Small Intestinal Bacterial Overgrowth
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Suggested CDR Learning Codes: 3005, 3020, 5220; Level 3
Suggested CDR Performance Indicators: 8.1.5, 8.3.1, 10.1.2

The importance of friendly bacteria in the large intestine is becoming clearer. In fact, the recent focus of research on the beneficial bacteria in the large intestine and their relationship with health outcomes has been hard to ignore. Study after study indicates that the gut microbiome is intricately related to our health and well-being. However, the extent of the benefits of the gut bacteria is dependent on several conditions. One of these is the location of the bacteria, which under normal circumstances is primarily the large intestine, where friendly gut bacteria ferment carbohydrates and synthesize micronutrients.

Several physiologic mechanisms keep the gut bacteria concentrated in the large intestine, and with good reason. If one or more of these mechanisms is compromised, bacteria may migrate and proliferate in the small intestine, leading to the undesirable condition known as small intestinal bacterial overgrowth (SIBO). SIBO may result in symptoms that affect nutritional status and quality of life, such as diarrhea, cramping, gas, and nutrient malabsorption. Unfortunately, because the symptoms are nonspecific, SIBO easily goes undiagnosed. With the rising prevalence of intestinal disorders and their association with nutritional status, RDs are important players in identifying SIBO as a condition to rule out.

Inherent Protection
The bacterial profiles between the small and large intestine present an interesting divergence. Normal bacterial counts in the colon are up to 1,014 colony-forming units (CFU)/mL. Bacteria in the colon are mainly from two bacterial phyla, Bacteroidetes and Firmicutes, but there are about 400 species represented in the gut flora profile. Colonic bacteria are beneficial in that they support the normal development of the gastrointestinal (GI) tract and immune system and synthesize micronutrients.\(^1\) Research in the last decade has pointed toward other positive health implications of colonic bacteria such as weight balance and reduced chronic disease risk.\(^2\)\(^-\)\(^4\)

Compared with the small intestine, the colon is an excellent environment for bacterial growth. The relatively low motility in the colon makes it easy for bacteria to proliferate, since bacteria are better able to survive in stagnant areas. The high amount of secretions in the small intestine that contain antimicrobial properties and make it difficult for bacteria to grow are largely absent in the large intestine. In stark contrast to the number of those in the colon, normal bacterial counts in the small intestine are relatively minimal—at or below 103 to 105 CFU/mL.\(^5\)

The stomach often is sterile due to its very low pH, and some individuals may have sterile duodenums based on measurements of bacteria levels in duodenal aspirations. Bacterial
counts typically are very low in the duodenum and increase progressively toward the ileum. The distal ileum normally has more bacterial growth compared with the upper small intestine, because of the proximity to the colon and because intestinal secretions are lower. Not only does the amount of bacteria differ, but the composition of the normal bacteria in the small intestine also is different from that in the colon. Usually, the bacteria in the small intestine are aerobic, while those in the colon are anaerobic. In SIBO, however, the bacteria that overpopulate the small intestine are those typically found in the colon—the anaerobic bacteria. This difference is helpful because if anaerobic bacteria are identified in the small intestine, it suggests abnormal growth. In light of the controversy over the number of bacteria in the small intestine that is normal, another differential to determine abnormal growth is helpful.

The balance of gut bacteria is heavily tipped toward the large intestine by physiologic factors, most important of which is intestinal motility. Motility drives intestinal contents toward the colon, preventing stasis, or inactivity, which allows for microbial proliferation. Peristaltic contractions, the pattern of intestinal motility following consumption of a meal, are triggered by the presence of food in the proximal small intestine and occur every few seconds to mix the food with digestive secretions as the bolus of food moves toward the large intestine. The migrating motor complex, the pattern of intestinal motility that happens between meals, sweeps the GI tract at 90-minute intervals.

Structurally, the ileocecal valve maintains one-way flow of contents from the small intestine to the large intestine, preventing the backflow of colonic contents, including bacteria, into the ileum. Chemically, gastric acid secretion keeps the pH of the stomach very low, at an approximate pH of 2. While pancreatic bicarbonate secretion neutralizes the acidic content from the stomach as it enters the duodenum, the pH is still low enough in the proximal small intestine to defend against microbial proliferation. Finally, while the mechanism is unclear, pancreatic and biliary secretions also protect against bacterial growth in the small intestine. Collectively, these defense mechanisms, intestinal motility, gastric acid secretion, pancreatic and biliary secretions, and the ileocecal valve, prevent bacterial overgrowth in the small intestine.

Pathophysiology and Clinical Manifestations
SIBO is defined as a bacterial count greater than 105 CFU/mL in the small intestine. As mentioned, the bacteria that overpopulate the small intestine are usually of the type normally found in the colon, which are anaerobic bacteria that ferment carbohydrates. Adverse effects, such as diarrhea, bloating, abdominal pain, malabsorption, and food intolerances may occur at counts greater than 103 CFU/mL. The symptoms and severity vary among individuals, and this variability, along with the nonspecificity of symptoms, makes it a condition that easily can evade diagnosis.

Gas, Bloating, and Diarrhea
Many of the clinical symptoms of SIBO—gas, bloating, and diarrhea—are a result of small intestinal bacterial fermentation, or the metabolism, of carbohydrates. Bacteria need energy to survive, and the source of this energy for bacteria that populate the GI tract often is the carbohydrate consumed in the diet. Byproducts of bacterial fermentation include gas, short chain fatty acids, and other osmotically active metabolites. In the large intestine, in which absorption rather than secretion is the primary action, bacterial fermentation is normal and generally isn’t a problem. If this occurs in the small intestine, in which secretion rather than
absorption is the primary action, bacterial fermentation is more likely to cause pain and discomfort. Osmotically active metabolic byproducts such as alcohol and fatty acids that are produced by the bacteria also may stimulate intestinal secretion and cause osmotic diarrhea. Because these symptoms are nonspecific, though, it may be difficult to determine whether they’re caused by SIBO, a condition that caused a predisposition to SIBO, or a different condition altogether.

Food Intolerances
The development of food intolerances, such as lactose and fructose intolerance, is another clinical manifestation of SIBO. This may occur in SIBO for several reasons, related to disrupted absorption. Epithelial cells that line the small intestine become inflamed, causing the villi to become shortened and reducing the absorptive surface area. Diarrhea may degrade the lining of the small intestine and disrupt the mucus layer. Injury to the absorptive epithelial cells of the small intestine has been documented in SIBO. In addition, bacteria may adhere to epithelial cells and secrete enterotoxins that damage the cells. And bacteria may be proteolytic, meaning protein digesting; enzymes lining the border of the small intestine such as lactase that digest carbohydrates may be destroyed by bacteria, thus preventing normal digestion and causing malabsorption. Collectively, inflammation during SIBO interferes with normal absorption, increasing the risk of malnutrition.

Fat Malabsorption
Moreover, fat malabsorption may occur with SIBO. Bacteria in the small intestine inactivate bile acids, thereby interfering with fat digestion and absorption. Under normal conditions, following consumption of a meal, bile acids are secreted into the duodenum through the bile duct. Bile acids are necessary for digestion of long chain fatty acids (the most predominant type of fat in the diet, consumed in the form of triglycerides). Bile acids emulsify the dietary lipid droplets to increase the surface area of the fat molecules to which digestive enzymes have access. Once lipase and other fat-digesting enzymes hydrolyze (cleave off, yielding water molecules) fatty acids off of triglycerides, the free fatty acids can be absorbed into the intestinal cells. The fatty acids pass through the intestinal cells for eventual entry into the bloodstream. Without adequate bile acids, dietary triglycerides remain largely undigested and pass on into the colon, leading to fat malabsorption and steatorrhea. Because bacteria in the small intestine inactivate bile acids, fat malabsorption and subsequent malnutrition may develop. Fat malabsorption is associated with energy deficiency due to the calories from fat that aren’t absorbed. Over time, fat malabsorption also can lead to a deficiency of micronutrients, since bile also is needed for absorption of the fat-soluble vitamins, A, D, E, and K.

Malnutrition
Along with fat malabsorption, carbohydrate malabsorption may occur due to digestion by the bacteria and decreased disaccharidase activity. Protein and energy malnutrition are possible but rare with SIBO. Protein losses may occur due to enteropathy and decreased absorptive function. Vitamin B12 deficiency is associated with SIBO because the anaerobic bacteria metabolize B12 before its absorption by the host. In addition, iron deficiency may occur due to increased sloughing of the epithelial cells that line the small intestine.

Unfortunately, the symptoms of SIBO are self-perpetuating. The metabolic byproducts of the bacteria damage the lining of the small intestine, causing carbohydrate malabsorption, and, thus, the greater availability of carbohydrate for the bacteria to ferment, allowing the cycle to
continue. Eradication of the bacterial overgrowth and resolution of the root cause of SIBO may interrupt this cycle and allow symptoms to resolve.

Causes
Several different clinical conditions or diseases may interfere with one or more of the defense systems that protect against bacterial overgrowth in the small intestine. These conditions fall under three categories—motility disorders, interference with antibacterial defenses, and structural abnormalities.

Normal intestinal motility is critically important for the protection against SIBO, and motility interference is one of the most common causes of SIBO.\textsuperscript{17} Supporting evidence indicates that when motility is compromised, SIBO is more likely to develop.\textsuperscript{17} Autonomic neuropathy in diabetes is associated with delayed gastric emptying, and reduced intestinal motility is common in diabetes. Two studies found that approximately one-tenth to two-thirds of patients with diabetes (depending on diagnosis methodology) had SIBO.\textsuperscript{18,19} A study of subjects with irritable bowel syndrome (IBS) and SIBO found that those with persistent overgrowth had lower frequency of major migratory complex contractions.\textsuperscript{20} The use of narcotics, which are known to slow GI motility, also is associated with SIBO.

Normal gastric pH is very low, which protects against bacterial growth. Reduced acidity in the stomach, or gastric achlorhydria, due to proton pump inhibitor use is associated with SIBO. Pancreatitis and cystic fibrosis also are associated with SIBO because of reduced pancreatic secretions, which have antibacterial properties. One study found that 15% of subjects with chronic pancreatitis had SIBO compared with 1% of healthy controls without pancreatitis.\textsuperscript{21} Another study found that 56% of patients with cystic fibrosis had SIBO compared with 20% in a control group.\textsuperscript{22} AIDS and other immunodeficiency syndromes are associated with increased risk of SIBO.\textsuperscript{23,24}

Structural abnormalities such as small intestine diverticula, tumors, strictures, and adhesions may cause SIBO by obstructing normal flow of intestinal content. Intestinal resection, particularly with the loss of the ileocecal valve that prevents backflow of colonic contents, is associated with SIBO.\textsuperscript{25}

Age also is a risk factor for SIBO, in part because age is associated with the above predisposing conditions. Up to 50% of those older than age 75 may have SIBO.\textsuperscript{26}

Understanding the conditions that predispose people to SIBO is important in order to know when to evaluate for SIBO. Some predisposing conditions, such as adhesions or strictures, often can be resolved, which increases the likelihood of successful intervention without recurrence.

Estimated Prevalence
The prevalence of SIBO is unknown because different methods of diagnosis may yield differing results, and because it’s likely to be underdiagnosed.\textsuperscript{13} Individuals with SIBO may be asymptomatic, or the nonspecific symptoms may be attributed to the underlying disease rather than the SIBO itself. Studies have found a range of 4% to 18% prevalence in healthy people.\textsuperscript{27,28}
Studies of individuals with an IBS diagnosis found that 30% to 85% of subjects had tests that indicated the presence of SIBO.\textsuperscript{27,29,30} A meta-analysis with 1,921 pooled subjects found that compared with healthy controls, those with IBS had almost four times the risk of SIBO.\textsuperscript{31} While this finding was statistically significant, there was significant heterogeneity among the results of the pooled studies.

A variety of other studies measured SIBO prevalence in association with various clinical conditions. Of the individuals with a celiac disease diagnosis that didn’t respond to a gluten-free diet, 11% had evidence of SIBO based on intestinal aspirate.\textsuperscript{32} In another study, 49% of those with liver cirrhosis tested positive for SIBO.\textsuperscript{33} One study found that 39% of patients with gastroparesis tested positive for SIBO.\textsuperscript{34} Obesity also may increase SIBO risk based on a study that found positive diagnoses in 17% of morbidly obese patients compared with 2.5% of healthy controls.\textsuperscript{35}

Unfortunately, prevalence estimates are based on relatively small samples of subjects. Obtaining a better understanding of true prevalence is important to understand the real impact that testing and treatment may have on nutritional status and quality of life. Increased awareness, standardized testing, and larger studies will facilitate more accurate measures of prevalence.

**Assessment and Diagnosis**

The actual prevalence of SIBO is unclear partly because of the different methods used to identify SIBO. A typical progression toward diagnosis usually begins when a clinician with awareness of SIBO suspects it in a patient or client. SIBO should be ruled out for any patient or client who complains of GI discomfort with typical symptoms. Physical examination and discussion with the patient may indicate nonspecific findings of SIBO, including abdominal distention, and complaints of diarrhea, abdominal pain and discomfort, and bloating. Nonspecific laboratory tests that may suggest SIBO include anemia, low B\textsubscript{12} levels, and elevated serum folate and vitamin K.

The two main methods to test for SIBO are quantitative culture of intestinal aspirations (a direct measure) and breath tests (an indirect measure). The direct measure of bacterial content in a jejunal aspirate is the gold standard for diagnosis.\textsuperscript{36} A catheter is used to collect a sample of the contents of the jejunum, which is cultured to determine bacterial count in CFUs. Although this has been the gold standard, it isn’t the most commonly used method to diagnose SIBO. Direct cultures aren’t routinely performed for SIBO diagnosis for several reasons. The collection procedure can be expensive and invasive; a single aspirate could miss the overgrowth, which can be sporadic; overgrowth can be distal and difficult to reach by endoscopy; the aspirate could be contaminated by bacteria from the mouth or pharynx, and many of the bacteria in the aspirate won’t grow in the culture (which could lead to a falsely negative test result).\textsuperscript{13} But there’s another more common method of diagnosis that’s often less expensive and more reliable called hydrogen breath testing.

In this procedure, an individual consumes a dose of glucose and/or lactulose. Intestinal bacteria metabolize the carbohydrate and as a result produce hydrogen as a byproduct, which is expelled in the breath and quantified. If there’s an unusually high amount of bacteria in the small intestine, hydrogen in the breath will be abnormally elevated.\textsuperscript{37} However, hydrogen breath testing isn’t a perfect measure, because if the dose of glucose is absorbed too quickly
in the proximal small intestine, bacterial overgrowth in the distal intestine won’t be detected since the bacteria wouldn’t be exposed to the glucose. Moreover, if the subject has rapid gut transit, as in short bowel syndrome, the glucose may reach the colon rapidly and cause elevated hydrogen in the breath to a point at which it’s misinterpreted as SIBO.13

Ultimately there’s no perfect test to confirm the presence or absence of SIBO, due to the inherent complexity of the intestinal environment. In some cases, empirical treatment with antibiotics indicates whether SIBO is present; however, the use of antibiotics when SIBO isn’t clearly indicated by a diagnosis is controversial.

**Intervention**

Intervention for SIBO will be different for each individual, but there are three main concepts involved in treatment. One is the identification and resolution of the predisposing condition that led to the development of bacterial overgrowth. The second is the eradication of the bacteria, and the third is support for any nutritional deficiencies that may have developed.6 Depending on the etiology of the bacterial overgrowth and the predisposing condition, SIBO may or may not be able to be resolved. Intestinal strictures or adhesions that are the root cause of SIBO can be removed, which would improve flow and motility. If a medication may be causing reduced motility and subsequent SIBO, other medications should be investigated as replacements. If a patient is on proton pump inhibitors to reduce gastric acid, other reflux interventions should be investigated. Resolution of the predisposing condition likely reduces risk of recurrence. Prokinetic agents may be helpful but there isn’t much supporting evidence. Avoiding foods that SIBO bacteria thrive on also may be helpful. Lactose avoidance and reducing or eliminating fermentable oligo-, di-, and monosaccharides may decrease symptoms.6 If fat malabsorption is a symptom, dietary fat avoidance and the use of medium chain triglycerides are helpful.

Most individuals diagnosed with SIBO use antibiotics to eliminate the bacterial overgrowth. There’s no consensus on which antibiotic is the most effective. In the last several years, Rifaximin has been a common choice because it generally has minimal side effects, doesn’t promote resistance, and has been shown to have a higher success rate than other antibiotics.38,39 If symptoms continue, breath testing can be repeated to determine if the overgrowth is still present and if a different antibiotic is worth trying. In some cases, the overgrowth may be eliminated but symptoms may persist due to other conditions. SIBO may recur depending on whether the root cause was resolved, and retreatment or long-term antibiotics may be necessary.40

The third pillar of SIBO treatment is to correct any nutritional deficiencies. The patient should be evaluated for malnutrition. Iron and vitamin B12 levels should be checked. Interventions to resolve nutritional deficiencies should be evidence-based and tailored to the individual.

Pre- and probiotics may or may not be helpful in SIBO cases. Of the few studies that evaluated the use of pre- and probiotics, one found that antibiotics with probiotics were more effective than those with prebiotics, although this finding wasn’t significant.41 Another study found that patients with longstanding bacterial overgrowth treated with lactobacillus were no better off than when they received a placebo.42 Until more definitive data exist on the use of pre- and probiotics for SIBO, general recommendations can’t be made.
**Relationship With IBS**

Untangling the relationship between SIBO and IBS is difficult since these conditions are characterized by similar symptoms. While it’s clear that people with IBS are more likely to have SIBO compared with controls, the estimates of SIBO in IBS vary widely among studies. A recent review article examined these studies to determine why there was such a wide range of estimated prevalence of SIBO in people with IBS.\(^4^3\) One explanation may be the heterogeneity of IBS itself; one study showed that those with diarrhea-predominant IBS (21.9%) were more likely to have SIBO compared with those with nondiarrheal IBS (8.5%).\(^4^4\) Individuals with IBS who have excess gas and bloating also may be more likely to have SIBO.\(^4^3\) Another possible explanation is the variety of methods to diagnose SIBO. One study compared the breath test with culture and found that the sensitivity of the breath tests was poor, suggesting that studies that use breath tests may be underestimating prevalence.\(^4^5\)

Some researchers believe IBS is caused by SIBO; however, this hasn’t been substantiated by research.\(^1^3\) IBS is diagnosed based on symptoms and by ruling out other conditions. If an individual with IBS and SIBO diagnoses were treated with antibiotics, retested for SIBO with negative results, and had simultaneous resolution of IBS, this may suggest that SIBO was the root cause of all symptoms, but not necessarily. A study by Pimental and colleagues found that out of 47 subjects with IBS and SIBO based on hydrogen breath tests, 25 had successful eradication following antibiotics, and one-half of these 25 no longer met criteria for an IBS diagnosis.\(^4^6\) Regardless of whether SIBO causes IBS, it’s important to prevent a misdiagnosis of IBS when in fact an individual has SIBO. The authors of the review article discussed above recommend that the IBS diagnostic algorithm include the direction that SIBO be ruled out before an IBS diagnosis.\(^4^3\) Increased awareness of SIBO and standards of SIBO diagnosis will help reduce the cases of SIBO that are misdiagnosed as IBS.

**Practical Application**

Most important, clinicians need to be aware of SIBO as a possible cause of GI symptoms. With the rise in incidence of celiac disease, nonceliac gluten sensitivity, inflammatory bowel disease, and IBS diagnoses, it can be difficult to determine what exactly may be causing adverse GI symptoms for which a patient would seek help. SIBO should be on the list of conditions to rule out in favor of other diagnoses. Fortunately, SIBO is fairly responsive to treatment, resolving symptoms and increasing quality of life. Thus, RDs should be aware of this condition and understand when it’s appropriate to evaluate a client/patient for this potential diagnosis. If SIBO is misdiagnosed as IBS, patients could go through the agonizing process of trying to determine which foods are causing their symptoms and end up avoiding certain foods, which has nutritional risk in and of itself. Thus, awareness of SIBO could dramatically improve the health and well-being of clients and patients.

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**References**


Examination

1. Which of the following is a defense mechanism for preventing bacterial overgrowth in the small intestine?
   A. Minimal gastric acid secretion to maintain a high pH
   B. Patterns of intestinal motility that keep intestinal contents moving in one direction
   C. The pyloric sphincter to prevent backflow of duodenal contents into the stomach
   D. Surgical manipulation to slow gastrointestinal (GI) transit

2. Why is the breath test preferred over culture of intestinal aspiration for small intestinal bacterial overgrowth (SIBO) diagnosis?
   A. The breath test is more invasive and expensive.
   B. Intestinal aspiration might perforate the GI tract.
   C. Not all bacteria that may be in the intestinal aspiration content will grow in culture, potentially resulting in an inaccurate count of colony-forming units.
   D. The breath test is the gold standard.

3. Why might estimates of SIBO prevalence in the irritable bowel syndrome (IBS) population vary widely?
   A. IBS is a heterogeneous condition, and SIBO might be more prevalent in a certain type of IBS.
   B. There’s no association between SIBO and IBS so there wouldn’t be a consistent prevalence from one group of IBS subjects to the next.
   C. Some researchers use lactulose, and some use lactose for the breath test.
   D. Instrumentation to measure hydrogen in the breath isn’t calibrated.

4. Why is malnutrition a concern for people with SIBO?
   A. Malnutrition is not a concern for people with SIBO.
   B. Because people with SIBO have other concurrent conditions causing malnutrition.
   C. Because people with SIBO are typically in extreme positive energy balance resulting in obesity.
   D. Because the small intestinal bacteria may digest dietary carbohydrate, and because disaccharidase activity may be reduced, resulting in malabsorption.

5. Why is bacterial growth in the small intestine a problem?
   A. Bacterial overgrowth in the small intestine increases risk of heart disease.
   B. Excess small intestinal bacteria inactivate bile acids, which are necessary for fat digestion.
   C. The bacteria produce osmotically active byproducts, which cause intestinal absorption and subsequent constipation.
   D. The bacteria are more likely to be absorbed and cause sepsis.
6. Which of the following are causes/predisposing factors of SIBO?
A. Excess consumption of dietary carbohydrates and subsequent intakes of B vitamins that are above the upper limit
B. Use of proton pump inhibitors, use of narcotics, older age, intestinal resection, pancreatitis, small intestinal strictures, and adhesions
C. Chronic diseases such as cancer, heart disease, obesity, and diabetes
D. Modifiable behavior including smoking and alcohol consumption

7. What are the approaches for SIBO treatment?
A. Surgical correction of anatomical abnormalities to allow for normal intestinal motility.
B. There’s no treatment aside from pain control.
C. Correct the underlying cause, treat with antibiotics, and resolve any nutritional deficiencies.
D. Enteral or parenteral nutrition for macro- and micronutrient deficiencies.

8. Which of the following is true about SIBO and IBS?
A. People with IBS are more likely to have SIBO than are people without IBS.
B. All people with IBS have SIBO.
C. SIBO and IBS have distinct symptoms.
D. All people with SIBO have IBS.

9. Why did researchers suggest that SIBO be ruled out before making an IBS diagnosis?
A. Because many individuals with IBS were misdiagnosed with SIBO
B. Because IBS is diagnosed by a laboratory test, which has results that may be similar to those in SIBO
C. To prevent a misdiagnosis of IBS when in fact SIBO, which is treatable, is the cause of symptoms
D. To increase the specificity and sensitivity of the IBS diagnostic algorithm

10. Which of the following cases would be worth testing for SIBO?
A. 80-year-old female with diarrhea-predominant IBS on long-term proton pump inhibitors
B. 25-year-old male with GI distress and alcoholism
C. 42-year-old female with cystic fibrosis and pancreatic insufficiency
D. 14-year-old male with short bowel syndrome and anemia