Small Intestinal Bacterial Overgrowth: A Comprehensive Review

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Abstract: Small intestinal bacterial overgrowth (SIBO), defined as excessive bacteria in the small intestine, remains a poorly understood disease. Initially thought to occur in only a small number of patients, it is now apparent that this disorder is more prevalent than previously thought. Patients with SIBO vary in presentation, from being only mildly symptomatic to suffering from chronic diarrhea, weight loss, and malabsorption. A number of diagnostic tests are currently available, although the optimal treatment regimen remains elusive. Recently there has been renewed interest in SIBO and its putative association with irritable bowel syndrome. In this comprehensive review, we will discuss the epidemiology, pathogenesis, clinical manifestations, diagnosis, and treatment of SIBO.

Small intestinal bacterial overgrowth (SIBO) is defined as the presence of excessive bacteria in the small intestine. SIBO is frequently implicated as the cause of chronic diarrhea and malabsorption. Patients with SIBO may also suffer from unintentional weight loss, nutritional deficiencies, and osteoporosis. A common misconception is that SIBO affects only a limited number of patients, such as those with an anatomic abnormality of the upper gastrointestinal (GI) tract or those with a motility disorder. However, SIBO may be more prevalent than previously thought. This apparent increase in prevalence may have occurred, in part, because readily available diagnostic tests have improved our ability to diagnose SIBO. This comprehensive review will discuss the epidemiology and pathophysiology of SIBO; review common clinical presentations, diagnostic tests, and their limitations; and discuss currently available treatment options.

Methods

Ovid MEDLINE and PubMed databases were used to search the published literature. For Ovid MEDLINE (1966 to December 2006, English language only) three primary search terms (bacte-

rial overgrowth, small intestine overgrowth, and small intestine bacterial overgrowth) were individually coupled with a larger number of secondary search terms (epidemiology, incidence, prevalence, populations at risk, symptoms, pathogenesis, pathophysiology, inflammation, malabsorption, complications, vitamin deficiency, motility disorders, scleroderma, gastroparesis, chronic intestinal pseudo-obstruction, celiac disease, irritable bowel syndrome, renal failure, cirrhosis, alcohol abuse, elderly, aging, diabetes, hypochlorhydria, surgery, malnutrition, diarrhea, evaluation, diagnosis, breath testing, duodenum, jejunum, aspirates, breath tests, lactulose, treatment, antibiotics, rifaximin, tetracycline, metronidazole, ciprofloxacin, amoxicillin/clavulanate, probiotics, duration, resistance). For PubMed (no time limit), a similar search process was followed. All identified articles were then manually searched for other relevant studies. Only published manuscripts are included in this review; abstracts are not included.

Definition

SIBO is defined as a bacterial population in the small intestine exceeding 10^5–10^6 organisms/mL.[1,2] Normally, less than 10^3 organisms/mL are found in the upper small intestine, and the majority of these are Gram-positive organisms.[3] In addition to the absolute number of organisms, the type of microbial flora present plays an important role in the manifestation of signs and symptoms of overgrowth.[4] For example, a predominance of bacteria that metabolize bile salts to unconjugated or insoluble compounds may lead to fat malabsorption or bile acid diarrhea. In contrast, microorganisms that preferentially metabolize carbohydrates to short-chain fatty acids and gas may produce bloating without diarrhea because the metabolic products can be absorbed. Gram-negative coliforms, such as *Klebsiella* species, may produce toxins that damage the mucosa, interfering with absorptive function and causing secretion, thereby mimicking tropical sprue.

Prevalence

An extensive literature search was unable to identify a study evaluating the incidence of SIBO in healthy volunteers. Only limited data are available regarding the prevalence of SIBO in healthy populations. In a study of 294 nonhospitalized older adults in which 34 younger adults (mean age 33.6 years) served as healthy controls, the prevalence of SIBO, as determined by glucose breath test, was 5.9% in the control group versus 15.6% in the older group.[5] A study of healthy older adults from Japan (mean age 74.7 years) found no patient with SIBO using a glucose breath test;[6] an Australian study detected SIBO from duodenal aspirates in 0% of healthy controls (mean age 59), although 13% were positive for SIBO using a lactulose breath test.[7] Healthy elderly volunteers from the United Kingdom had a 14.5% prevalence rate for SIBO based on a positive glucose breath test.[8] Finally, in a study of 111 patients with irritable bowel syndrome (IBS), 20% of healthy age- and sex-matched controls were found to have an abnormal lactulose breath test suggestive of SIBO.[9] In summary, although data are limited, the prevalence rates of SIBO in young and middle-aged adults appear to be low, whereas prevalence rates appear to be consistently higher in the older patient (14.5–15.6%); these rates, however, are dependent upon the diagnostic test used (see below).

Pathogenesis

SIBO develops when the normal homeostatic mechanisms that control enteric bacterial populations are disrupted. The two processes that most commonly predispose to bacterial overgrowth are diminished gastric acid secretion and small intestine dysmotility. Disturbances in gut immune function and anatomical abnormalities of the GI tract also increase the likelihood of developing SIBO. Once present, bacterial overgrowth may induce an inflammatory response in the intestinal mucosa, further exacerbating the typical symptoms of SIBO. Although not universally seen,[10] overgrowth of small bowel intestinal flora may result in microscopic mucosal inflammation. Analysis of small bowel biopsies in elderly patients with bacterial overgrowth revealed blunting of the intestinal villi, thinning of the mucosa and crypts, and increased intraepithelial lymphocytes, all of which reversed with antibiotic treatment.[11]

Gastric Acid

Gastric acid suppresses the growth of ingested bacteria, thereby limiting bacterial counts in the upper small intestine. Diminished acid production (hypochlorhydria) is a risk factor for SIBO, and can develop after colonization with *Helicobacter pylori* or as a consequence of aging.[12-14] Interestingly, bacterial overgrowth can lead to a false positive *H. pylori* diagnosis using urea-based testing given the presence of urease-positive bacterial strains.[15] Inhibition of acid secretion via histamine type 2 receptor blockers (H2RAs) or proton-pump inhibitors (PPIs) may predispose to SIBO, although conflicting results are found in the published literature. Treatment with H2RAs led to SIBO in 18 adult patients, as measured by bile acid breath tests and jejunal aspirates.[16] A prospective study of 47 outpatients treated with either omeprazole (20 mg/day) or cimetidine (800 mg/day) found that bacterial overgrowth was present in 53% of patients who received omeprazole,

compared to 17% who received cimetidine ($P<.05$).[17] Twenty patients treated with 4 weeks of omeprazole had a significant increase in duodenal bacterial counts (compared to baseline) as measured by endoscopic aspirate.[18] These disparate results may represent a true medication effect or, alternatively, reflect the small number of patients studied and differences in assay techniques.

Motility Disorders

Normal GI motility involves a complex, tightly coordinated series of events designed to move material through the GI tract. During periods of fasting, a migrating motor complex (MMC) develops approximately every 90–120 minutes to sweep residual debris through the GI tract. Several studies have demonstrated that abnormalities in the MMC may predispose to the development of SIBO.[19-21] Postprandial peristalsis includes irregular, high-amplitude contractions in the stomach (to assist with trituration and gastric emptying).[22] Gastroparesis, a chronic disorder of delayed gastric emptying, can develop secondary to long-standing diabetes, connective tissue disorders, a prior viral infection, and ischemia.[23] Impaired gastric peristalsis can lead to SIBO due to stasis of food and bacteria in the upper GI tract.

Small bowel motility disorders also predispose to the development of SIBO, because bacteria may not be effectively swept from the proximal bowel into the colon. Disruption of the MMC is associated with bacterial overgrowth in an experimental model.[24] Patients with cirrhosis and portal hypertension (compared to patients without portal hypertension) had retrograde pressure waves in the proximal duodenum, clustered contractions, and abnormalities of the MMC leading to a greater prevalence of SIBO.[25] Patients with chronic renal failure have neuropathic-like motor abnormalities in the small intestine and are more likely to develop bacterial overgrowth.[26] Neuropathic processes, such as chronic intestinal pseudo-obstruction (CIP), and myopathic processes, such as scleroderma and polymyositis, are likely to be associated with SIBO.[27] In a small group of systemic sclerosis patients with greater than 105 colony-forming units/μL via duodenal aspiration, 7 out of 8 patients had positive lactulose breath tests.[28] Other conditions that affect small bowel motility, which predispose patients to develop SIBO, are shown in Table 1.

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

- **Structural/Anatomic**
  - Small intestine diverticula
  - Small intestine strictures (radiation, medications, Crohn's disease)
  - Surgically created blind loops
  - Resection of ileocecal valve
  - Fistulas between proximal and distal bowel
  - Gastric resection
- **Motility Disorders**
  - Gastroparesis
  - Small bowel dysmotility
  - Celiac disease
  - Chronic intestinal pseudo-obstruction
- **Irritable Bowel Syndrome**
- **Metabolic Disorders**
  - Diabetes
  - Hypochlorhydria
- **Elderly**
- **Organ System Dysfunction**
  - Cirrhosis
  - Renal failure
  - Pancreatitis
  - Immunodeficiency states
  - Crohn's disease
  - Celiac disease
  - Malnutrition
- **Medications**
  - Recurrent antibiotics
  - Gastric acid suppression

Structural Abnormalities of the GI Tract

Structural abnormalities in the GI tract provide an ideal environment for bacterial colonization and overgrowth. GI tract surgeries that create a blind loop (eg, a Billroth II procedure or a Roux-en-Y anastomosis; Figures 1 and 2) predispose to bacterial stasis and overgrowth due to abnormal motility and ineffective clearance of retained food and secretions.[29] Patients who have undergone jejunoileal bypass, an end-to-side enteroenteric anastomosis, or the creation of a Koch distal ileal pouch, are also at risk to develop SIBO.

Small bowel diverticula occur in approximately 1–6% of the population, based on autopsy studies and a variety of radiographic studies. They are generally incidental, asymptomatic, and small in size.[30] However, large duodenal and jejunal diverticula can harbor bacteria and lead to symptoms of SIBO. Strictures of the small intestine, which can develop after surgery, after radiation, in association with Crohn's disease, or secondary to medication use, also predispose to the development of SIBO.[31] Finally, resection of the ileocecal valve increases the risk of developing SIBO, because retrograde movement of bacteria from the colon into the small intestine can now readily occur. One study of Crohn's patients found that resection of the ileocecal valve significantly increased the prevalence of SIBO from 18% to 30%.[32]

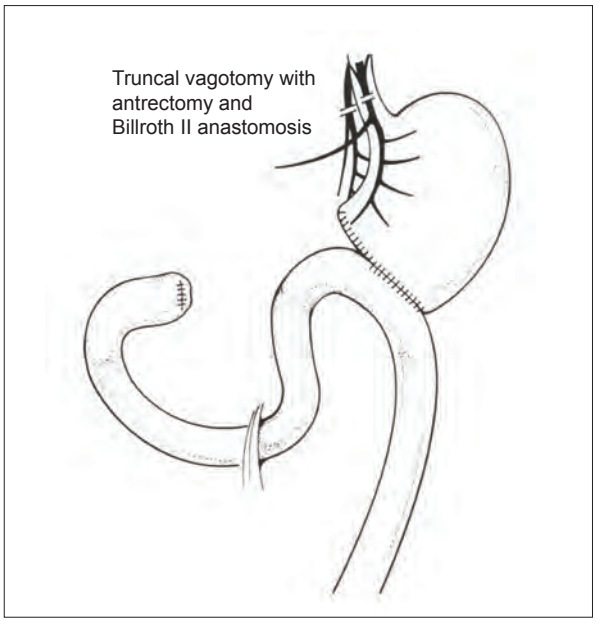

Figure 1. Billroth II anatomy that may predispose some patients to small intestinal bacterial overgrowth.

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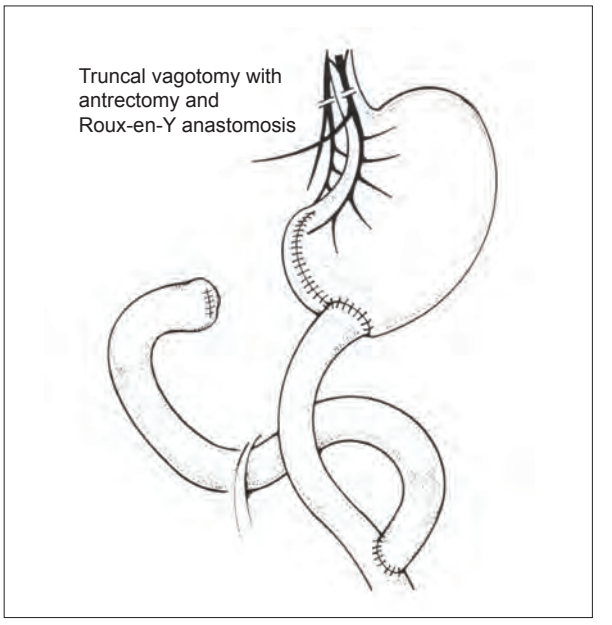

Figure 2. Roux-en-Y anastomosis that may predispose some patients to small intestinal bacterial overgrowth.

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Immune Function

Patients who are immunodeficient, whether due to an abnormal antibody response or T-cell response, are prone to bacterial overgrowth.[33] Patients with SIBO (compared to those with normal jejunal aspirates) were more likely to have abnormalities in intestinal mucosal immunity (evidenced by increased luminal immunoglobulin A [IgA] concentrations and lamina propria IgA plasma cell counts).[34,35] Patients with deficiencies in humoral or cellular immunity do not appear to be predisposed to SIBO, as they have normal intestinal microflora.[36,37]

Populations at Risk

SIBO can develop in a variety of patient populations (Table 1). Risk factors are reviewed below, along with a discussion of the prevalence of SIBO in these specific situations, where data are available. A review of the literature failed to identify any study evaluating the incidence of SIBO in specific populations.

Irritable Bowel Syndrome

There is a significant amount of interest on the possible role of SIBO in the generation of IBS. Many IBS symptoms are nonspecific (bloating, distention, cramping, abdominal discomfort) and can mimic symptoms of SIBO.[38] In an uncontrolled study, Pimentel and colleagues found that 78% of 202 patients who met the Rome I criteria for IBS had an abnormal lactulose breath test suggestive of SIBO.[39] A blinded, randomized study found that 84% of patients who met Rome I criteria for IBS had an abnormal lactulose breath test consistent with SIBO, compared to 20% of healthy volunteers,[9] while another group reported a prevalence rate of 65% in 98 consecutive IBS patients.[40] In contrast, other research groups have failed to replicate these interesting findings. In 85 consecutive patients meeting the Rome II criteria for IBS, none had SIBO using glucose breath testing;[41] Walters and Vanner reported that only 10% of their IBS patients (Rome II criteria) had SIBO using the lactulose breath test.[42]

Given these widely discordant results, there is considerable debate in the scientific community about the potential relationship between IBS and SIBO. Delayed transit, disordered motility, or abnormalities in the MMC, all of which can occur in IBS patients, could potentially predispose these patients to SIBO.[36,43]

Metabolic Disorders

Long-standing and poorly controlled diabetes can injure the enteric nervous system leading to disordered GI

motility. Diabetic gastroparesis and neuropathic small bowel motility disorders are both associated with SIBO (see above). A recent study found that SIBO was present in 43% of diabetic patients with chronic diarrhea, and 75% had a significant improvement in their symptoms after being treated with antibiotics.[44] Additionally, in a group of 82 diabetic patients, of those who had carbohydrate malabsorption on an oral glucose tolerance test, 75% were diagnosed with SIBO.[45]

Aging

Mitsui and colleagues, using a glucose breath test, found that 33% of disabled older adults had SIBO.[6] Parlesak and coworkers, also using a glucose breath test, showed that 15.6% of older, nonhospitalized adults had SIBO;[5] Lewis and associates reported similar data (14.5%).[8] Although it is commonly believed that SIBO develops in the elderly because of age-associated decline in GI tract motility, most studies have not shown a significant decrease in GI motility with aging.[46,47] Rather, other pathophysiologic processes likely play a role, including medications and agents that slow GI motility, a decline in mobility, the onset of new diseases (eg, diabetes), dietary changes that lead to malnutrition, and changes in gut immune function.

Celiac Disease

Long-standing celiac disease can disturb gut motility, leading to small intestine dysmotility.[48] A study of 15 celiac patients with persistent symptoms despite adherence to a strict gluten-free diet found that 66% had bacterial overgrowth on lactulose breath testing.[49] All of these patients noted a resolution of their symptoms after being treated for bacterial overgrowth.

Chronic Diarrhea

A recent study evaluated the role of SIBO in 87 consecutive patients with chronic diarrhea. All patients underwent extensive testing to exclude structural, metabolic, inflammatory, and acute infectious processes. In addition, celiac disease and inflammatory bowel disease were ruled out by both laboratory and endoscopic testing. The authors reported that SIBO was present in 33% of the patients using small bowel culture, compared to 0% in healthy controls.[7]

Other Organ Dysfunction

GI symptoms are common in patients with renal failure and include nausea, early satiety, bloating, and abdominal pain. Although often attributed to uremia, these symptoms may reflect altered gut motility and SIBO. A study of 22 patients with chronic renal failure found that 50% had evidence of a neuropathic motility disorder, as measured by antroduodenojejunal manometry.[25] SIBO was more prevalent in patients with neuropathic motility disorders (55%) compared to those without (18%; P=.07).

Table 2. Symptoms Associated With Bacterial Overgrowth

- Abdominal pain/discomfort
- Bloating
- Abdominal distension
- Diarrhea
- Flatulence
- Weakness

Surgically induced obstructive jaundice can lead to bacterial overgrowth and increased bacterial translocation from the GI tract in laboratory animals.[50] Clinical studies have shown that patients with advanced liver disease are more likely to have abnormalities in gut motility compared to those with lower Child-Pugh scores.[24,51,52] These include abnormalities in the MMC and an increase in the frequency of clustered contractions—both of which may promote bacterial stasis and the development of SIBO—in 31–68% of patients.[53-56] SIBO does not appear to be an independent risk factor for liver injury, however.

Recent animal studies have demonstrated that acute pancreatitis can alter the MMC[57] and that acute necrotizing pancreatitis disturbs the jejunal MMC leading to SIBO.[58] A study of 35 patients with chronic pancreatitis and pancreatic insufficiency found that 34% had SIBO, as determined by a glucose breath test.[59]

Chronic alcohol use may predispose patients to SIBO. A study from Sweden compared 22 alcoholics with epigastric pain and nausea to 12 nonalcoholic patients with dyspeptic symptoms.[60] Using both gastric and duodenal biopsies and aspirates, bacterial overgrowth was identified in 90% of alcoholics compared to 50% of controls (P<.01). Of note, 7 of the control patients had used acid suppressants, which may explain the high rate of bacterial overgrowth in the control population.

Finally, antibiotics can alter the normal balance of gut flora leading to changes in the population of bacteria within the GI tract. No prospective studies in this area were identified in the literature.

Clinical Manifestations

Symptoms of SIBO are nonspecific and include bloating, abdominal distension, abdominal pain or discomfort, diarrhea, fatigue, and weakness. The frequency and severity of symptoms likely reflect both the degree of bacterial overgrowth along with the extent of mucosal inflamma-

tion. However, symptoms may also reflect the underlying cause of SIBO (eg, small bowel dysmotility). Other symptoms can reflect complications of SIBO, including malabsorption, nutritional deficiencies, and metabolic bone disorders (Table 2).[61] The nonspecific nature of these complaints makes SIBO difficult to distinguish clinically from other disease entities, such as IBS, lactose intolerance, or fructose intolerance. No study has evaluated the specificity of these symptoms; therefore, objective testing is recommended.

Complications

Complications of SIBO range from mild, including diarrhea and minimal vitamin deficiencies, to severe, including malabsorption and neuropathies due to fat-soluble vitamin deficiencies. The nutritional consequences of SIBO result from maldigestion and malabsorption of nutrients in the intestinal lumen (Table 3).[62] The latter occurs secondary to microscopic damage to the small intestinal mucosa which diminishes the absorptive capacity of the microvilli.

Fat malabsorption occurs as a result of bacterial deconjugation of bile salts. In addition, free bile acids are toxic to the intestinal mucosa, resulting in mucosal inflammation and malabsorption.[63,64] Deconjugated bile salts are reabsorbed in the jejunum rather than the ileum, leading to impaired micelle formation, fat malabsorption, and deficiencies in fat-soluble vitamins (A, D, E, and K). Fortunately, symptoms rarely develop; however, in severe cases night blindness (vitamin A), osteomalacia and tetany due to hypocalcemia (vitamin D), prolonged prothrombin times (vitamin K), or neuropathy, retinopathy, and impairments in T-cell function can occur.[59]

Carbohydrate malabsorption develops as a result of premature breakdown of sugars by bacteria in conjunction with decreased disaccharidase activity secondary to disruption of the intestinal brush border.[65] Protein malabsorption can occur because of digestion by bacteria, whereas protein-losing enteropathies can develop as a result of mucosal damage.[66]

A common complication of bacterial overgrowth is cobalamin (vitamin B_{12}) deficiency. Patients with normal intestinal enteric flora rely on gastric intrinsic factor to bind to vitamin B_{12} to permit absorption in the ileum. An animal model of SIBO demonstrated competitive uptake of vitamin B_{12} by bacteria (especially aerobes).[67] Human subjects with atrophic gastritis and bacterial overgrowth absorbed significantly less protein-bound vitamin B_{12} compared to controls, although this was reversed with antibiotic therapy.[68] Folate levels can be normal but frequently are elevated due to increased synthesis of folate by small bowel bacteria.[69,70]

Table 3. Clinical Manifestations of Small Intestinal Bacterial Overgrowth

- Weight loss
- Steatorrhea
- Vitamin/mineral deficiency
  - Fat-soluble vitamins (A, D, E, K)
  - Vitamin B_{12}
  - Iron
- Vitamin excess
  - Folate
- Hypoproteinemia/hypoalbuminemia
- Decreased xylose absorption

Diagnosis

The diagnosis of SIBO is controversial. There is substantial disagreement in the literature regarding which test is the most appropriate in either the clinical or research setting. Two tests are commonly employed: bacterial culture and breath tests.

The most direct method of assessing the bacterial population is to perform anaerobic and aerobic colony counts of small bowel luminal contents;[2] however, this method is saddled with several technical hurdles. First, the small bowel must be intubated. In years past, a long tube was passed under fluoroscopic guidance and fluid aspirated through the tube. Today, few diagnostic centers use this cumbersome, time-consuming method, and instead, a catheter is passed into the distal duodenum through an endoscope and fluid aspirated for culture. The cost of endoscopy, as well as its low but measurable risk, makes this approach less than ideal. Second, many bacterial species do not grow in routine culture media, and quantitative culture may underestimate the bacterial population. Third, there are multiple problems inherent in performing this procedure including contamination of the endoscope and catheter as the instrument is passed through the GI tract, difficulty aspirating a sufficient sample, and insufflation of air into the lumen, which prevents accurate sampling. Finally, regardless of which approach is used to culture luminal contents, prompt and proper specimen handing poses yet another hurdle.

The challenges of directly measuring small bowel bacterial contamination led to the development of several indirect tests to diagnose SIBO.[71] Breath testing is now the predominant method to evaluate patients for potential overgrowth because of its simplicity, safety, and lack of invasiveness. These methods all rely on the modification of a substrate by bacteria. The substrate most commonly

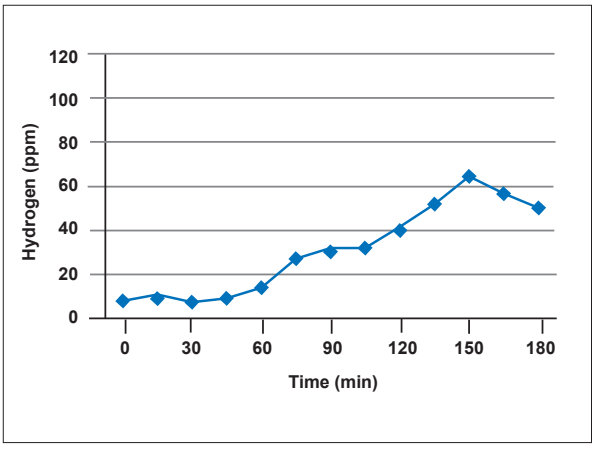

Figure 3. Lactulose breath test in a patient without evidence of small intestinal bacterial overgrowth.

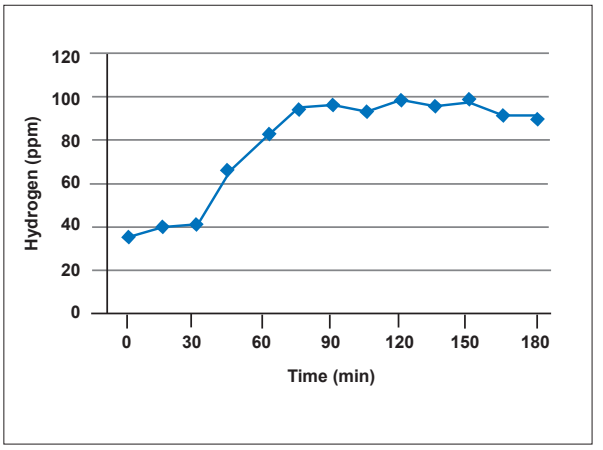

Figure 4. Lactulose breath test in a patient with small intestinal bacterial overgrowth—note the elevated fasting hydrogen level and subsequent rise greater than 20 ppm.

used is a readily metabolized carbohydrate, such as lactulose, glucose, sucrose, or xylose. Complex carbohydrates, such as rice, are neither sensitive nor specific.[72] Other investigators have used bile salt cogeners as substrates for bacterial modification; however, these are less sensitive and specific when compared to xylose.[73]

All breath tests rely on the recovery and quantification of an exhaled gas produced by the bacterial metabolism of the ingested substrate. The development of inexpensive, commercially available gas chromatographs to measure exhaled hydrogen and/or methane has led to the widespread use of breath testing for the diagnosis of bacterial overgrowth.

Another method of breath sample analysis utilizes substrates such as xylose or glycocholic acid labeled with ^{13}C and ^{14}C isotopes followed by mass spectrographic or scintillation counting of breath samples for isotopic CO_2.[74-76] Obviously, ^{14}C-labeled substrates are not appropriate for testing children and pregnant women. The use of a bile salt cogener, ^{75}Se homocholic-tauro acid, has been proposed but is expensive and not proven to be of value.[77]

There are several points that deserve mention regarding the accuracy and utility of breath testing. First, there is no consensus regarding a gold standard for diagnosing SIBO. Most experts advocate bacterial culture as the benchmark; however, as noted, there are multiple problems inherent to this technique. Second, several substrates have been studied, but none has been identified as being superior to another. Third, differences in bacterial flora among patients can determine their response to breath testing. For example, about 10% of adults and 15% of children may not be colonized with bacteria capable of producing hydrogen. These individuals have flora-producing methane from hydrogen.[78] Fourth, the optimum protocol for the administration, timing, and collection of breath specimens is not known. Fifth, proper interpretation of results in the setting of rapid or delayed gastric emptying has not been validated. Sixth, special populations of patients (eg, postgastrectomy, obesity surgery, advanced age) may require different standards.[79,80] Seventh, recent antibiotic use may alter the results, although the ideal antibiotic-free interval prior to testing is not known.[2] Lastly, the effects of H2RAs and PPIs on breath test results remain controversial.[81]

All the caveats outlined above make breath testing an easy procedure to perform but a difficult procedure to interpret. At present, the lactulose or glucose hydrogen breath test is the most commonly performed. The collection of the samples relies on collecting alveolar air samples. Patients are generally instructed to avoid ingesting unfermentable carbohydrates (eg, whole grain breads, pasta). After an overnight fast, a baseline hydrogen sample is collected and then 10 g of lactulose, or 50–80 g of glucose, is administered in 120–200 mL of water. Serial end-expiratory breath samples are collected every 15–30 minutes for a total of 3–4 hours (Figure 3). Results from patients with chronic obstructive pulmonary disease or those who cannot cooperate in breath sample collection may be invalid. Smokers are advised not to smoke for 1–2 hours prior to testing.

At present, there are no accepted criteria for what constitutes a positive hydrogen breath test. Generally, an increase from the baseline fasting hydrogen concentration to a value greater than 10–12 parts per million (ppm) after a 50-g glucose load[5,82] or greater than 20 ppm following lactulose,[83] during the first 90 minutes of the test

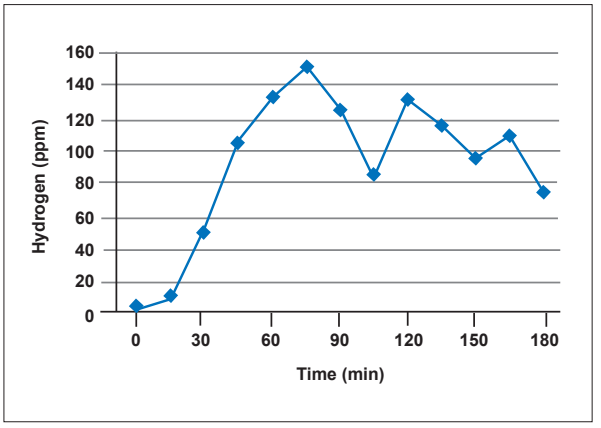

Figure 5. Lactulose breath test with a double peak seen in some patients with small intestine bacterial overgrowth.

has been accepted as proof of SIBO (Figure 4). Higher cutoff values increases the specificity at a loss of sensitivity. A second criteria often accepted as proof of overgrowth is a double peak (Figure 5). This consists of an initial hydrogen peak prior to 90 minutes, followed by a fall of more than 5 ppm over two consecutive samples, and then a second peak in breath hydrogen as the substrate enters the cecum.[37]

King and colleagues found that 1 g of xylose labeled with 1 µCi ^{14}C xylose was superior to hydrogen breath testing for the diagnosis of (culture-proven) SIBO.[72] The xylose test had a 95% sensitivity compared to less than 50% sensitivity for lactulose and 25% for glucose breath testing. However, others have not been able to confirm the superiority of the ^{14}C xylose test, instead reporting that the 50-g glucose hydrogen test is superior in patients with more than 10^5 coliform bacteria/mL.[84,85] Corazza and colleagues reported that the glucose and lactulose breath tests have sensitivities of 60–70%, with specificities of 40–80%.[2] However, a recent study reported that glucose and lactulose breath tests, when compared to culture of an endoscopic small bowel aspirate, have lower sensitivities (glucose 44%, lactulose 31%) but higher specificities (glucose 80%, lactulose 86%) than previously thought.[86] Studies have found that the specificity of the 10-g lactulose breath test and the ^{14}C-labeled 1-g xylose test were 100% when radionuclide scintigraphy was done during the test to assess gastric emptying.[87,88] Elevated fasting breath hydrogen (>19 ppm or methane >10 ppm) are excellent predictors of overgrowth, being highly specific (>90%) but not sensitive (<30%).[89] However, a normal fasting value should not obviate performing a complete test.

Treatment

The goals of treatment for SIBO are threefold: 1) correct the underlying cause; 2) provide nutritional support, if necessary; and 3) treat the overgrowth.

Treatment aimed at correcting the underlying cause includes dietary, surgical, and medical therapies. Strict adherence to diet may lead to symptom improvement in patients with celiac disease and bacterial overgrowth. Surgical revision of altered small bowel anatomy may be beneficial in patients with SIBO secondary to small bowel diverticulosis, fistulas, or strictures. Medications should be reviewed to determine if they are playing a role in the development of symptoms. Patients with gastroparesis or small bowel dysmotility as the underlying cause of SIBO may benefit from the use of prokinetic agents. Patients with cirrhosis and SIBO (demonstrated with hydrogen breath testing) and small bowel dysmotility (manometry-proven) had an improvement in overgrowth and manometric parameters after treatment with cisapride, as compared to placebo.[90] Their improvement was comparable to that found in patients treated with alternating neomycin and norfloxacin. Octreotide improves small bowel dysmotility and, in a small group of patients, decreased SIBO.[91,92] Larger trials have not yet confirmed these findings.

Nutritional support, particularly in those patients with weight loss or vitamin and mineral deficiencies, is an important component of SIBO treatment. Supplementation and maintenance of vitamin B_{12} and fat-soluble vitamins, with correction of calcium and magnesium deficiencies, are key components of treatment. Lactase and fructase deficiency may develop due to inflammation of the small bowel brush border, and dietary restrictions are often advocated, although this has not been prospectively studied.

The mainstay of treatment for SIBO remains antibiotic therapy. Antibiotics reduce or eliminate the bacterial overload and reverse the mucosal inflammation associated with overgrowth and malabsorption.[11] Some authors advocate for the empiric treatment of suspected SIBO without diagnostic testing.[93] However, this approach is problematic because of a large placebo effect, the high cost of antibiotics, the potential for treatment complications (eg, resistance, drug interactions, side effects), and the need for recurrent courses of antibiotics. In fact, one trial demonstrated an average duration of symptom improvement of only 22 days, which translates into a need for at least 12 courses (presuming 7 days) of antibiotics per year to provide persistent symptom relief.[94]

A variety of antibiotics have been used in the treatment of SIBO, most with little supporting evidence. Ideally, antibiotic therapy would be based on bacterial culture and sensitivity data. However, this approach is

impractical in the clinical setting and treatment is thus directed at likely organisms based on reports of culture data from SIBO patients.[4] Tetracycline (and its derivatives) was the first drug to be recommended, although no published data are available on its efficacy. A recent trial showed decreased efficacy of chlortetracycline at improving hydrogen breath tests and symptoms of SIBO compared to newer antibiotics.[95] Other broad-spectrum antibiotics advocated for the treatment of SIBO include amoxicillin/clavulanate,[11,42] ciprofloxacin,[83] and doxycycline.[8] However, these recommendations are based on uncontrolled data. More recently, direct comparisons between antimicrobial agents have emerged. Rifaximin (Xifaxan, Salix; a nonabsorbed rifamycin derivative) proved better than chlortetracycline at improving hydrogen breath testing and symptoms of SIBO.[95] However, a recent randomized crossover trial comparing rifaximin and metronidazole demonstrated superiority of metronidazole at improving hydrogen breath test results and symptoms of SIBO.[94] In a group of patients with Crohn's disease and abnormal breath hydrogen tests, both metronidazole and ciprofloxacin normalized breath tests and improved bloating, loose stools, and abdominal pain.[96] A randomized controlled trial comparing norfloxacin and amoxicillin/clavulanate demonstrated similar efficacy at improving hydrogen breath analysis and diarrhea output compared to *Sacchromyces boulardii* and placebo; however, there was no improvement in other abdominal symptoms including bloating, flatus, abdominal pain, and borborygmi.[97]

A randomized, double-blinded trial of 111 patients who met Rome I criteria for IBS suggested improvements in symptoms (a composite score of pain, constipation, and diarrhea) with a 10-day course of neomycin compared to placebo; however, only 20% of patients normalized their abnormal lactulose breath tests.[98] More recently, Pimentel and colleagues published a randomized, double-blinded trial comparing rifaximin (400 mg tid for 10 days) to placebo in 87 patients who met Rome I criteria for IBS.[99] Although the rifaximin group showed a greater percentage of global symptom improvement, this was limited to bloating, as scores for abdominal pain, diarrhea, and constipation did not improve significantly.

The optimal duration of antibiotic therapy is not known, and most trials employed a 7- to 10-day course. Some studies have incorporated cyclic antibiotic regimens (eg, 10 days per month), although there are no data to support this approach as being more effective than a single course. Finally, the commonly employed practice of rotating antibiotics to improve efficacy and reduce resistance has not been studied.

Attempts at treating SIBO with probiotics (nonpathogenic strains of bacteria) have shown mixed results. A placebo-controlled trial of *Lactobacillus* showed an improvement in diarrhea and a reduction in hydrogen breath levels that was sustained for 21 days after completing treatment.[100] Other trials have not shown such encouraging results,[94,101] and further studies are needed to define the role of probiotic therapy in SIBO.

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