MAYO CLINIC

Small Intestinal Bacterial Overgrowth: A Primary Care Review

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Abstract

Gastrointestinal symptoms are commonly seen in the primary care setting.[1] These patient presentations can be nonspecific, leading to a broad differential diagnosis. Small intestinal bacterial overgrowth is a clinical entity that can present with many of these nonspecific gastrointestinal symptoms. The recent interest in the microbiome by those in the medical and lay communities has made this syndrome all the more relevant. This review gives the primary care provider an up-to-date understanding of the etiology, risk factors and predisposing factors, presentation, diagnostic testing, and management of small intestinal bacterial overgrowth.

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BACKGROUND

Gastrointestinal (GI) symptoms are commonly seen in the primary care setting, accounting for 15.9 million visits per year in the United States by recent estimation.[1] This statistic highlights the importance of understanding the presentation, etiologies, and management of common GI syndromes. One of these syndromes, small intestinal bacterial overgrowth (SIBO), is a diagnosis often entertained in the primary care and gastroenterology settings. This dysbiosis syndrome is most often referred to as *SIBO* but is less frequently referred to as

blind loop or *stagnant loop syndrome*.[2] The syndrome was first described by Faber in 1897 when he described a case of "blind loop syndrome" in a patient with underlying intestinal strictures.[3] Although the prevalence of SIBO has been difficult to determine, estimates range from 0% to 15.6% in healthy individuals, with increasing prevalence with age and medical comorbidities.[4]

Small intestinal bacterial overgrowth is often considered in the differential diagnosis owing to its nonspecific presentation. A consensus on the exact definition of SIBO has been difficult to establish, but SIBO can be broadly defined as excessive bacteria in the small intestine. More recently, the definition has been widely accepted as an increase in the number of bacteria in the small bowel to greater than 10^5 CFU/mL, with some arguing for a threshold of 10^3 CFU/mL.[5] The clinical implications, and even the diagnostic criteria themselves, have been debated recently. This review focuses on current understanding of predisposing risk factors, clinical manifestations, diagnostic options, and, finally, clinical management in the primary care setting.

ETIOLOGY

As with many conditions, there does not seem to be a single unifying underlying etiology for SIBO. Abnormalities in anatomy, motility, pH, and immunity are all contributors to the development of dysbiosis. These allow for local proliferation of coliform bacteria or penetration of oral-type bacteria.[6] This dysbiosis is characterized by colonic-type bacteria that ferment carbohydrates, leading to gas production.[7] Anatomical risk factors can be intrinsic, traumatic, or iatrogenic. Intrinsic anatomical risk factors of the small intestine include obstruction, diverticula, and fistulas.[8] Individuals with a history of abdominal surgical intervention can be at increased risk due to either intentional alteration in existing anatomy (ie, Roux-en-Y) or postoperative complications, including strictures and adhesions.[9] These anatomical alterations can lead to dysmotility, which can independently increase the risk of SIBO.[10]

Primary dysmotility can be seen, but secondary dysmotility is much more common. Secondary dysmotility can be a consequence of systemic disease, irradiation, or medication use. Underlying systemic diseases known to alter motility and associated with SIBO include Parkinson disease, systemic sclerosis, hypothyroidism, and diabetes mellitus.[11,12] The increasing incidence of SIBO with age is also likely secondary to changes in intestinal motility. Medications, as always, are an important consideration, and narcotics are infamous for their effects on GI motility. Another class of medications that has been implicated recently is the proton pump inhibitors due to their effect on the gastric pH barrier between the upper and lower GI tracts. There has been some controversy as to their contribution, but recent evidence suggests that there is a strong association.[13] The incidence of hypochlorhydria is also known to increase with age. This, along with changes in motility and, inevitably, polypharmacy, helps explain the increased risk of SIBO with aging.[6,14] Outside of these classic risk factors, studies have shown a higher prevalence of SIBO in patients with cirrhosis, celiac disease, morbid obesity, pancreatitis, and, somewhat controversially, irritable bowel syndrome (IBS).[4,15] This IBS controversy has implications in the primary care setting because functional GI disorders are quite common.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Often, SIBO is entertained in the differential diagnosis due to the variety of people at risk and its nonspecific presentation. The classic presentation of SIBO is that of steatorrhea, abdominal bloating, and weight loss, but this is an infrequent presentation. More commonly, patients with SIBO report bloating, flatulence, abdominal pain, and diarrhea. In more severe cases, patients can experience malabsorption leading to weight loss and malnutrition.[6] Patients with severe symptoms are at risk for a variety of deficiencies, most notably vitamins A, D, E, B_{12}, and iron. These deficiencies, in turn, can lead to either macrocytic or microcytic anemia, polyneuropathy, and metabolic bone disease.[16,17] Of note, vitamin K is usually unaffected because it is a by-product of bacterial metabolism.

The nonspecific presentation makes for a broad differential diagnosis and difficulty in making a clinical diagnosis with a high degree of pretest confidence. In fact, recent studies

TABLE 1. Risk Factors for the Development of Small Intestinal Bacterial Overgrowth

Category	Etiologies
Anatomical	• Small-bowel obstruction • Adhesions • Small-bowel diverticula • Fistula • Postsurgical anatomical alteration
Dysmotility	• Primary dysmotility (ie, gastroparesis) • Parkinson disease • Scleroderma • Hypothyroidism • Diabetes mellitus • Gastroparesis • Narcotic medications
Alteration in pH	• Achlorhydria • Proton pump inhibitors • Advanced age
Immune	• IgA deficiency • Combined variable immunodeficiency • Human immunodeficiency virus
Miscellaneous	• Cirrhosis • Morbid obesity • Pancreatitis • Irritable bowel syndrome

have shown a similar prevalence of classic symptoms in those with positive vs negative diagnostic testing.[10,18] Therefore, effective clinical tests are essential to the diagnosis of SIBO. Several testing options have been extensively studied, including therapeutic trials of antibiotics, small-bowel aspiration and culture, and breath testing, all of which have strengths and weaknesses.

A method often used is a therapeutic trial of antibiotics due to the potential for both diagnostic and therapeutic benefits. However, if patients do not respond, the diagnosis has not been ruled out. Dispensing antibiotics to patients with the nonspecific, common symptoms associated with SIBO is not without risks, including concerns regarding antibacterial stewardship, risk of unwanted adverse effects, antibiotic resistance, and *Clostridium difficile* colitis. Another concern of empirical treatment is that there are no criteria in place to define a response to therapy. This concern is especially true in patients who have other comorbidities potentially contributing to their symptoms, such as IBS. These patients may experience an improvement in symptoms, but this is likely due to the effect on colonic rather than small-bowel fermentation.[19] This can lead to recurrent antibiotic regimens and a higher risk of the detrimental effects of antibiotic agents. In the end, patients with classic risk factors for SIBO (Table 1) and compatible symptoms may be appropriate candidates for empirical antibiotic therapy as long as the providers clearly communicate the risks to their patients.

Breath testing is the most widely available, least expensive method of testing for SIBO. Breath tests detect the presence of methane and hydrogen, both of which the human body is unable to produce.[20] Metabolism of carbohydrates in the small bowel, if colonic-type bacteria are present, leads to changes in hydrogen and methane concentrations. Lactulose and glucose solutions are used as carbohydrate substrates. Before testing, patients must be off antibiotics for 2 weeks, avoid high-fiber foods (ie, vegetables and coarse breads) the day before, and fast 12 hours before administration of the substrate. Results of testing can be variable owing to a variety of host factors, such as the types and proportions of colonizing bacteria, residual carbohydrates, the absorptive capacity of the gut, and even patient age and sex.[21] Although breath testing gives an objective diagnostic threshold, there is a lack of consensus on interpretation. Studies seeking to validate breath testing have calculated sensitivities and specificities ranging from 31% to 77% and 44% to 100%, respectively,[5,22,23] leading to high false-positive rates.[24,25] These factors have led to controversy regarding the diagnostic utility of breath testing in SIBO. Glucose breath testing was endorsed as a useful testing option when there is suspicion of SIBO by the Rome Consensus Conference in 2009,[26] but more recent evidence has argued against breath testing as a diagnostic tool.[27]

Although there is no agreed-on gold standard test, the most widely accepted test of choice is small-bowel jejunal aspiration and culture. However, in practice, most aspirates are obtained from the duodenum during upper endoscopy. Quantification of bacterial growth from small-bowel aspirate is currently the most widely

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TABLE 2. Summary of the Approach to Diagnosis and Treatment of Small Intestinal Bacterial Overgrowth (SIBO)

Category	Steps
Patient factors	1. Assess for signs and symptoms consistent with SIBO • Diarrhea • Bloating • Abdominal discomfort • Bloating/increased intestinal gas • Weight loss 2. Assess for the risk factors outlined in Table 1 3. If signs and symptoms are present in patients with risk factors, consider diagnostic evaluation - No/few risk factors, benign symptoms → consider another etiology (ie, celiac disease, functional gastrointestinal syndromes) before testing for SIBO
Diagnosis and testing	1. No tests available → consider empirical antibiotic therapy 2. Breath test available → consider for first-time diagnosis 3. Upper endoscopy indicated to rule out another etiology → duodenal aspirate
Treatment	1. Eliminate risk factors as able 2. First-line therapy: ciprofloxacin 250 mg twice daily for 7 d - Second-line therapy options: doxycycline, amoxicillin, metronidazole, and rifaximin 3. Recurrent symptoms (<3 occurrences per year): repeat the same antibiotic course 4. Recurrent symptoms (>3 occurrences per year) with high diagnostic certainty: rotate antibiotics every 1-2 mo

accepted definition of SIBO itself. Therefore, aspiration and culture is the definitive test. However, even this test has limitations outside of the obvious hurdles of invasiveness of the upper endoscopy, time consumption, need for sedation, and cost. The diagnostic capability of the test is limited by a consensus on what defines a diagnosis of SIBO. Most gastroenterologists accept a threshold of bacterial growth greater than 10^5 CFU/mL, but some argue for 10^3 CFU/mL.[5] Furthermore, the test has technical limitations, including esophageal and oral bacterial contamination, leading to false-positives,[10] and the inability of the scope to reach the distal small bowel, leading to false-negatives.

The previously mentioned tests all have strengths but also severe limitations, leading to the need for better diagnostic tests. This is of particular importance in patients with IBS and other functional GI syndromes. As noted previously, empirical therapy is a less-than-desirable option, and noninvasive testing is of little, if any, utility in these patients. Recurrent invasive testing carries the concerns of both expense and safety, further limiting diagnostic options. Ongoing research is promising for techniques to improve breath testing's specificity, which may be helpful in this patient population.[27]

MANAGEMENT

The management of SIBO, much like the diagnosis, can be difficult. Antibiotics are the hallmark therapy because this is a syndrome of pathologic bacterial growth. In a recent meta-analysis, antibiotic therapy was shown to be superior to placebo use in the resolution of SIBO as measured by normalization of the breath test.[28] A variety of antibiotics have been used, the most common of which include ciprofloxacin, metronidazole, neomycin, rifaximin, and tetracycline. In the aforementioned meta-analysis, the overall rate of breath test normalization with antibiotic therapy was 50% compared with 10% for placebo. The best-studied antibiotic is rifaximin, which had similar efficacy compared with ciprofloxacin and metronidazole in the meta-analysis. Rifaximin may be preferable due to its intrinsic lack of systemic bioavailability, but the cost of rifaximin can be limiting. Commonly used regimens include ciprofloxacin 250 mg orally twice daily for 7 days, metronidazole 250 mg orally

twice daily for 7 days, and rifaximin 550 mg orally twice daily for 7 days.

In patients who have contraindications to antibiotics or who prefer to avoid antibiotics, there are other limited options. One option is the trial of an elemental diet, which includes only nutrients absorbed in the proximal small bowel. This type of diet has been shown to lead to breath test normalization and improvement in symptoms in a large proportion of patients.[29] However, the widespread use of elemental diets is unlikely given the amount of restriction required. Many have championed probiotics for the treatment of multiple GI conditions, but evidence for probiotics as a treatment strategy for SIBO is inconclusive at best, leading to little utility as a therapeutic option.[21] Herbal and homeopathic regimens have also been evaluated, but there is a lack of evidence to support a specific regimen.

Finally, SIBO is often a relapsing condition given it is a secondary process. As discussed previously herein, a variety of predisposing factors lead to the development of SIBO. Alteration of these factors is preferable (ie, removal of intra-abdominal adhesions), but most often is not possible. Recurrent infections can be treated with a repeated antibiotic course or with alternating antibiotic regimens. Studies evaluating prokinetics report promising results for the use of prokinetics to prevent recurrence, but more data are needed to determine their potential for broad use.[30]

CONCLUSION

Small intestinal bacterial overgrowth is a clinical syndrome caused by the pathologic proliferation of colonic-type bacteria in the small bowel, usually seen in patients with predisposing conditions. This can lead to nonspecific GI symptoms, leading patients to seek medical care from their primary care providers. There is a lack of agreement on the diagnostic and treatment approaches, but there are options available, and an approach is outlined in Table 2. In the community setting, empirical treatment trials and breath testing are potential options. In larger health care settings, small-bowel aspirate is available as the definitive test but comes with higher cost and risk. Regardless of the diagnostic approach, the foundation of treatment is the conscientious and discerning use of antibiotic therapy along with eliminating or altering predisposing risk factors as able.

Abbreviations and Acronyms: **GI** = gastrointestinal; **IBS** = irritable bowel syndrome; **SIBO** = small intestinal bacterial overgrowth

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REFERENCES

1. Peery AF, Dellon ES, Lund J, et al. Burden of gastrointestinal disease in the United States: 2012 update. *Gastroenterology*. 2012;143(5):1179-1187.
2. Miazga A, Osinski M, Cichy W, Zaba R. Current views on the etiopathogenesis, clinical manifestation, diagnostics, treatment and correlation with other nosological entities of SIBO. *Adv Med Sci*. 2015;60(1):118-124.
3. Neale G, Gompertz D, Schonsby H, Tabaqchali S, Booth CC. The metabolic and nutritional consequences of bacterial overgrowth in the small intestine. *Am J Clin Nutr*. 1972;25(12):1409-1417.
4. Dukowicz AC, Lacy BE, Levine GM. Small intestinal bacterial overgrowth: a comprehensive review. *Gastroenterol Hepatol (N Y)*. 2007;3(2):112-122.
5. Khoshini R, Dai SC, Lezcano S, Pimentel M. A systematic review of diagnostic tests for small intestinal bacterial overgrowth. *Dig Dis Sci*. 2008;53(6):1443-1454.
6. Sachdev AH, Pimentel M. Gastrointestinal bacterial overgrowth: pathogenesis and clinical significance. *Ther Adv Chronic Dis*. 2013;4(5):223-231.
7. Sachdev AH, Pimentel M. Antibiotics for irritable bowel syndrome: rationale and current evidence. *Curr Gastroenterol Rep*. 2012;14(5):439-445.
8. Bures J, Cyrany J, Kohoutova D, et al. Small intestinal bacterial overgrowth syndrome. *World J Gastroenterol*. 2010;16(24):2978-2990.
9. Petrone P, Sarkisyan G, Fernandez M, et al. Small intestinal bacterial overgrowth in patients with lower gastrointestinal symptoms and a history of previous abdominal surgery. *Arch Surg*. 2011;146(4):444-447.
10. Jacobs C, Coss Adame E, Attaluri A, Valestin J, Rao SS. Dysmotility and proton pump inhibitor use are independent risk factors for small intestinal bacterial and/or fungal overgrowth. *Aliment Pharmacol Ther*. 2013;37(11):1103-1111.
11. Barboza JL, Okun MS, Moshiree B. The treatment of gastroparesis, constipation and small intestinal bacterial overgrowth syndrome in patients with Parkinson's disease. *Expert Opin Pharmacother*. 2015;16(16):2449-2464.
12. Lauritano EC, Bilotta AL, Gabrielli M, et al. Association between hypothyroidism and small intestinal bacterial overgrowth. *J Clin Endocrinol Metab*. 2007;92(11):4180-4184.
13. Lo WK, Chan WW. Proton pump inhibitor use and the risk of small intestinal bacterial overgrowth: a meta-analysis. *Clin Gastroenterol Hepatol*. 2013;11(5):483-490.
14. Husebye E, Skar V, Hoverstad T, Melby K. Fasting hypochlorhydria with gram positive gastric flora is highly prevalent in healthy old people. *Gut*. 1992;33(10):1331-1337.
15. Sabate JM, Jouet P, Harnois F, et al. High prevalence of small intestinal bacterial overgrowth in patients with morbid obesity: a contributor to severe hepatic steatosis. *Obes Surg*. 2008;18(4):371-377.

16. Grace E, Shaw C, Whelan K, Andreyev HJN. Review article: small intestinal bacterial overgrowth: prevalence, clinical features, current and developing diagnostic tests, and treatment. *Aliment Pharmacol Ther*. 2013;38(7):674-688.
17. Di Stefano M, Veneto G, Malservisi S, Corazza GR. Small intestine bacterial overgrowth and metabolic bone disease. *Dig Dis Sci*. 2001;46(5):1077-1082.
18. Baker JC, Saad WJ. Common gastrointestinal symptoms do not predict the results of glucose breath testing in the evaluation of suspected small intestinal bacterial overgrowth. *Am J Gastroenterol*. 2015;(110):S1004.
19. Ringel-Kulka T, Choi CH, Temas D, et al. Altered colonic bacterial fermentation as a potential pathophysiological factor in irritable bowel syndrome. *Am J Gastroenterol*. 2015;110(9):1339-1346.
20. Levitt MD, Bond JH Jr. Volume, composition, and source of intestinal gas. *Gastroenterology*. 1970;59(6):921-929.
21. Rezaie A, Pimentel M, Rao SS. How to test and treat small intestinal bacterial overgrowth: an evidence-based approach. *Curr Gastroenterol Rep*. 2016;18(2):8.
22. Erdogan A, Lee YY, Badger C, Hall P, O'Banion ME, Rao SS. What is the optimal threshold for an increase in hydrogen and methane levels with glucose breath test (GBT) for detection of small intestinal bacterial overgrowth (SIBO)? *Gastroenterology*. 2014;146(5):S532.
23. Erdogan A, Rao SSC, Gulley D, Jacobs C, Lee YY, Badger C. Small intestinal bacterial overgrowth: duodenal aspiration vs glucose breath test. *Neurogastroenterol Motil*. 2015;27(4):481-489.
24. 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(2):203-208.
25. Posserud I, Stotzer PO, Bjornsson ES, Abrahamsson H, Simren M. Small intestinal bacterial overgrowth in patients with irritable bowel syndrome. *Gut*. 2007;56(6):802-808.
26. Gasbarrini A, Corazza GR, Gasbarrini G, et al. Methodology and indications of H2-breath testing in gastrointestinal diseases: the Rome Consensus Conference. *Aliment Pharmacol Ther*. 2009;29(suppl 1):1-49.
27. Sellin JH. A breath of fresh air. *Clin Gastroenterol Hepatol*. 2016;14(2):209-211.
28. Shah SC, Day LW, Somsouk M, Sewell JL. Meta-analysis: antibiotic therapy for small intestinal bacterial overgrowth. *Aliment Pharmacol Ther*. 2013;38(8):925-934.
29. Pimentel M, Constantino T, Kong Y, Bajwa M, Rezaei A, Park S. A 14-day elemental diet is highly effective in normalizing the lactulose breath test. *Dig Dis Sci*. 2004;49(1):73-77.
30. Pimentel M, Morales W, Lezcano S, Sun-Chuan D, Low K, Yang J. Low-dose nocturnal tegaserod or erythromycin delays symptom recurrence after treatment of irritable bowel syndrome based on presumed bacterial overgrowth. *Gastroenterol Hepatol (N Y)*. 2009;5(6):435-442.