

# Bacterial Overgrowth of the Small Intestine Breath Test

Ref #58 omeprazole induces altered bile acid metabolism

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## INTRODUCTION

Small intestinal bacterial overgrowth (SIBO) is an abnormal colonization within the small bowel by bacteria normally found in the colon, mouth, or pharynx.<sup>1</sup> Also called BOSI (bacterial overgrowth of the small intestine), "blind-loop," or "stagnant loop,"<sup>2</sup> SIBO is a potentially serious disorder that leads to problems such as malabsorption, anemia and weight loss, malnutrition,<sup>3</sup> increased intestinal permeability ("leaky gut"),<sup>4</sup> and bone loss.<sup>5</sup> Breath testing for hydrogen and methane provides a simple noninvasive means of detecting SIBO. Once SIBO has been identified, antimicrobials are typically administered to eradicate the bacteria. Further treatment then can be commenced to address the underlying causes of SIBO to prevent a recurrence.

### Frequency of Small Intestinal Bacterial Overgrowth

Bacterial overgrowth of the small intestine is a frequently overlooked contributing factor in several common disorders.<sup>6</sup> For example, irritable bowel syndrome (IBS), responsible for up to 40% of referrals to gastroenterologists,<sup>7</sup> is frequently associated with SIBO. One study of more than 200 patients with IBS found that 78% tested positive for SIBO. Of those successfully treated for SIBO, 48% no longer met the Rome criteria for IBS.<sup>8</sup>

Patients with fibromyalgia<sup>9</sup> and chronic fatigue syndrome<sup>8</sup> also have been observed to have a high rate of SIBO (78% and 77% of subjects, respectively).

About half of such patients who tested positive for SIBO in one study experienced marked subjective improvement after antibiotic administration. Interestingly both of these disorders have been observed to overlap with IBS.<sup>10</sup>

Other groups of patients particularly prone to bacterial overgrowth of the small intestine include those with intestinal dysmotility syndromes associated with systemic disease (e.g., diabetes, scleroderma, and intestinal pseudoobstruction), prior intestinal surgery, and strictures of the small bowel. Both jejunal diverticulosis<sup>6</sup> and Crohn's disease<sup>11</sup> have been associated with SIBO, particularly in patients with Crohn's disease who have undergone previous intestinal surgery. Interestingly most patients with celiac disease whose gastrointestinal symptoms persist with a gluten-free diet have been shown to have SIBO, with amelioration of symptoms after bacterial eradication.<sup>12</sup>

The incidence of bacterial overgrowth increases with age, particularly in people 80 years and older.<sup>13</sup> It has been found that 64% of individuals older than 75 years with chronic diarrhea have colonic-type flora in their small bowels<sup>6</sup> and that SIBO is the most common cause of clinically significant malabsorption in elderly persons.<sup>2</sup>

### Pathophysiology

Although the concentration of bacteria increases exponentially toward the distal end of the small intestine, particularly the ileum,<sup>2</sup> far fewer bacteria normally

inhabit the small intestine than the colon.<sup>14</sup> Two major factors control the numbers and kinds of bacteria found within the small bowel: intestinal peristalsis and gastric acid secretion.<sup>2,14</sup> Consequently SIBO has been associated with both intestinal stasis and hypochlorhydria.<sup>15</sup> Other factors that discourage small intestinal flora overgrowth are pancreatic enzyme secretion,<sup>16</sup> disaccharidase production by intestinal microvilli,<sup>17</sup> the ileocecal valve,<sup>18</sup> bile salts, luminal pH, and oxidation-reduction potential.<sup>14</sup> Intestinal immunoglobulin secretion and a mucus barrier that prevents bacterial adherence are unproven mechanisms for limiting bacterial growth in humans.<sup>15</sup>

Alterations in any of these normal functions (whether endogenous or drug-induced) favor uncontrolled bacterial proliferation in the small intestine.<sup>14</sup> A variety of anatomic and motor disorders of the small bowel may also lead to SIBO, such as surgical loops, diverticula, strictures, adhesions, tumors, fistulas,<sup>2</sup> scleroderma,<sup>19</sup> intestinal pseudoobstruction,<sup>20</sup> and diabetic enteropathy.<sup>21</sup> All have as a common feature the stasis of small bowel contents, which allows bacterial concentrations increasingly to resemble those of the large intestine (Box 12-1).<sup>14,15</sup>

The composition of small bowel flora varies among individuals with SIBO; however, the concentration of organisms is always higher than normal. The predominant flora is composed of coliform organisms and strict anaerobes (both rare in the small bowel), such as *Bacteroides*, *Clostridium*, and *Bifidobacterium*.<sup>14</sup>

To have clinical consequences, SIBO appears to require an adequate concentration of organisms with particular metabolic properties within specific locations of the small intestine. For example a heavy concentration of strict anaerobes and coliforms in the proximal small intestine is more likely to be associated with malabsorption than a flora consisting of fewer strict anaerobes or coliforms or when strict anaerobes or coliforms are located in the distal small intestine.<sup>14</sup> For this reason SIBO may be asymptomatic in some individuals, whereas in others

#### Box 12-1 When to Consider Breath Testing for Small Intestinal Bacterial Overgrowth

- Gas, bloating, or diarrhea, usually after eating
- Unexplained weight loss
- Evidence of malabsorption
- Chronic hypochlorhydria or achlorhydria
- Use of acid-blocking medications
- Prior intestinal surgery, chronic constipation, or other causes of intestinal stasis
- Intolerance of disaccharides (lactose)
- Unexplained vitamin B<sub>12</sub> deficiency, weight loss, or bone loss
- Unexplained nutrient insufficiencies (e.g., calcium, magnesium, fat-soluble vitamins)
- Elevations of fecal short chain fatty acids
- Unexplained "leaky gut"

#### Box 12-2 Causes of Small Intestinal Bacterial Overgrowth

- Achlorhydria, hypochlorhydria, drug-induced hypoacidity
- Chronic constipation
- Stasis resulting from structural changes (e.g., diverticulosis, blind loops, radiation damage, stricture, fistulas, intestinal pseudoobstruction, adhesions resulting from prior surgery)
- Chronic pancreatic insufficiency
- Disaccharidase deficiencies (lactase)
- Damaged ileocecal valve
- Immunodeficiency (especially of secretory immunoglobulin A)
- Diabetes mellitus
- Scleroderma
- Crohn's disease

#### Box 12-3 Signs and Symptoms of Bacterial Overgrowth

- Gas, bloating, and flatulence
- Diarrhea
- Abdominal cramping
- Steatorrhea
- Lactose intolerance
- Megaloblastic anemia

it may produce a variety of signs and symptoms. Box 12-2 outlines clinical signs and symptoms that alert the practitioner to consider testing for SIBO.

## Diagnosis

### Signs and Symptoms

Although many of the bacteria found in SIBO play beneficial roles within the colon, these same microorganisms may have deleterious effects within the delicate environment of the small intestine.

The classic SIBO syndrome is characterized by megaloblastic anemia resulting from vitamin B<sub>12</sub> deficiency, and weight loss and diarrhea secondary to fat malabsorption.<sup>14</sup> However, many patients present with nonspecific symptoms such as bloating, flatulence, and abdominal pain resulting from bacterial fermentation of intraluminal sugars and associated gas production (Box 12-3).<sup>8,12</sup>

Via secretory and osmotic processes, diarrhea may occur even in the absence of significant steatorrhea. Unabsorbed fats and bile salts are modified by bacteria in the colon to hydroxylated fats and free bile acids, respectively, which stimulate colonic secretion of water and electrolytes.<sup>14</sup>

Bile salts, which are essential to emulsification and assimilation, must be conjugated with either taurine or glycine to function properly. In SIBO, bacteria in the proximal small intestine (predominantly anaerobes such as *Bacteroides*, *Bifidobacterium*, *Veillonella*, enterococci, and *Clostridium*)<sup>15</sup> are capable of deconjugating bile salts

to form free bile acids.<sup>14</sup> This deconjugation can have two major clinical repercussions: (a) the free bile acids may become concentrated enough to cause mucosal damage (Figure 12-1), resulting in reduced brush-border enzyme activities (especially lactase),<sup>22</sup> defects in mucosal uptake of sugars and amino acids, enteric blood loss, and protein-losing enteropathy, or (b) the conjugated bile salt concentration may fall below the concentration necessary for effective micelle formation, leading to fat malabsorption and steatorrhea (fecal fat).<sup>14,15</sup> This fat malabsorption may lead to insufficiencies of fat-soluble vitamins (e.g., E, A, K, and D).<sup>3</sup>

Electron microscopy research also has revealed the presence of a pseudomembrane that mechanically interferes with the absorption of fats in many cases of SIBO. This pseudomembrane is thought to represent a maladaptive defense mechanism against the bacterial overgrowth.<sup>23</sup> Thus, two possible mechanisms appear to be involved in fat malabsorption in patients with SIBO, deconjugation of bile acids and maladaptive pseudomembranes that block the absorption of fats.

Intraluminal fatty acids from fat malabsorption may form insoluble soaps with calcium and magnesium, thus rendering them unavailable for assimilation.<sup>3</sup> Osteomalacia, night blindness, hypocalcemic tetany,<sup>2</sup> and metabolic bone disease<sup>5</sup> have been known to develop as a consequence of lipid malabsorption in patients with SIBO. Although rare, iron deficiency anemia may result from blood loss.<sup>3</sup>

SIBO may lead to vitamin B<sub>12</sub> deficiency, with associated megaloblastic anemia and low serum cobalamin

levels.<sup>2,14</sup> Although intrinsic factor is not altered by anaerobic bacteria, these microbes are capable of detaching vitamin B<sub>12</sub> from intrinsic factor as well as directly using B<sub>12</sub>.<sup>18</sup> Either mechanism has the effect of rendering the vitamin unavailable to the host. Vitamin B<sub>12</sub> bound to bacteria also may be partially metabolized to inactive analogues that compete with normal vitamin B<sub>12</sub> binding and absorption.<sup>24</sup> Paradoxically, serum folate values usually are normal or even elevated in SIBO, a result of the ability of bacteria to synthesize the vitamin.<sup>25</sup>

Hypoproteinemia also may occur in SIBO, secondary to protein-losing enteropathy and protein malabsorption.<sup>3,15</sup> In addition bacteria may metabolize proteins to ammonia and fatty acids, thereby rendering them unavailable to the host.<sup>22</sup>

## LABORATORY ASSESSMENT

The composition of the bacterial populations contaminating the small bowel is complex and variable.<sup>2</sup> In one study, the main bacteria recovered from patients with SIBO consisted of the microaerophilic bacteria *Streptococcus*, *Escherichia coli*, *Staphylococcus*, *Micrococcus*, *Klebsiella*, and *Proteus* and the anaerobic bacteria *Lactobacillus*, *Bacteroides*, *Clostridium*, *Veillonella*, *Fusobacterium*, and *Peptostreptococcus*.<sup>1</sup> However, the diagnosis of SIBO tends to be oriented less to the identification of specific microorganisms and more to overall bacterial concentrations.<sup>2</sup>

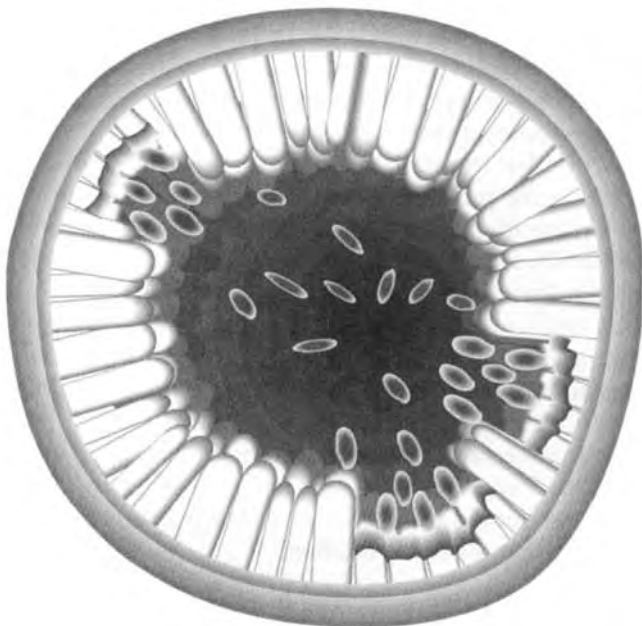
## Endoscopy

Culture of a small bowel aspirate via endoscopy is considered the most direct method for diagnosing SIBO. High bacterial counts (exceeding 10<sup>4</sup> organisms/ml from the jejunum or 10<sup>7</sup> organisms/ml from the ileum) confirm the diagnosis.<sup>15</sup> This method offers good sensitivity, although fairly low specificity. Because the aspirate is typically taken from only one location, overgrowth located in the more distal end of the small bowel or concentrated in a large diverticulum or blind loop may be missed.<sup>26</sup> Intubation methods are also time consuming, uncomfortable, and expensive.

## Breath Testing

Breath tests were devised as less invasive alternatives to endoscopy and intubation. Breath tests have good sensitivity,<sup>27</sup> are simple to administer, and offer greater patient comfort and convenience compared with intubation and culture.

Most breath tests are based on the ability of intestinal microbes to ferment carbohydrates, producing hydrogen or methane in the process. A fraction of these gases naturally diffuses from the bowel to the circulation and is excreted with expired air. Because there is no other metabolic production of hydrogen and methane, the



**Figure 12-1** In small intestinal bacterial overgrowth, free bile acids can damage the brush border, resulting in reduced enzyme activity and maldigestion. (Courtesy Great Smokies Diagnostic Lab, Asheville, NC.)

= biofilm

pulmonary excretion may be used as a measure of bacterial fermentation during the passage through the gastrointestinal tract.<sup>28</sup>

The lactulose breath test is commonly used for the diagnosis of SIBO. Typically the patient ingests a challenge dose of lactulose (a synthetic, nonabsorbed disaccharide) after 2 days of a fiber-restricted diet and a 12-hour fast.<sup>29</sup> Glucose has also been used as a challenge agent, although the sensitivity is reduced for distal ileum bacterial overgrowth because of rapid absorption of the glucose,<sup>27</sup> and the agent clearly is not suitable for patients with diabetes, hypoglycemia, or other blood sugar disorders. Other compounds that have been used in breath testing are <sup>14</sup>C-glycocholic acid and D-xylose (fermented to CO<sub>2</sub>),<sup>2</sup> both of which have some limitations.<sup>11,27</sup> No matter which agent is used, intestinal bacteria modify the challenge substance in such a way that an early peak in breath gas value is produced in patients with SIBO. In the case of lactulose, which offers the advantage of traveling the full length of the small intestine, the early hydrogen/methane peak is typically followed by a prolonged peak representing colonic bacterial activity.<sup>27,30</sup>

In the lactulose breath test, breath specimens are collected by having the subject exhale into a special mouthpiece that is connected to a vacuum-sealed collection tube. A fasting (prechallenge) breath sample is collected, 10 g of lactulose is ingested (lesser amounts for small children), and then five more breath specimens are collected at timed intervals over a 2-hour period. Breath levels of hydrogen and methane are plotted over time; early rises in breath gas values are thought to correlate with more proximal portions of the small intestine. Hydrogen appears in the breath about 8 minutes after lactulose comes into contact with gut bacteria.<sup>31</sup> This speed of response allows one to distinguish between small bowel bacterial overgrowth and the normally dense colonic flora, the latter of which typically gives a later, more prolonged yield of breath gas levels (roughly 90 minutes into the collection process).

### Hydrogen versus Methane

Many studies using carbohydrate challenges have measured only breath hydrogen (H<sub>2</sub>). However, 30% to 50% of H<sub>2</sub> producers also produce methane (CH<sub>4</sub>),<sup>32</sup> most likely because "methanogenic" bacteria consume H<sub>2</sub> and produce CH<sub>4</sub> in the process.<sup>29</sup> Individuals who harbor methanogenic bacteria (primarily *Methanobrevibacter smithii*)<sup>33</sup> in their intestines typically produce greater amounts of breath CH<sub>4</sub> during the breath test; thus those with SIBO may be missed by a test that examines only H<sub>2</sub>.<sup>34</sup> Consequently the addition of methane to the analysis provides a more thorough assessment of bacterial overgrowth.<sup>29,32</sup>

Various researchers have noted clinical correlations between various disorders and the production of

hydrogen or methane. One study found that individuals who produce higher amounts of H<sub>2</sub> relative to CH<sub>4</sub> reported significantly increased bloating and cramping after carbohydrate ingestion, whereas individuals who produce high CH<sub>4</sub> reported no significant increase in these symptoms.<sup>35</sup> Patients with IBS have been found to excrete significantly more H<sub>2</sub> than healthy controls, although the total volumes of hydrogen and methane produced by the two groups did not differ.<sup>36</sup> Still other researchers observed associations between breath gas values and specific IBS symptoms; methane production was associated 100% with constipation-predominant IBS, whereas hydrogen production was associated with diarrhea.<sup>37</sup>

Correlations between breath CH<sub>4</sub> values and colon cancer have been reported in the literature,<sup>38</sup> but subsequent studies failed to substantiate the correlation.<sup>39</sup>

Interestingly, in vitro research suggests a possible role for bile acids in the accumulation of hydrogen gas in the intestine; bile acids were found to inhibit methanogenesis in a dose-response fashion.<sup>40</sup>

### Interpretation

Lactulose is not fermented in a healthy subject until it reaches the colon. As a result the typical fasting breath sample contains less than 20 ppm of hydrogen or methane. An increase in breath gas levels in the fifth or sixth breath specimen (90 and 120 minutes, respectively) usually reflects colonic bacterial fermentation and is considered normal. Lack of the expected colonic peak may result from antibiotics or an acidic colonic pH.<sup>33,41</sup> However, this should not affect results for the small intestine.<sup>29</sup>

In patients with SIBO, the lactulose is fermented in the small intestine. This process leads to an earlier peak in breath gas values followed by a larger, more prolonged peak reflecting colonic fermentation.<sup>27</sup>

A positive test result (indicating SIBO) is defined by either (a) the presence of a total hydrogen/methane gas peak more than 15 ppm above baseline levels, occurring within 90 minutes of lactulose ingestion or (b) an elevated baseline (fasting) breath gas concentration, even if there is not a large rise from baseline over the next few samples.<sup>42</sup> Elevated fasting values occur in up to one third of cases<sup>33</sup> and are thought to relate to the fermentation of endogenous brush-border glycoproteins in patients with SIBO.<sup>43</sup>

In some cases of slow transit, high levels of gases in the fifth or sixth breath specimens may indicate SIBO in the distal ileum rather than the usual colonic peak, thus complicating the interpretation.

### False-Positive and False-Negative Results

Various factors may interfere with the lactulose breath test, resulting in false-negative or false-positive results.

Detailed instructions for breath collection are aimed at minimizing this interference and must be followed carefully.

### False-Positive Results

The following factors may account for a false-positive result on a breath test:

- Failure to fast for at least 12 hours before the test or to avoid dietary fiber the day before collection may result in a high "background noise" that contributes significantly to the overall concentration of breath gases.<sup>28</sup>
- Sleeping, smoking, or eating shortly before or during sample collection can increase concentrations of breath gases.<sup>44</sup>
- Fermentation by mouth and oropharyngeal flora may lead to early, transient elevations in breath gases after carbohydrate ingestion.<sup>45</sup> As a result, thorough teeth and tongue brushing before specimen collection is recommended.

### False-Negative Results

False-positive results on a breath test can be caused by the following factors:

- Diarrhea or the recent administration of antimicrobials can temporarily reduce the concentration of gut bacteria,<sup>46</sup> leading to a false-negative result. Laxatives and enemas may have a similar effect.<sup>47</sup> It is recommended that the patient wait at least 1 week after antibiotic therapy before performing the test.
- SIBO that is confined to the distal ileum may go undetected if the breath gas peak produced in the ileum merges with the breath gases produced by the colonic flora.<sup>27</sup>
- Rapid intestinal transit time may cause delayed increases in breath gases, leading to a rise only after the lactulose has already reached the cecum.<sup>48</sup> This is particularly relevant for patients with SIBO who have undergone small bowel resection.

## TREATMENT OF BACTERIAL OVERGROWTH

### Bacterial Eradication

More often than not, addressing only the contributing factors to SIBO fails to adequately resolve the bacterial overgrowth; therefore the primary treatment of SIBO is directed at altering the intestinal flora with antibiotics.<sup>15</sup>

Most patients with clinically significant SIBO host an intestinal flora consisting largely of anaerobes; however, some patients harbor a predominance of gram-negative

aerobes, such as *Escherichia coli*, *Klebsiella*, and *Pseudomonas*.<sup>49</sup> Therefore it is generally agreed that the most effective antimicrobial agent is one that targets both aerobic and anaerobic microorganisms.<sup>2</sup>

### Antibiotics

The first-line antibiotic for SIBO has traditionally been tetracycline (250 mg QID).<sup>2</sup> However, the high prevalence of bacterial resistance to the drug (up to 60% of patients with SIBO)<sup>2</sup> has led to the use of alternative antibiotics. The most effective alternative agents, shown either empirically or by clinical trials, are the quinolones (e.g., ciprofloxacin or norfloxacin), amoxicillin with clavulanic acid (Augmentin), clindamycin, and metronidazole.<sup>50,51</sup> Other antibiotics that have been reported to be effective in SIBO are ampicillin, erythromycin, lincomycin, oral aminoglycosides, cephalosporins (Keflex), and chloramphenicol. Antibiotics that show poor activity against anaerobes probably should be avoided in the treatment of SIBO (e.g., penicillin, ampicillin, and the oral aminoglycosides kanamycin and neomycin).<sup>2</sup>

The use of more poorly absorbed antibiotics may help minimize the risk of side effects. Rifaximin, a non-absorbable rifamycin derivative, compared favorably with tetracycline in one study; a 7-day course of rifaximin at 400 mg TID normalized breath hydrogen excretion in 70% of patients with SIBO, whereas tetracycline normalized breath hydrogen excretion in only 27% of patients.<sup>52</sup>

In most patients, a single course of antibiotic therapy (7 to 10 days) is adequate; in others, cyclic therapy (1 week out of every 4) or continuous therapy (1 to 2 months) may be needed.<sup>2</sup> Prolonged antibiotic therapy significantly raises the risk of diarrhea, *Clostridium difficile* infection, and bacterial resistance.<sup>2</sup> The administration of probiotics usually helps to minimize such side effects.<sup>17</sup>

A poor response to antibiotics may indicate slowly reversible or irreversible mucosal disease, antibiotic resistance, antibiotic-associated diarrhea, or an incorrect diagnosis.<sup>18,53</sup>

### Antibiotic Alternatives

Aromatic oils have been shown to be effective antimicrobials. Peppermint oil, which has been used successfully in patients with IBS, has demonstrated antimicrobial properties in vitro.<sup>54</sup> In a case study, enteric-coated peppermint oil (dose of 0.2 ml tid) was seen to dramatically reduce gastrointestinal symptoms in a patient with SIBO.<sup>55</sup> Follow-up breath testing indicated some persistent bacterial overgrowth; the addition of an established antimicrobial agent such as berberine may help to improve the results.<sup>56</sup> Research on the effectiveness of other botanical agents in SIBO is clearly needed.

A small double-blind study examined the effect of oral probiotics (combined *Lactobacillus acidophilus* and *L. casei* strains) on SIBO. A significant decrease in breath hydrogen concentration was noted as early as 1 week into treatment, providing evidence that *Lactobacillus* strains may be effective in the treatment of bacterial overgrowth.<sup>57</sup>

### Addressing the Underlying Cause

Bacterial overgrowth of the small intestine may recur easily if the root causes are not addressed.

### Restoration of Gastric Acidity

Because gastric acidity is an important deterrent to SIBO, the restoration of normal stomach pH in the patient with hypochlorhydria or achlorhydria is essential. This may include the use of betaine hydrochloride with meals or the discontinuation of antacid medications. SIBO has been found in both patients with ulcer and healthy subjects after even short-term (5-week) administration of omeprazole (a proton pump inhibitor). The bacterial overgrowth was associated with greater deconjugation of bile acids and fat malabsorption and was thought to be induced by a shift to neutral pH in the gastric juice.<sup>58</sup>

### Normalization of Intestinal Motility

Intestinal stasis, whether functional or anatomic, is another major contributing factor to SIBO that should be

addressed. When not resulting from anatomic or organic causes, reduced motility may be improved with measures such as increased dietary fiber, water, probiotics, stress management, and exercise. Surgical correction of anatomic causes of intestinal stasis, such as small bowel diverticula, may be warranted.<sup>59</sup>

### Supportive Measures

Patients may become lactose intolerant secondary to an acquired disaccharidase deficiency caused by SIBO.<sup>21</sup> Avoiding lactose as well as other disaccharides such as sucrose, maltose, and isomaltose (concentrated in grains) may help to "starve" the excess bacteria and allow healing of the intestinal lining.<sup>60</sup>

Substituting more easily absorbed medium-chain triglycerides for most dietary fat may be helpful in patients with diarrhea and steatorrhea.<sup>2</sup>

Probiotics and prebiotics are recommended to help restore normal balance of intestinal flora, especially in patients with a history of antibiotic use. Various strains of *Lactobacillus* and *Bifidobacterium* have been used successfully to treat SIBO.<sup>17,57</sup>

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