free radicals and reduces inflammation of the intestinal mucosa, protecting against oxidative stress caused by bacterial overgrowth. This anti-inflammatory effect helps relieve symptoms such as abdominal pain and discomfort **[13]**.
- **Action on Intestinal Motility:** In SIBO, reduced intestinal motility is a risk factor for bacterial buildup. Ginger, for example, contains gingerol, which stimulates gastric emptying and promotes intestinal motility, helping to move bacteria from the small intestine to the colon, where they should reside. Improving intestinal motility is essential to preventing recurrent SIBO and can help maintain the results of antibiotic treatment **[13]**.

Prebiotics serve as nutrients for beneficial bacteria, but in the context of SIBO, their use is complex. Slow-fermenting prebiotics, such as certain types of beta-glucans, can selectively feed beneficial bacteria without exacerbating gas production. By carefully adjusting the dose and type of fiber, it is possible to promote the growth of beneficial strains without stimulating the overgrowth of fermentative bacteria in the small intestine **[13]**.

In a synergistic approach, using prebiotics with probiotics - a combination known as synbiotics - can help promote a more robust, pathogen-resistant intestinal ecosystem. This is particularly useful in cases of recurrent SIBO, where maintaining a stable microbial balance is desirable **[13,14]**. Specific diets, such as the low-FODMAP diet, an eating plan that restricts fermentable carbohydrates found in certain foods such as wheat, dairy, fruits, and vegetables -which stands for "Fermentable Oligosaccharides, Disaccharides, Monosaccharides, and Polyols" - have been used to reduce fermentation symptoms without directly affecting the microbiological balance. Furthermore, intermittent fasting strategies can improve small bowel movement, facilitating the natural "cleansing" of bacteria through the migrating motor complex (MMC) - a mechanism that transports bacteria to the large intestine and prevents bacterial buildup in the small intestine **[14,15]**.

An integrated approach, combining dietary management, probiotics, prebiotics, herbal remedies,

and other supplements, may offer a more sustainable management strategy for SIBO. Probiotics help restore beneficial microbiota and strengthen the intestinal barrier, while herbal remedies exert direct antimicrobial effects and help keep inflammation under control. However, the choice of specific probiotic strains and herbal remedies should be based on the characteristics of SIBO (such as the predominant type of exhaled gas) and individual tolerance **[15,16]**.

SIBO and Quality of Life: A Disabling Disease

The impact of SIBO on patients' quality of life is significant and, in some cases, comparable to that of debilitating chronic conditions. Studies focusing on the quality of life of SIBO patients show that associated symptoms such as bloating, abdominal pain, diarrhea, and constipation affect not only physical well-being but also emotional and social well-being. Patients with SIBO often report a decrease in quality of life due to the recurrent nature of symptoms and the limitations these manifestations impose on daily life **[16]**.

Several studies use assessment instruments such as the SF-36 (Short Form Health Survey) to measure the quality of life in SIBO patients. In the study by Pimentel et al., patients with SIBO had lower scores in the domains of physical health, vitality, and social functioning compared to individuals without SIBO. Abdominal pain and frequent discomfort directly impact the ability to perform daily activities and energy levels, impairing performance at work and in social and family relationships **[16]**.

Another study by Lauritano et al. **[17]** investigated the effect of rifaximin treatment on the quality of life of patients with SIBO, using the SF-36 questionnaire to compare pre-and post-treatment scores. The study revealed that, after a course of rifaximin, patients experienced significant improvements in physical pain, social functioning, and mental health. Reductions in bloating and diarrhea symptoms were particularly associated with improvements in physical functioning and emotional wellbeing, indicating that symptom relief has a direct and positive effect on quality of life.

A study published in Digestive Diseases explored not only the physical symptoms but also the psychosocial impact of SIBO. The study found that, before treatment, many SIBO patients experienced high levels of anxiety and stress, related to physical discomfort and the unpredictability of symptoms. After combined interventions, including a low-FODMAP diet and the use of probiotics after antibiotic treatment, patients reported improvements in symptoms and a significant reduction in anxiety and depressive symptoms, suggesting that SIBO management can also alleviate emotional distress **[18]**.

Recurrence of SIBO symptoms is a factor that also impacts quality of life. A longitudinal study by Ghoshal et al. **[19]** followed SIBO patients treated with rifaximin and probiotics for one year and found that, although many patients experience immediate symptom relief and an improvement in quality of life, recurrence rates (estimated at approximately 45% after six months) are associated with a subsequent decline in quality of life. These patients reported frustration and concern about the longterm effectiveness of treatment and the need to maintain constant monitoring of symptoms, which impacts psychological and social well-being. These studies indicate that, while treatment for SIBO can result in significant improvements in quality of life, the recurrent nature of the condition and the multidimensional impact of symptoms require effective therapeutic management through a comprehensive approach. The entire therapeutic arsenal must also be combined with ongoing psychological support for patients, helping them cope with the persistent and variable effects of SIBO on their daily lives.

SIBO and Systemic Diseases: The Connection with Chronic Diseases

The association of SIBO with metabolic and liver diseases suggests that this condition should not be considered a localized gastrointestinal problem, but rather a potential risk factor for systemic complications. Studies indicate that SIBO contributes to increased intestinal permeability and bacterial translocation, potentiating systemic inflammation. In patients with type 2 diabetes, for example, SIBO can exacerbate glycemic dyscontrol and worsen gastrointestinal neuropathy. Therefore, identifying and managing SIBO in patients with these conditions can have significant implications for chronic disease management and quality of life **[19,20]**.

A recent review article provides a comprehensive analysis of SIBO, highlighting its connection to twelve disease groups, significantly expanding our understanding of the impacts of this condition. SIBO is not limited to the gastrointestinal tract; it is associated with a wide range of conditions, including autoimmune, metabolic, cardiovascular, neurological, and even oncological diseases. This range of associations reinforces the view that SIBO should be considered a multifactorial condition with systemic effects, capable of affecting metabolism, immunity, and neurological health **[20]**.

In metabolic diseases, SIBO is widely prevalent in patients with obesity and diabetes, where bacterial overgrowth compromises glycemic control, worsening the inflammatory state and hindering glucose management. Furthermore, SIBO affects nutrient

metabolism, which can exacerbate nutritional deficiencies in these patients, contributing to an increased risk of long-term metabolic complications. In autoimmune diseases such as scleroderma, where intestinal dysmotility is common, SIBO aggravates gastrointestinal symptoms and can intensify the inflammatory response, creating a cycle of dysbiosis and inflammation that worsens the clinical picture **[20]**.

The relationship between SIBO and neurological conditions, including Parkinson's disease, is another crucial aspect raised by the same study cited above. Intestinal dysbiosis has been associated with neuroinflammation and blood-brain barrier dysfunction, mechanisms that can potentiate neurological symptoms. Therefore, by investigating the presence of SIBO in patients with neurological diseases, practitioners may be able to implement treatments that aim not only to alleviate gastrointestinal symptoms but also to stabilize the neurological condition **[20]**.

The Connection Between SIBO and Dyspepsia

A recent review article notes a significant overlap between *H. pylori* and SIBO, suggesting that both conditions can coexist and interact, complicating the clinical picture. Approximately 49.1% of patients with H. pylori infection also have SIBO, compared with 24.5% among patients without *H. pylori* infection. This association suggests that the presence of *H. pylori* may alter the gastric and intestinal environment, favoring bacterial overgrowth in the small intestine **[21]**.

Furthermore, the overlap of SIBO and *H. pylori* was associated with higher gastrointestinal symptom scores, indicating greater symptom severity compared to those with only one of the conditions. The therapeutic implications of this relationship suggest that treating dyspepsia may require a dual approach, involving both *H. pylori* eradication and SIBO evaluation and treatment. Antibiotic therapy for *H. pylori* is effective in eradicating the infection, but the impact on symptoms may be limited if SIBO is also present and left untreated. In cases where SIBO is identified, the use of small intestine-specific antibiotics, such as rifaximin, in combination with probiotics may improve microbial balance and reduce persistent dyspepsia symptoms **[21]**.

Future Research and Personalized Approaches

With advances in genetic sequencing technologies, it is possible to analyze each patient's microbial profile with greater precision, identifying the specific species involved in SIBO. This personalized medicine approach allows interventions to be targeted to the exact type of microbial imbalance, choosing the most appropriate probiotics, herbal remedies, and dietary strategies **[22]**.

Some of these strategies represent future research directions to improve SIBO treatment:

- **Use of Bacteriophages and Precision Therapies:** The use of bacteriophages – viruses that infect and destroy specific bacteria – may be a future option for modulating the microbiota in SIBO, attacking only the bacteria causing the overgrowth without affecting the beneficial microbiota **[21,22]**.
- **Fecal Microbiota Transplantation (FMT):** This procedure reintroduces a healthy microbiome into the patient's gut and can potentially help stabilize the gut microbiota and reduce SIBO recurrence. A recent randomized, controlled study, albeit with a small sample size, showed a clinical response and improved exhaled gas levels compared to placebo in patients undergoing FMT **[23]**.

Modulating the gut microbiota in SIBO goes beyond simply reducing bacterial overgrowth. It involves restoring diversity, strengthening the intestinal barrier, and balancing the immune system to prevent recurrences. An integrated and personalized approach is the future of SIBO management, providing patients with sustained improvements in gut health and quality of life.

Conclusion

It was concluded that SIBO represents a significant public health problem due to its association with several chronic diseases and its impact on quality of life. Diagnostic variability and management complexity highlight the need for standardized diagnostic criteria and more personalized treatments. Combination therapies, including probiotics, herbal remedies, and supplements, appear promising for symptom control and can be integrated with current antibiotic treatments. The lack of a gold standard for SIBO diagnosis limits the reliability of prevalence data and suggests the need for standardized diagnostic methods. Additionally, expanding understanding of the role of the microbiome and microbial interactions can open new therapeutic perspectives, improving patients' quality of life and promoting more assertive clinical practice. Finally, it is recommended that healthcare professionals consider the diagnosis of SIBO in patients with chronic gastrointestinal symptoms, adopting a treatment approach that includes integrated management of diet, prebiotics, probiotics, herbal remedies, and specific antibiotic therapies. Future research directions should include longitudinal, multicenter studies that explore the benefits of integrative therapeutic approaches, the role of the microbiome in the development and progression of SIBO, and the systemic implications of the condition. Ultimately,

a holistic approach to SIBO, combined with advances in diagnosis and treatment, can optimize clinical care and improve the health and well-being of our patients.

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