# Management of Small Intestinal Bacterial Overgrowth

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Similar to that of all mammals, the human gastrointestinal tract is colonized by 100 trillion bacteria shortly after birth. Remarkably, in the open-tube arrangement of the intestine, this bacterial population is tightly compartmentalized to the distal gut. Contamination of the small intestine with colonic bacterial flora or small intestinal bacterial overgrowth (SIBO) has been understood previously as a complication of uncommon conditions associated with obvious intestinal stasis. However, SIBO has also been found in 78% to 84% of patients with the common condition of irritable bowel syndrome (IBS). In this paper, the diagnostic and treatment approaches to SIBO are reconsidered within the larger framework of the patient with IBS.

## Introduction

Small intestinal bacterial overgrowth (SIBO) occurs when the proximal ileum, jejunum, or duodenum becomes colonized by large numbers of endogenous symbiotic bacterial flora normally restricted to the colon and terminal ileum. It is thus differentiated from infection by an invading gut pathogen such as *Campylobacter jejuni*. Gastrointestinal symptoms of SIBO include bloating; nausea; cramping and pain; excessive flatus; and altered bowels, including diarrhea, constipation, or alternating patterns, particularly in response to a meal. Extraintestinal manifestations may include flulike symptoms of general malaise, fatigue, anxiety, depression, myalgia, and impaired cognition. Malnutrition may result as the patient seeks to avoid precipitating symptoms by fasting. The problem of diminished intake is further exacerbated by maldigestion related to the bacterial overgrowth because bacterial deconjugation of bile acids impairs micellar formation leading to steatorrhea.

Symbiotic bacteria are normally compartmentalized to the distal gut. Both the ileocecal valve and the normal interdigestive motility, notably phase III of the migrating motor complex (MMC), contribute to this localization. This powerful, lumen-obliterating "intestinal housekeeper wave" normally propels the luminal content distally to clear the proximal gut of food debris and bacteria. When the ileocecal valve is compromised, as in ileal disease (*eg*, celiac, Crohn disease, ulcerative colitis) or resection, or when phase III of the MMC is abnormal, for example, in irritable bowel syndrome (IBS) [1••], distal gut bacteria normally resident in the colon may migrate to the proximal gut, which is normally considered sterile in the healthy person. This proximal expansion of gut bacteria or SIBO permits an abnormal interaction between gut bacteria and meals, resulting in the production of large volumes of gas as byproducts of bacterial fermentation. These gases then contribute to discomfort and distention. In addition, by producing osmotically active metabolites, fermentation accelerates transit of the luminal content and contributes to diarrhea. The defensive response of the small intestine to SIBO may include hyperperistalsis and hypersecretion, which may further worsen the diarrhea. Up to 78% to 84% of IBS patients have SIBO, as evaluated by lactulose breath test, a noninvasive, indirect diagnostic test [2,3••]. In IBS patients who excrete only methane, constipation is the biologic effect of methane in slowing intestinal transit.

When a patient complains of postprandial nausea, bloating, pain, and diarrhea, the diagnostic challenge is to differentiate between rapid transit and SIBO because these two possibilities share similar symptoms. Rapid transit results in early fermentation of a maldigested and malabsorbed meal because there is insufficient time to complete assimilation of the meal content. In contrast, SIBO may result in early fermentation of a meal and impairment of digestion and absorption. These two causes may also happen concurrently. In patients with a history of intestinal resection, rapid transit may be further complicated by concurrent SIBO. Conversely, rapid transit may arise as a result of SIBO when the small intestine becomes distended by gas that is produced by bacterial fermentation. In that case, the treatment should be directed at eradicating SIBO, which will, in turn, eliminate the secondary dysfunction of rapid transit. In patients with IBS, however, the problem is SIBO rather than accelerated transit. We have shown that the abnormal hydrogen profiles of constipation-predominant (slow transit) and diarrhea-predominant (fast transit) IBS patients overlap almost perfectly, demonstrating that the abnormally premature rise of

breath hydrogen concentration in IBS patients is explained by expansion of gut bacterial flora proximally rather than accelerated transit [3••].

## Diagnosis and Treatment

Accurate direct identification of SIBO requires thorough sampling along a 500-cm length of the small intestine and the ability to grow the bacteria that are present in the gut. Because an upper gastrointestinal endoscope cannot reach past the ligament of Treitz (~60-cm length of proximal small intestine) and a lower gastrointestinal endoscope cannot reach proximally past the terminal ileum, the majority of the 500-cm length of the small intestine cannot be sampled. Thus, direct aspiration obtains samples that reflect only a single or very few locations along the entire gut and are not representative of the entire intestine [4]. Even if the technical challenge of sampling the luminal content along the full length of the small intestine could be overcome, the culture result of the aspirate might still be unrevealing. Of the estimated 500 to 1000 species that inhabit the human gastrointestinal tract, less than 20% can be grown in laboratory culture. Accordingly, our current microbiologic methodologies are quite limited, leading to a significant underestimation of the number of bacteria and species actually present [5–7]. Although we are still limited by a significant gap in our knowledge of human commensal flora, more reliable approaches that bypass the need to culture are possible. These include polymerase chain reaction (PCR), quantitative real-time PCR (QRT-PCR), or fluorescence in situ hybridization (FISH) to identify genera or individual species by 16S ribosomal RNA (rRNA) fingerprinting. Although these methods can identify the presence of nonculturable bacteria [5,7,8], often, these bacteria have not even been named or characterized. Once again, the limitations of even these non-culture techniques include reliance on direct sampling and availability of known 16S rRNA sequences for only a minority of species. Furthermore, the composition of gut flora is highly variable between individuals [9], limiting the development of a "gold standard" or "normal control" gut population profile.

A hallmark of SIBO is abnormal fermentation of the luminal content and production of gaseous byproducts of bacterial fermentation. The noninvasive lactulose breath test (LBT), which relies on fermentation of a carbohydrate substrate, provides an indirect approach to the diagnosis of SIBO that is not limited by the difficulties of aspiration and culture. Although carbohydrates such as glucose or lactose may be used for breath hydrogen testing, they have the distinct disadvantage of being readily assimilated and removed from the intestinal lumen, which greatly increases the chance of a false-negative result. In addition, LBT may falsely suggest lactase deficiency when the actual problem is SIBO [10•]. In contrast, lactulose, a poorly digested disaccharide, is available to gut bacteria along the entire length of the intestine and is readily fermented by gut bacteria to produce hydrogen and, in turn, converted to other gases ($H_2S$, $CH_4$, and others). These gases enter the blood circulation and then the pulmonary bed and are excreted principally by the lungs. Because not every enteric bacterial species produces hydrogen and a considerable amount of hydrogen is converted to other nonexplosive gases by hydrogen-consuming bacteria, simultaneous monitoring of the production of other gases, such as $CH_4$ and $H_2S$, by methanogenic or sulfate-reducing bacteria, may reveal SIBO in patients who do not excrete $H_2$ in their breath. It is important for the clinician to know the actual pattern of breath excretion of these gases in order to accurately interpret the breath test. An important limitation of interpreting LBT only on the basis of the hydrogen excretion profile is that breath excretion of intestinally derived gases reflects only net excretion and does not account for metabolic consumption of hydrogen within the intestinal lumen by gut bacteria. Thus, the hydrogen excretion profile may, occasionally, be surprisingly low in a patient whose symptoms are highly suggestive of SIBO in whom consumption approaches production, resulting in a net hydrogen excretion that may measure as low as zero over the entire testing period. A frequently cited limitation of LBT is the acceleration of transit by lactulose. Although lactulose can increase luminal osmotic load to accelerate transit, this effect is dose dependent [11] and does not affect the ability of the observer to compare two test results and detect a change. The usefulness of the LBT result is therefore greatly enhanced when the breath gas profiles before and after antibiotic treatment are compared, with a focus on the relative change between the two. When an abnormal profile becomes normalized after a 10-day course of antibiotics, SIBO, rather than accelerated transit, would be the correct diagnosis. The treatment response of suspected SIBO may therefore provide confirmatory evidence for the diagnosis. A normal breath hydrogen profile is based on the appearance of a clearly distinct hydrogen peak no earlier than 90 minutes and a peak concentration no greater than 20 parts per million. Any other pattern should be considered abnormal. Breath hydrogen testing measurement of SIBO has a reproducibility of 92%, compared with 38% for culture of a direct luminal aspirate [4]. By providing the patient with a diagnosis based on an abnormal LBT, unnecessary diagnostic testing and misdirected treatments can be avoided. The LBT is an objective measure of success or failure of a single course of treatment in achieving the goal of normalizing the breath hydrogen profile. The therapeutic and diagnostic endpoint is reached when LBT is normalized and the patient's symptoms are resolved. At that time, the cause and effect relationship between SIBO and the patient's symptoms can be firmly established.

## Therapeutic Strategies

Small intestinal bacterial overgrowth represents a disruption in the normal ecology of approximately 100 trillion resident microbes of the gut (500–1000 species), a condition quite different from gastrointestinal infection resulting from invasion by a single pathogenic species, such as acute *Salmonella* gastroenteritis.

Probiotics are cultures of a handful of normally benign or beneficial species of enteric bacteria that are taken orally in an attempt to re-establish "normal" gut ecology in IBS, inflammatory bowel disease, and SIBO. However, this therapeutic approach is necessarily limited because we are ignorant of the numbers and distribution of species within the complex ecology of the gut. Hope remains that one or more species will be identified that can shift microbial ecology in the human gut to a more benign state. For example, a group at the University of Cork recently identified a *Bifidobacterium infantis* subspecies [12] that reduces symptoms of IBS in some patients and is associated with a normalization of the ratio between the level of an anti-inflammatory and a proinflammatory cytokine [13••]. This approach provides a hopeful glimpse of a future in which commensal gut bacterial populations are better characterized and probiotic blends might be formulated to modulate specific, desirable host responses.

Based on 15 years of experience in treating SIBO in IBS patients we have developed several management strategies. Short-term normalization of symptoms can be achieved by treating patients with an elemental diet for 2 weeks [14••], a 10-day course of traditional systemic antibiotics [3••], or a 10-day course of a nonabsorbable antibiotic. The likelihood of success in normalizing the LBT with these approaches ranges from 5% to 80%.

Patients should be educated about their problem with SIBO, which is characterized by a chronic relapsing clinical course. As such, symptoms will recur after successful treatment. However, this condition can be successfully managed to delay the time to relapse in many patients. Without intervention, relapse may occur in as short a time period as 2 months.

Symptoms during treatment may paradoxically worsen transiently before they improve. Different therapeutic approaches are associated with different patterns of exacerbation and subsequent improvement. With a course of traditional systemic antibiotics, symptoms may worsen for a couple of days 3 to 4 days into the treatment, followed by resolution of symptoms, which may be delayed until 2 weeks after completion of treatment for gastrointestinal symptoms and up to 2 to 3 months for extraintestinal symptoms after completion of the antibiotic course. Treatment with an elemental diet and a nonabsorbable antibiotic often produces an exacerbation of symptoms after about a week, followed by normalization.

Because there is a lag in the resolution of symptoms, symptomatic improvement alone cannot be used as the primary indicator of successful treatment when the patient is seen 2 weeks after completion of a therapeutic intervention. This underscores the need for LBT as an objective measure of successful treatment. LBT results are therefore a biologic marker that can be used to guide the management of patients with SIBO.

The goal for treatment is normalization of subjective and objective criteria. Both gastrointestinal and extra-intestinal symptoms and LBT must be normalized for treatment to be considered successful. If normalization of LBT is not achieved after a full course of treatment, a different therapeutic approach should be tried until the LBT is normalized.

Some patients with IBS may have abnormal interdigestive intestinal motility that can be diagnosed with small intestinal manometry and treated as a separate issue [1••]. In these patients, it may be possible to use prokinetic agents to normalize the dysmotility and achieve a delay in the time to relapse of SIBO. This possibility should be tested in a randomized treatment trial. However, such an intervention should be done only after normalization of SIBO symptoms and LBT gas profile. When a recurrence is noted, the same cycle of diagnosis and treatment may be repeated. In chronic intestinal disease or anatomic alteration, such as multiple small intestinal diverticulae, it may not be possible to delay the time to relapse with a prokinetic agent. In such cases, the patient may need periodic, rotating courses of antibiotics to maintain remission.

## Conclusions

The patient's hope and the physician's goal is that treatment will extend well beyond reduction of symptoms to full restoration of normal functioning with complete elimination of symptoms. Normalization is a goal that may be within reach for disorders that are driven by SIBO, such as IBS [15••]. Currently available treatment modalities offer the encouraging possibility of elimination of symptoms or a complete remission. Modest success is also possible in delaying the time to relapse of SIBO with the use of prokinetic agents in patients with infrequent or absent intestinal housekeeper wave. Whereas further research is underway to understand gut ecology and to develop non-antibiotic approaches in treating SIBO, accurate diagnosis and monitoring of therapy with LBT puts within reach the hope for significant improvement in the management of this important problem.

## Acknowledgments

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