SIBO: Dysbiosis Has A New Name

by Steven Sandberg-Lewis, ND, DHANP and Allison Siebecker, ND, MSOM

Many patients with bloating, abdominal pain, constipation, or diarrhea are diagnosed with irritable bowel syndrome and never get adequate responses to treatment. Others are given no diagnosis at all for their suffering, which leads to even less chance of recovery. Our experience is that many of these perplexing patients have commensal microbial overgrowth. This article details the complex issue of small intestine bacterial overgrowth (SIBO)

SIBO is a condition in which abnormally large numbers of commensal bacteria (or other microorganisms) are present in the small intestine. SIBO is a common cause of IBS – in fact it is involved in over half the cases of IBS and as high as 84% in one study using breath testing as the diagnostic marker.[2] It accounts for 37% of cases when endoscopic cultures of aerobic bacteria are used for diagnosis.[3] Eradication of this overgrowth leads to a 75% reduction in IBS symptoms.[4] Either bacterial overgrowth or the overgrowth of methanogenic archaea leads to impairment of digestion and absorption and produces excess quantities of hydrogen, hydrogen sulfide, or methane gas. Hydrogen and methane are not produced by human cells but are the metabolic products of fermentation of carbohydrates by intestinal organisms. When commensals (oral, small intestine, or large intestine flora) multiply in the small intestine to excessive numbers, IBS is likely. Hydrogen/methane breath testing is the most widely used diagnostic method for this condition. *Stool analysis has no value in diagnosing SIBO.*

Symptoms of SIBO include:

- bloating/abdominal gas
- flatulence, belching
- abdominal pain, discomfort, or cramps
- constipation, diarrhea, or a mixture of the two
- heartburn
- nausea
- malabsorption: steatorrhea; iron, vitamin D, vitamin K, or B12 deficiency with or without anemia; and osteoporosis[5]
- systemic symptoms: headache, fatigue, joint/muscle pain, and certain dermatology conditions

Other diseases associated with SIBO include hypothyroidism, lactose intolerance, gallstones, Crohn's disease, systemic sclerosis, celiac disease, chronic pancreatitis, diverticulitis, diabetes with autonomic neuropathy, fibromyalgia and chronic regional pain syndrome, hepatic encephalopathy, non-alcoholic steatohepatitis, interstitial cystitis, restless leg syndrome, acne rosacea, and erosive esophagitis.[6–21] Based on clinical experience, we suspect that biliary dyskinesia and lymphocytic colitis may also be associated with SIBO.

In our practices we have found that the following indicators increase the chances that a patient's IBS is caused by SIBO:

- when a patient develops IBS following a bout of acute gastroenteritis (postinfectious IBS);
- when a patient reports dramatic transient improvement in IBS symptoms after antibiotic treatment;
- when a patient reports worsening of IBS symptoms from ingesting probiotic supplements that also contain *pre*biotics;
- when a patient reports that eating more fiber increases constipation and other IBS symptoms;
- when a celiac patient reports insufficient improvement in digestive symptoms even when carefully following a gluten-free diet;
- when a patient develops constipation type IBS (IBS-C) after taking opiates;
- when a patient has a chronic low ferritin level with no other apparent cause;
- when abdominal imaging reveals a large gas accumulation obscuring the pancreas
- when small bowel follow-through imaging reveals areas of "flocculation."[22]

Mechanisms by Which Overgrowth Is Prevented

An important protective mechanism against SIBO is proper small intestine motility via the migrating motor complex because stasis promotes bacterial growth.[23] Also key in prevention are gastric, pancreatic,

➤

➤

and gall bladder secretions, since hydrochloric acid, enzymes, and bile are bactericidal/static.[24] Conditions that disrupt the glycocalyx and microvillus portions of the brush border may fuel overgrowth. The pathophysiology involved is the loss of disaccharidases in these areas and the resulting carbohydrate malabsorption which provides excess substrate for microbial growth. The role of proper ileocecal valve function in preventing cecoileal reflux of colonic bacteria into the small intestine may also be important.[25,26] Surprisingly, a recent study suggests that surgical removal of the gall bladder reduces the risk as well.[27] Mucosal biofilms may be preventive or may be a risk.[28,29] Heavy drinking, as well as moderate use of alcohol, is significantly associated with increased SIBO risk.[30] The use of proton pump inhibitors encourages overgrowth, especially of the hydrogen-producing type.[31,32]

Definition

Traditionally, $\geq 10^5$ colony-forming units (CFU) per mL of proximal jejunal aspiration has been the definition of SIBO in culturing studies. $\geq 10^3$ CFU is now the suggested definition from more recent studies revealing that $\leq 10^3$ CFU is the normal level in healthy controls.[33,34] The bacteria which are most commonly overgrown are both commensal anaerobes – *Bacteroides* 39%, *Lactobacillus* 25%, *Clostridium* 20% – and commensal aerobes – *Streptococcus* 60%, *Escherichia coli* 36%, *Staphylococcus* 13%, *Klebsiella* 11%.[35] A more recent study found the aerobes to be *Escherichia coli* 37%, *Enterococcus* spp 32%, *Klebsiella pneumonia* 24%, and *Proteus mirabilis* 6.5%.[36] Colonic hydrogen production is believed to be anti-inflammatory and antineoplastic, whereas excessive small intestine hydrogen causes the symptoms and signs of diarrhea-type irritable bowel syndrome (IBS-D).[37] In addition to bacteria, the source of methane generation in SIBO is the archaeon *Methanobrevibacter smithii*. This organism has been linked to obesity in humans.[38] In addition, sulfate-reducing bacteria, such as *Desulfovibrio* species, are anaerobes that reduce sulfate to hydrogen sulfide (H2S). In addition to its role in SIBO, H2S is being studied as a possible etiologic factor in ulcerative colitis and colonic carcinogenesis.[39] In normal low levels H2S has GI protective activity.[40]

Pathophysiology of SIBO: Autoimmunity

Postinfectious IBS (PI-IBS) has been shown to have an autoimmune etiology in both murine and human studies (see figure 1). Infectious gastroenteritis is the most significant environmental risk factor for IBS.[41] Organisms that trigger PI-IBS include *Campylobacter, Salmonella, Shigella, E. coli*, viruses, and *Giardia*.[42–45]

Cytolethal distending toxin (CDT) is produced by enteric pathogens that cause PI-IBS. *Campylobacter jejuni* is the prototypical bacterium that produces CDT.[46] Other bacteria that produce CDT include *Haemophilus ducreyi* (chancroid), *Aggregatibacter actinomycetemcomitans* (periodontitis), *Escherichia coli* (traveler's diarrhea), *Shigella dysenteriae* (dysentery), *Salmonella enterica* (typhoid fever), and *Campylobacter upsaliensis* (enterocolitis).

The interstitial cells of Cajal (ICC) are fibroblast-like cells that act as pacemakers for the migrating motor complex (MMC). A key underlying cause of SIBO is thought to be deficiency of the MMC, which moves debris and bacteria down into the large intestine during fasting at night and between meals.[47] The number of ICC is reduced in post-*Campylobacter jejuni* gastroenteritis infected rats that eventually develop SIBO.[48] Three months after *C. jejuni* gastroenteritis, 27% of rats had SIBO. These rats had a lower number of ICC than controls in the jejunum and ileum (0.12 ICC/villus was the threshold for developing SIBO).

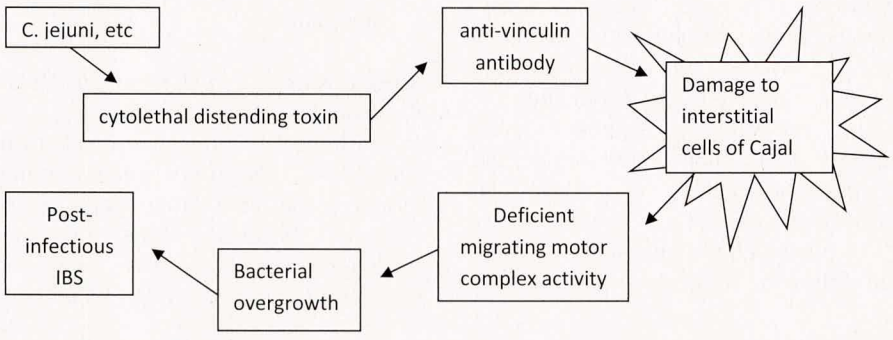
CDT toxin may destroy the interstitial cell of Cajal by stimulating the production of autoantibodies against a cytoskeletal protein known as vinculin. The antigen-antibody complexes between antivinculin antibodies and cytolytic distending toxin lead to autoimmune destruction of ICC.[49,50]

How SIBO Causes the Symptoms of IBS

There are two main pathophysiological issues involved in SIBO. First, bacteria can ferment carbohydrates and consume other nutrients ingested by the host simply by their inappropriate location in the small intestine. This allows them premature exposure to host nutrition before there is time for absorption. Bacterial fermentation produces hydrogen and/or hydrogen sulfide gas. In addition *M. smithii* produces methane.[51] *M. smithii* may be present in the intestinal tracts of up to 95.7% of humans.[52] Microbial gas leads to the IBS symptoms of bloating, pain, altered bowel movements, eructation, and flatulence (Figure 2).

The quantity of gas may be extensive, causing severe bloating and distention.[53] It is estimated that with normal levels of enteric flora, the quantity of lactose in an ounce of milk fuels the production of 50 cc of gas. With microbial overgrowth, gas levels produced from 1 ounce of milk may approach 5000 cc.[54] Excess gas can then exit the body as flatulence or eructation. A portion is also absorbed into the blood and eventually filters through the pulmonary alveolus to exit on exhalation. The intestines are sensitive to pressure, and therefore the pressure of distention can lead to abdominal pain. In addition, visceral hypersensitivity, a feature of IBS, may

Figure 1



create a lower threshold for pain/discomfort and a hyperresponsiveness of muscular contraction in response to the gas, leading to cramps.[55,56] The gases also affect bowel motility. Hydrogen has a greater association with diarrhea, and methane has an almost exclusive association with constipation.[57,58] Methane has been shown to slow gastrointestinal motility by 59% in animal studies, and the volume of methane overproduction correlates with the severity of constipation.[59,60] Therefore when both hydrogen and methane are present, diarrhea, constipation, or a mixture of both can be present based on the relative amounts of these gases.[61] It appears that the pressure created by either gas or the decreased gastric motility may lead to gastric distention resulting in gastroesophageal reflux (GERD).[62] The bacterial consumption and uptake of host nutrients, such as B12 and iron, can lead to macrocytic and/or microcytic anemia or chronic low ferritin levels in addition to general malabsorption and malnutrition in more severe cases.[63,64] The increased motility of diarrhea may also induce malabsorption. Finally, continuous fermentation of host nutrition by repeated exposure to daily meals perpetuates bacterial overgrowth and IBS symptoms, creating a vicious cycle (Figure 2).

The second mechanism is microbial damage to the digestive and absorptive function of the small intestine. Unlike the colon, the small intestine is not designed for heavy bacterial colonization. Commensal organisms may synthesize glycosidase, leading to damage of glycocalyx or disaccharidases. The gastrointestinal and systemic symptoms induced by these changes are listed in Figure 3. Key factors include bacterial deconjugation of bile, which induces fat malabsorption, steatorrhea, and fat–soluble vitamin deficiencies; bacterial digestion of disaccharidase enzymes, which furthers carbohydrate malabsorption, fermentation, and gas; and increased intestinal permeability (leaky gut), which often leads to systemic symptoms.[65–68]

Diagnosis of SIBO

As mentioned above, hydrogen/methane breath testing is the most common method of assessing SIBO. Instrumentation is available from Quintron Instrument Company in Milwaukee, Wisconsin. It builds and distributes the Breathtracker, which is used to measure these gases following a 24- to 48-hour prep diet and an overnight fast. After collection of the fasting baseline specimen, a solution of lactulose – an unabsorbable synthetic sugar – is ingested as the substrate for bacterial fermentation. Lactulose is nonabsorbable because only bacteria, not humans, produce the enzymes to digest it. Lactulose is a disaccharide solution of galactose and fructose in a base which also contains a minute quantity of lactose and epilactose.[69] Transit time for lactulose through the stomach and small bowel is approximately 120 minutes. Glucose may also be used as a test substance, but because of its rapid absorption in the proximal small intestine, it may fail to identify more distal SIBO.[70] Serial breath specimens are taken every 20 minutes during this time and for a third hour as well. Breath may be sampled and immediately analyzed at a lab, or these samples may be acquired at home using a series of tubes and a transfer device for later analysis. Home breath samples are exhaled into special vials similar to a Vacutainer tube, which store the labeled sample until it can be delivered to the lab. Not all labs have the equipment to test for methane, and the methodology for hydrogen sulfide is currently being perfected and is therefore not yet available. Testing for methane in addition to hydrogen is important because treatment varies based on the type of gas. The unique symptom of H2S production is "rotten egg" odor to the belching or flatus.

Preparation for the test varies from lab to lab, but a typical prep diet is limited to white rice, fish/poultry/meat, eggs, hard cheeses, clear beef or chicken broth (not bone broth or bouillon), oil, salt, and pepper. The purpose of the prep diet is to get a clear reaction to the lactulose solution by eliminating fermentable foods the day prior to testing. In cases of constipation, 2 days of prep diet may be needed to reduce baseline gases to negative. Antibiotics should not be used for at least 2 weeks prior to an initial test, although some sources recommend 4 weeks.[71] If symptoms allow, proton pump inhibitors should also be eliminated for at least seven days before testing.[72]

Interpretation of the test varies among practitioners. The criteria provided by Quintron for a positive test are as follows:

➤

Figure 2

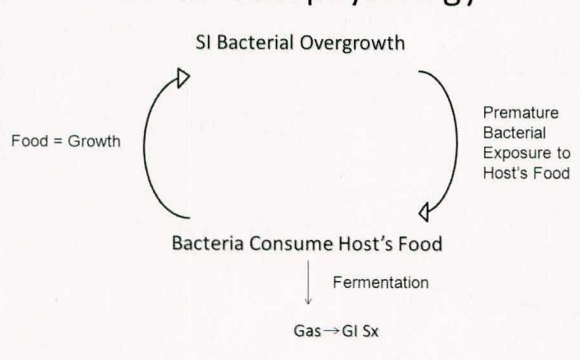
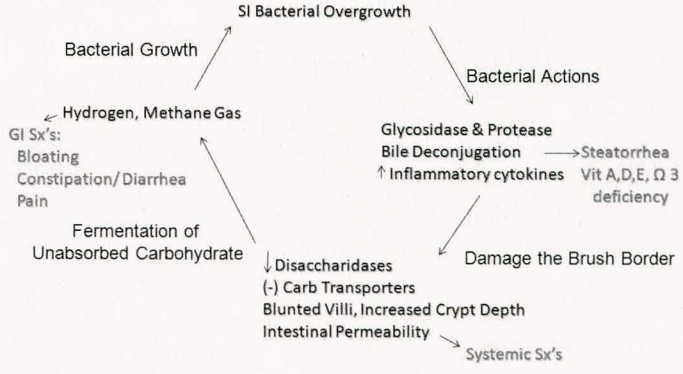


Figure 3



SIBO

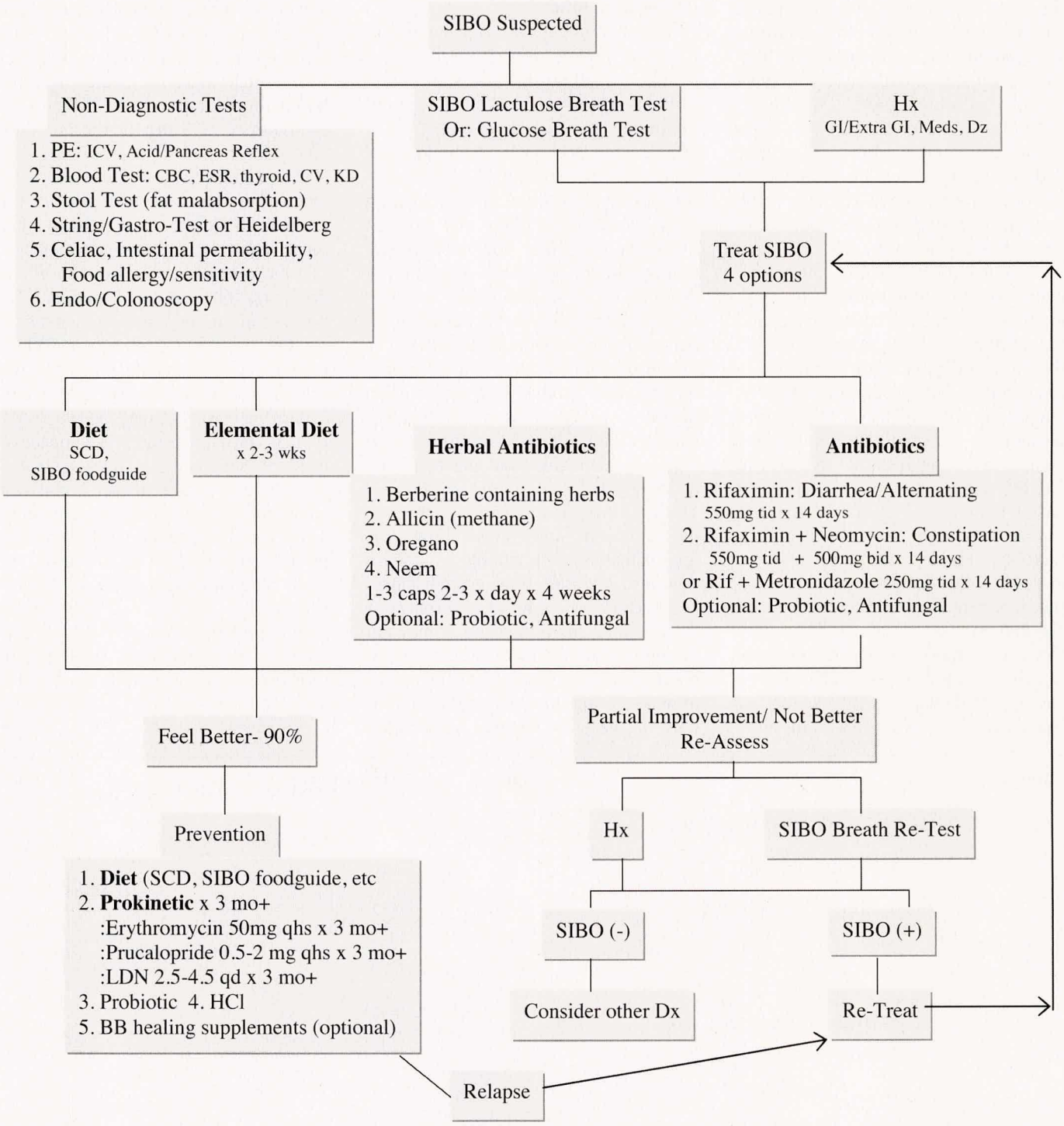
➤

- a rise over baseline in hydrogen production of 20 parts per million (PPM) or greater within 120 minutes after ingesting the test substrate;
- a rise over baseline in methane production of 12 ppm or greater within 120 minutes after ingesting the test substrate;
- a rise over baseline in the sum of hydrogen and methane production of 15 ppm or greater within 120 minutes after ingesting the test substrate.

Additional testing and interpretation parameters:

- Hydrogen sulfide SIBO may be suspected when the typical symptoms are present but the breath test shows "flat-line" hydrogen and methane levels.[73]

Figure 4: SIBO Treatment Protocol
Variation of the Cedars-Sinai Protocol (Pimentel 2006)
Siebecker & Sandberg-Lewis (2014)



- Modest levels of methane gas at any level equal or greater than 3 ppm at any sample on a 3-hour lactulose breath test may be a cause of methane-induced constipation.[74]
- A "spot methane" level may be used for follow-up testing in methane-positive individuals. When testing methane alone, there is no need for a preparatory diet or fasting prior to this single breath sample.

IBS subjects who have elevated breath methane are constipated in most cases. In murine studies, methane infusion prolonged intestinal transit time.[75]

We have found that an absolute level of gases, without a rise over baseline, correlates well with clinical SIBO. This is especially true for methane gas, which can have a pattern of elevated baseline which remains elevated for the duration of the test. In cases such as these, methane may only rise a few ppm over baseline, but the level is consistently above positive. Interpretation of elevated hydrogen or methane on the baseline specimen (pre-lactulose ingestion) is controversial, but at the SIBO Center we prefer to consider a high baseline methane to be a positive test.[76]

The classic positive for SIBO has been considered to be a double peak, with the first peak representing the small intestine and the second peak representing the normal large intestine bacteria. It is not essential to have a second peak in order to have an accurate test. We find that a single peak which rises highest in the third hour may also represent distal SIBO followed by the normal colonic gas levels.

Breath testing may be used in pediatric cases, so long as the child can follow instructions to collect the samples. For those under 3 years old, testing is best done on site at a lab due to differences in collection methods versus at-home kits. Pediatric lactulose dosing is 1 g/kg body weight with a maximum of 10 g (22 pounds and above receive the max/adult dose of 10 g).[77] Lactulose is available only by prescription.

Treatment of SIBO

In 2006, Pimentel shared his treatment algorithm for SIBO, which included the use of antibiotics, elemental diet or both.[78] Our approach offers two additional options: diet and herbal antibiotics (Figure 4).

Diet

We advise the use of the Specific Carbohydrate Diet or the SIBO Specific Diet.[79,80] The latter (see www.siboinfo.com/diet.html) is a combination of the Specific Carbohydrate Diet, the low-FODMAP diet, and the clinical experience of Siebecker in the treatment of SIBO with diet. Bacteria use carbohydrates as their energy source and ferment them to gases; therefore, a low-carbohydrate diet can directly reduce symptoms by decreasing the amount of gas produced.[81] Reducing carbohydrates may also decrease the overall microbial load, though formal studies to validate this are lacking. The Specific Carbohydrate Diet and the SIBO Specific Diet greatly reduce the intake of polysaccharides, oligosaccharides, and disaccharides by eliminating all grains, starchy vegetables, lactose, and sweeteners other than honey or dextrose. Legumes are often avoided in initial phases of these diets. Many patients experience a rapid and significant decrease in symptoms after starting a SIBO diet. The Specific Carbohydrate Diet has been reported to have an 84% success rate for inflammatory bowel disease, a condition commonly associated with SIBO.[82,83] Patients who find the Specific Carbohydrate Diet or SIBO Specific Diet approach too restrictive can follow the Cedars-Sinai diet as described at www.gidoctor.net/diet-ibs-sibo.php.

The low-FODMAP diet is a nutritional plan that greatly reduces the fermentable levels of carbohydrate-containing foods and has a success rate of 76% in IBS.[84, 85] The low-FODMAP diet is not specifically designed for SIBO and therefore does not eliminate polysaccharide and disaccharide sources such as grains, starch, starchy vegetables, and sucrose. Eliminating these poly- and disaccharides is helpful in SIBO because these carbohydrates – which normally feed the host – also feed the increased numbers of microflora in the small intestine (Figure 2).

Diet alone has proved successful for infants and younger children, but for older children and adults, one or more of several treatment options are often needed to reduce bacteria quickly, particularly in cases in which the patient's diet becomes excessively limited in an attempt to obtain symptomatic relief. Additionally, any of the diets discussed above need to be customized to the individual by trial and error over time.

Low-carbohydrate diets often induce weight loss. Particular attention must be paid to underweight patients. Increased intake of winter squash, glucose, or honey may be recommended in these circumstances. White rice (jasmine/sticky variety is best) or white potato may also be needed to maintain weight along with medium-chain triglyceride sources such as coconut and other oils.

Diet is also essential for prevention of relapse following successful SIBO eradication. Pimentel recommends postponing any dietary changes until after the effective treatment of the microbial overgrowth, rather than during the treatment phase.[86] Our clinical experience with the SIBO Specific Diet is that it is beneficial for both the treatment and prevention phases.

Elemental Diet

An elemental diet can be used in place of antibiotics or herbal antibiotics to rapidly decrease bacteria. In the treatment of SIBO, elemental diet is used to the exclusion of all other food sources. These products are a powdered mix of free-form amino acids, fat, vitamins, and minerals as well as rapidly absorbed carbohydrates. The concept behind this treatment is that the nutrients will be absorbed before reaching the involved organisms, thus feeding the patient but starving the flora. It is used in place of all meals, for 2 to 3 weeks, and has a success rate of 80% to 85% using the Nestlé product Vivonex Plus.[87] Two versions of a homemade recipe for elemental diet can be found at www.siboinfo.com/elemental-formula.html. Elemental diets are not protein powders or typical detoxification formulas. They are available over the counter and are not reimbursed by most insurance coverage, which can make this treatment costly. Patients should be warned that Vivonex Plus or homemade

➤

elemental diets are very bitter tasting. Elemental diets may not be suitable to underweight patients who cannot afford to lose weight.

Herbal Antibiotics

While there have only been two published reports of herbal antibiotics in the treatment of SIBO, our experience is that they have similar effectiveness to antibiotics.[88,89] Chedid et al. studied patients with SIBO based on a positive lactulose breath test. A negative breath test after treatment was seen in 34% of the rifaximin- or triple-antibiotic-treated group vs. 46% of the herbal-treated group.

The study employed a pair of herbal formulas. The dosage was 2 capsules of each b.i.d. for 30 days. The two different paired formulas are listed in Table 1 below (FC-Cidal plus Dysbiocide or Candibactin-AR plus Candibactin-BR):

Table 1: Herbal Preparations for the Treatment of Small Intestine Bacterial Overgrowth

FC-Cidal	Dysbiocide	Candibactin-AR	Candibactin-BR
Proprietary blend, 500 mg: 1 capsule	Proprietary blend, 950 mg per 2 capsules	1 capsule, 408 mg contains:	1 capsule, 400 mg contains:
Tinospora cordifolia	*Antheum graveolens*	*Thymus vulgaris*	*Coptis chinensis*
Equisetum arvense	*Stemona sessilifolia*	*Origanum vulgare*	*Berberis aquifolium*
		Salvia officinalis	
Pau d'arco	*Artemisia absinthium*	*Melissa officinalis*	Berberine HCl
Thymus vulgaris	*Brucea javanica*		*Scutellaria baicalensis*
Urtica dioica	*Pulsatilla chinensis*		*Phellodendron chinense*
Artemisia dracunculus	*Hedyotis diffusa*		*Zingiber officinale*
Olea europaea	*Picrasma excelsa*		*Glycyrrhiza uralensis*
	Acacia catechu		*Rheum officinale*
	Achillea millefolium		

Antibiotics

The most studied and successful prescription antibiotic for SIBO is rifaximin (brand name Xifaxan). It has a broad spectrum of activity and is nonabsorbable. Its luminal status allows it to act locally, and it is therefore less likely to cause systemic side effects common to other antibiotics.[90] Rifaximin has up to a 91% success rate and is given at 550 mg t.i.d. × 14 days.[91,92] Many physicians continue to prescribe a lower dosage of 1200 mg b.i.d. × 10 days, although research shows a 22% increase in breath test normalization with the higher dosage. Suggested pediatric dosages are 200 mg t.i.d. × 7 days for ages 3 to 15 or 10 to 30 mg/kg.[93,94]

Additionally, rifaximin has several unique benefits: it purportedly does not cause yeast overgrowth and it decreases antibiotic resistance in bacteria by reducing plasmids.[95,96] Antibiotic resistance does not develop to rifaximin, making it effective for retreatments, and it has anti-inflammatory properties, decreasing intestinal inflammatory cytokines and inhibiting NF-κβ via the PXR gene.[97,98] Rifaximin as a solo antibiotic is best used for SIBO when only the hydrogen levels are elevated. When methane gas is also increased, double therapy of rifaximin plus neomycin (500 mg b.i.d. × 14 days) is more effective.[99] Many gastroenterologists use metronidazole (250 mg t.i.d. × 14 days) as an alternative to neomycin (unpublished). Since different antibiotic regimens are recommended based on the gas type, breath testing is necessitated when considering this treatment.

Furnari et al. compared the percentage of breath test normalization using rifaximin 1200 mg q.d. vs. rifaximin 1200 mg q.d. plus partially hydrolysed guar gum (5 g q.d.) for 10 days. The combination treatment was proved to be 23% more effective than rifaximin monotherapy.[100]

If hydrogen sulfide SIBO is suspected the same treatments as those used for methanogen overgrowth are indicated.

Biofilm Disruptors

Mucosal methanogenic organisms can elaborate biofilms.[101] The use of N-acetylcysteine, nattokinase, serrapeptase, or lumbrokinase may be considered in addition to herbal or prescription antibiotic treatment to provide mucolytic and biofilm disruption effects. As mentioned earlier in this article, there is evidence both for and against enteric mucosal biofilms and SIBO.

At our center we have used the following botanicals: *Allium sativum* (garlic), *Hydrastis canadensis* and other berberine-containing herbs, *Origanum vulgare* (oregano), and *Azadirachta indica* (neem). We have used these as both single agents and in various combinations at dosages that are at the upper end of label suggestions × 30 days. Specific single dosages that we have used include allicin extract of garlic: 450 mg b.i.d.-t.i.d., goldenseal/berberine: 5 g q.d. in divided dosage, emulsified oregano: 100 mg b.i.d. and a formula that contains 300 mg of neem plus a proprietary blend containing a total of 200 mg of the following: *Emblica officinalis, Terminalia chebula, Terminalia belerica, Tinospora cordifolia,* and *Rubia cordifolia*. The latter formula is dosed at 1 capsule t.i.d. Researchers at Johns Hopkins have studied other herbal combinations that are listed in Table 1. Our breath testing has validated the need for the longer treatment period of 30 days for herbal antibiotics compared with 14 days for prescription antibiotics. Note that although whole garlic is a high-FODMAP food, we do not observe purified allicin to provoke symptoms in our patients. Allicin is the only herb which we have noted so far that can reduce breath methane levels. We have also observed that some patients experience prolonged die-off reactions with herbal treatment that can last for the duration of the treatment course. More studies on herbal antibiotics for SIBO are needed, particularly to identify botanicals effective in reducing methane.

Prevention

SIBO is a disease that relapses because eradication itself does not always correct the underlying cause.[102,103] Pimentel's 2006 treatment algorithm includes 2 essential preventions: diet and a prokinetic (motility agent). Our approach offers additional options: hydrochloric acid, probiotics, and brush border healing supplements. Also worth consideration are physical exercises, breathing techniques, acetylcholine precursors and modulators of neural inflammation.

Prokinetics

A key underlying cause of SIBO is thought to be deficient activity of the migrating motor complex (MMC). An intact MMC moves debris and bacteria down into the large intestine during fasting at night and between meals.[104] Prokinetics stimulate the MMC, symptomatically correcting this underlying cause. Iberogast is a German compound botanical tincture with possible prokinetic action.[105] This formula includes alcoholic extracts of *Iberis amara totalis recens, Angelicae radix, Cardui mariae fructus, Chelidonii herba, Liquiritiae radix, Matricariae flos, Melissae folium, Carvi fructus,* and *Menthae piperitae folium*. It has been used to treat functional dyspepsia and IBS since the 1960s. One study found symptom improvement, but no increase in gastric emptying, which suggests that if this formula is prokinetic, it is likely not the only mechanism underlying its action in IBS.[106] A double-blind controlled trial compared Iberogast with cisapride (a prescription prokinetic with limited special use in the US due to cardiovascular side effects). The herbal formula performed as well as the prokinetic drug for functional dyspepsia and was superior to metoclopramide in a retrospective cohort study of 961 patients.[107,108] It has also been shown to be effective for IBS in children.[109,110]

Prescription prokinetics studied for SIBO include low dose naltrexone 2.5 mg q.h.s. for IBS-D or 2.5 mg b.i.d. for IBS-C, low-dose erythromycin 50 mg q.h.s., and tegaserod 2 to 6 mg q.h.s.[112,111] Tegaserod has a higher success rate for SIBO prevention versus erythromycin but has been withdrawn from the US for safety reasons.[113] Prucalopride (Resolor), 0.5 to 2 mg q.h.s., is not yet available in the US but is a safer alternative to tegaserod.[114] It is presently available in Canada and Europe. A trial removal of a prokinetic at ≥3 months is suggested but continued long term use may be needed for some patients.[115]

Diet

A lower-carbohydrate diet is used in combination with a prokinetic to discourage a return of bacterial overgrowth. Once the breath test has normalized and small intestine damage has healed, the diet can be expanded beyond the strictness of the Specific Carbohydrate and SIBO Specific diets. The time frame for this is uncertain. Two studies have examined the rate of healing post SIBO and found that intestinal permeability normalized 4 weeks after successful SIBO eradication in 75% to 100% of patients.[116,117] While these reports are very encouraging, they may or may not reflect the other repair needed post SIBO. Therefore, we currently suggest continuing a SIBO diet for 1 to 3 months post successful eradication. At this point, the Cedars-Sinai Diet, low-FODMAP Diet, or a similar diet may be adopted long term, as the patient tolerates.[118,119] These diets allow more carbohydrates in the form of grains, gluten-free grains, cane sugar, and soy, though they still limit overall carbohydrate load.

Spacing meals 4 to 5 hours apart, with nothing ingested but water, allows for activity of the MMC.[120] We have found this to be very helpful clinically. If a low-carbohydrate SIBO diet does not correct hypoglycemia, this strategy will need to be altered to allow for more frequent meals.

Optional Supplements

Hydrochloric acid or herbal bitter supplements, which encourage hydrochloric acid (HCl) secretion, may be used to decrease the load of incoming bacteria.[121] When considering HCl supplementation, Heidelberg testing for HCl levels and response to treatments is the gold standard. Heidelberg testing reveals achlorhydria, frank hypochlorhydria, and hidden hypochlorhydria and allows individualization of dosing.

Probiotics are a controversial intervention in SIBO because lactobacilli have been cultured in SIBO and there is also concern about adding to the bacterial overload.[122] Despite this, the few studies that have focused directly on probiotics for treatment of SIBO have shown good results. *Bacillus clausii* as a sole treatment normalized the breath test in 47% of cases.[123] An 82% clinical improvement in SIBO was found using a combination of *Lactobacillus casei* and *plantarum, Streptococcus faecalis,* and *Bifidobacterium brevis* (Bioflora).[124] Probiotic yogurt containing *Lactobacillus johnsonii* normalized cytokine responses, thereby reducing the low-grade chronic inflammation found in SIBO after 4 weeks.[125] We have used various multistrain and single probiotics as well as yogurt and cultured vegetables with our SIBO patients with good results. A key point for the use of probiotic supplements in SIBO is to avoid *pre*biotics as main ingredients. Prebiotics are fermentable food for bacteria that can exacerbate symptoms during active SIBO and encourage bacterial growth post SIBO. Common prebiotics found in probiotic supplements include FOS (fructooligosaccharide), inulin, arabinogalactan, MOS (mannose-oligosaccharide), and GOS (galactooligosaccharide). Prebiotics may be tolerated in small amounts used as base ingredients, but this depends on the individual.

Brush border healing supplements may be given to assist the repair of small intestine tissue. While mucilaginous herbs are traditionally employed for this purpose (licorice, slippery elm, aloe vera, marshmallow), their use is controversial post SIBO, due to their high level of mucopolysaccharides, which are fermentable and could encourage bacterial regrowth. Specific nutrients we have used include lactose-free colostrum, 2 to 6 g q.d.; L-glutamine, 375 mg to 1500 mg q.d.; zinc carnosine, 75 mg b.i.d.; vitamins A and D, often given as cod liver oil, 1 tbsp q.d.; curcumin, 400 mg to 3 g q.d.; resveratrol, 250 mg to 2 g q.d. glutathione (oral liposomal), 50 to 425 mg q.d.; or glutathione precursor N-acetylcysteine 200 to 600 mg q.d.,

➤

➤

Supplements are given for 1 to 3 months, though may be continued long term for general benefit if desired. Higher dosages of curcumin and resveratrol are given for 2 weeks for the purpose of downregulating NF-κβ, a mediator of increased intestinal permeability, and then reduced to maintenance levels.[126–128] Herbal cholinergic support may include phosphatidyl choline, pantothenic acid, huperzine A (from *Huperzia serrata*), and N-aceytl-L-carnitine.[129] Pranayama (yogic alternate nostril breathing) has been shown to have benefits in IBS-D by normalizing parasympathetic tone.[130]

If dampening of CNS inflammation is indicated, consider the use of green tea catechins, *Curcuma longa*, bioflavonoids, *Scutellaria*, resveratrol, *Chrysanthemum morifolium* leaf, and *Matricaria chamomilla*.[131]

In our practices we have found that the following circumstances increase the chances for an unsatisfactory patient outcome:

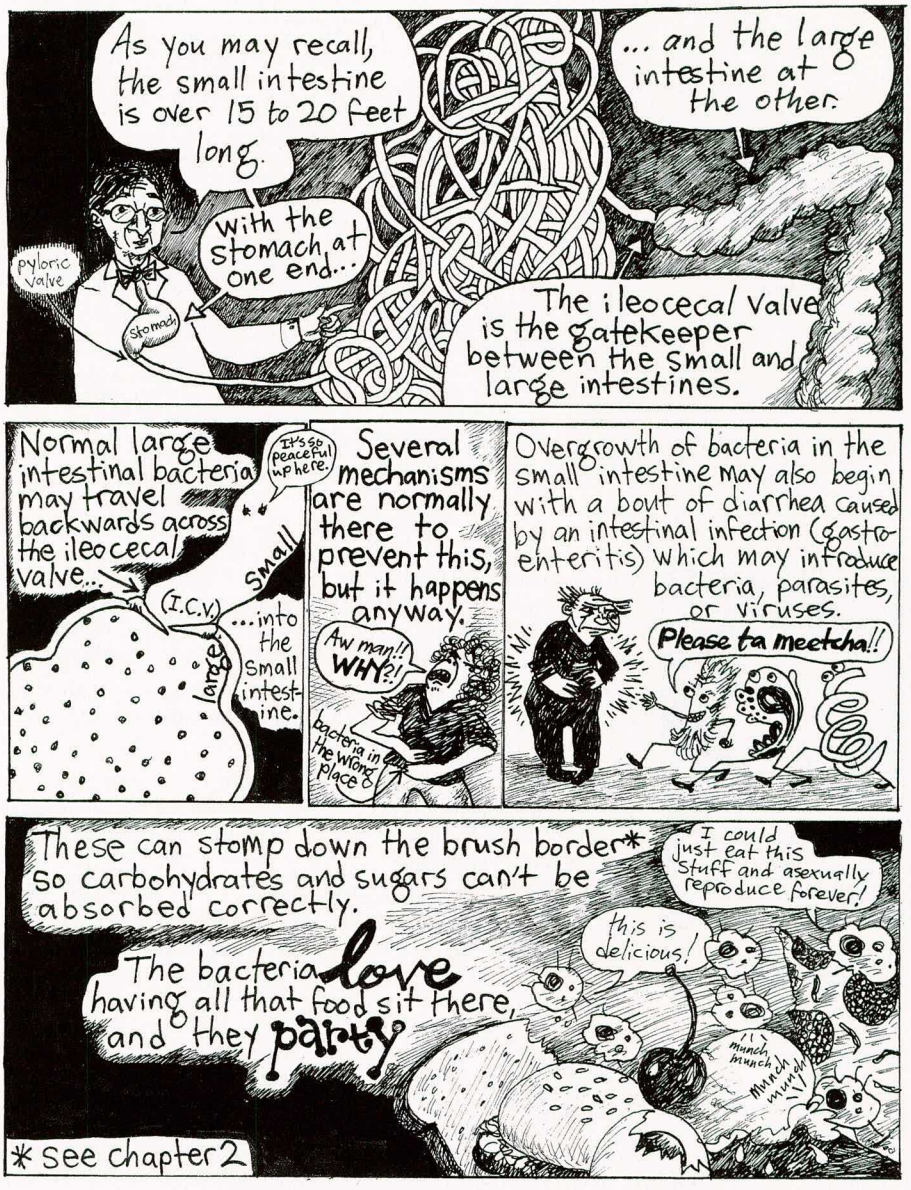
- *Failure to continue treatment courses until SIBO is eradicated (negative breath test or patient ≥90% better).* This crucial process of successive treatment is indicated by the long go-back arrow on the right side of our algorithm (Figure 4, p. 70).
- *Failure to use double antibiotic therapy for methane producers.* Methanogenic flora need different antibiotic treatment than hydrogen-producing bacteria.
- *Failure to utilize breath testing to identify if patients have SIBO, the type of gas that they produce, and the overall level of gas.* This information is necessary for diagnosis, treatment choice/duration, and prognosis.
- *Failure to use a prokinetic immediately following treatment.* Prokinetics along with diet are needed to prevent relapse of this commonly recurring condition. Antibiotic treatment as a sole therapy typically leads to recurrence of hydrogen SIBO within 3 months and methane SIBO within 1 month.[127]
- *Failure to use a low-carb preventative diet following treatment.* Diet along with prokinetics is needed to prevent relapse of this commonly recurring condition.
- *Failure to tailor diet to individual tolerances with personal experimentation.* No fixed diet can predict an individual's complex bacterial, digestive, absorptive, immunological, and genetic circumstances; therefore customizing is necessary.
- *Failure to identify underlying causative conditions.* One report found that the following conditions led to a poor response to antibiotics: anatomical abnormalities (adhesions, blind loops, diverticuli, superior mesenteric artery syndrome, etc.), chronic narcotic use, Addison's disease, scleroderma, colonic inertia, inflammatory bowel disease, and NSAID-induced intestinal ulceration.[128] Some of these patients will need long term cyclical rotation of herbal treatments or, very rarely, a 550 mg single dose of rifaximin every other day in order to stay asymptomatic.
- Failure to find the underlying causes to allow for repair or modulation of the MMC will lead to a less desirable outcome.

Notes

1. Peralta S et al. Small intestine bacterial overgrowth and irritable bowel syndrome-related symptoms: experience with Rifaximin. *World J Gastroenterol.* 2009 Jun 7;15(21):2628–2631.
2. Lin HC, et al. Small intestinal bacterial overgrowth: a framework for understanding irritable bowel syndrome. *JAMA.* 2004 Aug 18;292(7):852–858.
3. Pyleris E et al. The prevalence of overgrowth by aerobic bacteria in the small intestine by small bowel culture: relationship with irritable bowel syndrome. *Dig Dis Sci.* 2012 May;57(5):1321–1329.
4. Pimentel M, Chow EJ, Lin HC. Normalization of lactulose breath testing correlates with symptom improvement in irritable bowel syndrome. A double-blind, randomized, placebo-controlled study. *Am J Gastroenterol.* 2003 Feb;98(2):412–419.
5. Anantharaju A Klamut M, Small intestinal bacterial overgrowth: a possible risk factor for metabolic bone disease. *Nutr Rev.* 2003 Apr;61(4):132–135.
6. Lauritano EC et al. Association between hypothyroidism and small intestinal bacterial overgrowth. *J Clin Endocrinol Metab.* 2007 Nov;92(11):4180–4184.
7. Almeida JA et al. Lactose malabsorption in the elderly: role of small intestinal bacterial overgrowth. *Scand J Gastroenterol.* 2008;43(2):146–154.
8. Kaur J, Prolonged orocecal transit time enhances serum bile acids through bacterial overgrowth, contributing factor to gallstone disease. *J Clin Gastroenterol.* 2014 Apr;48(4):365–369.
9. Klaus J et al. Small intestinal bacterial overgrowth mimicking acute flare as a pitfall in patients with Crohn's Disease. *BMC Gastroenterol.* 2009 Jul 30;9:61.
10. Marie I, Ducrotté P, Denis P, Menard JF, Levesque H. Small intestinal bacterial overgrowth in systemic sclerosis. *Rheumatology (Oxford).* 2009 Oct;48(10):1314–1319. Epub 2009 Aug 20.
11. Rubio-Tapia A, et al. Prevalence of small intestine bacterial overgrowth diagnosed by quantitative culture of intestinal aspirate in celiac disease. *J Clin Gastroenterol.* 2009 Feb;43(2):157–161.
12. Mancilla A C et al. [Small intestine bacterial overgrowth in patients with chronic pancreatitis]. *Rev Med Chil.* 2008 Aug;136(8):976–980.
13. Tursi A, Assessment of small intestinal bacterial overgrowth in uncomplicated acute diverticulitis of the colon. *World J Gastroenterol.* 2005 May 14;11(18):2773–2776.
14. Ojetti V et al. Small bowel bacterial overgrowth and type 1 diabetes. *Eur Rev Med Pharmacol Sci.* 2009 Nov–Dec;13(6):419–423.
15. Goebel A et al. Altered intestinal permeability in patients with primary fibromyalgia and in patients with complex regional pain syndrome. *Rheumatology (Oxford).* 2008 Aug;47(8):1223–1227.
16. Gupta A et al. Role of small intestinal bacterial overgrowth and delayed gastrointestinal transit time in cirrhotic patients with minimal hepatic encephalopathy. *J Hepatol.* 2010 Nov;53(5):849–855.
17. Shanab AA et al. Small intestinal bacterial overgrowth in nonalcoholic steatohepatitis: association with toll-like receptor 4 expression and plasma levels of interleukin 8. *Dig Dis Sci.* 2011 May;56(5):1524–1534.
18. Weinstock LB, Klutke CG, Lin HC, Small intestinal bacterial overgrowth in patients with interstitial cystitis and gastrointestinal symptoms. *Dig Dis Sci.* 2008 May;53(5):1246–1251.
19. Weinstock LB, Walters AS, Restless legs syndrome is associated with irritable bowel syndrome and small intestinal bacterial overgrowth. *Sleep Med.* 2011 Jun;12(6):610–613.
20. Parodi A et al. Small intestinal bacterial overgrowth in rosacea: clinical effectiveness of its eradication. *Clin Gastroenterol Hepatol.* 2008 Jul;6(7):759–764.
21. Kim KM, Erosive esophagitis may be related to small intestinal bacterial overgrowth. *Scand J Gastroenterol.* 2012 May;47(5):493–498.
22. Pimentel M. Personal communication. 2014
23. Husebye E. The patterns of small bowel motility: physiology and implications in organic disease and functional disorders. *Neurogastroenterol Motil.* 1999 Jun;11(3):141–161.
24. Bures J. 2010 Small intestinal bacterial overgrowth syndrome. *World J Gastroenterol.* 2010 Jun 28;16(24):2978–2990.
25. Machado WM et al. The small bowel flora in individuals with cecoileal reflux. *Arq Gastroenterol.* 2008 Jul–Sep;45(3):212–218.
26. Roland BC. Low ileocecal valve pressure is significantly associated with small intestinal bacterial overgrowth (SIBO). *Dig Dis Sci.* 2014 Jun;59(6):1269–1277.
27. Gabbard SL. The impact of alcohol consumption and cholecystectomy on small intestinal bacterial overgrowth. *Dig Dis Sci.* 2014 Mar;59(3):638–644.
28. Chedid V. Herbal therapy is equivalent to rifaximin for the treatment of small intestinal bacterial overgrowth. *Glob Adv Health Med.* 2014 May;3(3):16–24.
29. Macfarlane S. Microbial biofilm communities in the gastrointestinal tract. *J Clin Gastroenterol.* 2008 Sep;42 Suppl 3 Pt 1:S142–S143.
30. Gabbard SL. The impact of alcohol consumption and cholecystectomy on small intestinal bacterial overgrowth. *Dig Dis Sci.* 2014 Mar;59(3):638–644.
31. Pyleris E et al. The prevalence of overgrowth by aerobic bacteria in the small intestine by small bowel culture: relationship with irritable bowel syndrome. *Dig Dis Sci.* 2012 May;57(5):1321–1329.
32. Jacobs C. Dysmotility and proton pump inhibitor use are independent risk factors for small intestinal bacterial and/or fungal overgrowth. *Aliment Pharmacol Ther.* 2013 Jun;37(11):1103–1111.
33. Khoshini R, Dai SC, Lezcano S, Pimentel M. A systematic review of diagnostic tests for small intestinal bacterial overgrowth. *Dig Dis Sci.* 2008 Jun;53(6):1443–1454.
34. Pimentel M. Gut microbes and irritable bowel syndrome [webcast]. GastroIntestinal Health Foundation. July 20, 2012. http://www.gihealthfoundation.org/coe/ibs/webcast/2012/july/MPimentel/?link=2012/july/MPimentel&cme_proj_id=12&actionPage=topics/Gut_Microbes_and_IBS/request-for-credit.cfm?cme_proj_id=12. Accessed on October 27, 2012.
35. Bouhnik Y et al. Bacterial populations contaminating the upper gut in patients with small intestinal bacterial overgrowth syndrome. *Am J Gastroenterol.* 1999 May;94(5):1327–1331.
36. Pyleris E et al. The prevalence of overgrowth by aerobic bacteria in the small intestine by small bowel culture: relationship with irritable bowel syndrome. *Dig Dis Sci.* 2012 May;57(5):1321–1329.
37. Carbonero F. Microbial pathways in colonic sulfur metabolism and links with health and disease. *Front Physiol.* 2012 Nov 28;3:448.
38. Million M. Correlation between body mass index and gut concentrations of Lactobacillus reuteri, Bifidobacterium animalis, Methanobrevibacter smithii and Escherichia coli. *Int J Obes (Lond).* 2013 Nov;37(11):1460–1466.
39. Medani M. Emerging role of hydrogen sulfide in colonic physiology and pathophysiology. *Inflamm Bowel Dis.* 2011 Jul;17(7):1620–1625
40. Elsheikh W. Enhanced chemopreventive effects of a hydrogen sulfide-releasing anti-inflammatory drug (ATB-

346) in experimental colorectal cancer. *Nitric Oxide*. 2014 Sep 15;41:131–137.
41. Rodríguez LA. Ruigómez A. Increased risk of irritable bowel syndrome after bacterial gastroenteritis: cohort study. *BMJ*. 1999 Feb 27;318(7183):565–566.
42. Ibid.
43. Beatty JK. Post-infectious irritable bowel syndrome: mechanistic insights into chronic disturbances following enteric infection. *World J Gastroenterol*. 2014 Apr 14;20(14):3976–3985.
44. Zanini B. Incidence of post-infectious irritable bowel syndrome and functional intestinal disorders following a water-borne viral gastroenteritis outbreak. *Am J Gastroenterol*. 2012 Jun;107(6):891–899.
45. Hanevik K. Development of functional gastrointestinal disorders after Giardia lamblia infection. *BMC Gastroenterol*. 2009 Apr 21;9:27.
46. Pokkunuri V. Role of cytolethal distending toxin in altered stool form and bowel phenotypes in a rat model of post-infectious irritable bowel syndrome. *J Neurogastroenterol Motil*. 2012 Oct;18(4):434–442.
47. Pimentel M. Low-dose nocturnal tegaserod or erythromycin delays symptom recurrence after treatment of irritable bowel syndrome based on presumed bacterial overgrowth. *Gastroenterol Hepatol (N Y)*. 2009 Jun;5(6):435–442.
48. Pokkunuri. Op cit.
49. Sung J et al Effect of repeated Campylobacter jejuni infection on gut flora and mucosal defense in a rat model of post infectious functional and microbial bowel changes. *Neurogastroenterol Motil*. 2013 Jun;25(6):529–537.
50. Pimentel M et al. Autoimmunity links vinculin to the pathophysiology of functional bowel changes following Campylobacter jejuni infection in a rat model. *Dig Dis Sci*. Epub 2014 Nov.
51. Kim G. Methanobrevibacter smithii is the predominant methanogen in patients with constipation-predominant IBS and methane on breath. *Dig Dis Sci*. 2012 Dec;57(12):3213–3218.
52. Dridi B. High prevalence of Methanobrevibacter smithii and Methanosphaera stadtmanae detected in the human gut using an improved DNA detection protocol. *PLoS One*. 2009 Sep 17;4(9):e7063.
53. Youn YH, Park JS, Jahng JH, et al. Relationships among the lactulose breath test, intestinal gas volume, and gastrointestinal symptoms in patients with irritable bowel syndrome. *Dig Dis Sci*. 2011 Jul;56(7):2059–2066.
54. Gottschall E. *Breaking the Vicious Cycle: Intestinal Health Through Diet*. Baltimore, ON: Kirkton Press Ltd.; 1994.
55. Elsenbruch S. Abdominal pain in Irritable Bowel Syndrome: a review of putative psychological, neural and neuro-immune mechanisms. *Brain Behav Immun*. 2011 Mar;25(3):386–394. Epub 2010 Nov 20.
56. Pimentel M. *A New IBS Solution*. Sherman Oaks, CA; Health Point Press; 2006.
57. Pimentel M, Mayer AG, Park S, Chow EJ, Hasan A, Kong Y. Methane production during lactulose breath test is associated with gastrointestinal disease presentation. *Dig Dis Sci*. 2003 Jan;48(1):86–92.
58. Kunkel D et al. Methane on breath testing is associated with constipation: a systematic review and meta-analysis. *Dig Dis Sci*. 2011 Jun;56(6):1612–1618.
59. Pimentel M, Lin HC, Enayati P, et al. Methane, a gas produced by enteric bacteria, slows intestinal transit and augments small intestinal contractile activity. *Am J Physiol Gastrointest Liver Physiol*. 2006 Jun;290(6):G1089–G1095.
60. Chatterjee S et al. The degree of breath methane production in IBS correlates with the severity of constipation. *Am J Gastroenterol*. 2007 Apr;102(4):837–841.
61. Pimentel M, Mayer AG, Park S, Chow EJ, Hasan A, Kong Y. Methane production during lactulose breath test is associated with gastrointestinal disease presentation. *Dig Dis Sci*. 2003 Jan;48(1):86–92.
62. Kim KM, Erosive esophagitis may be related to small intestinal bacterial overgrowth. *Scand J Gastroenterol*. 2012 May;47(5):493–498.
63. Singh VV, Toskes PP. Small bowel bacterial overgrowth: presentation, diagnosis, and treatment. *Curr Treat Options Gastroenterol*. 2004 Feb;7(1):19–28.
64. Leung Ki EL. Small intestine bacterial overgrowth. *Rev Med Suisse*. 2010 Jan 27;6(233):186–188,190–191.
65. DiBaise JK. Nutritional consequences of small intestinal bacterial overgrowth. *Prac Gastroenterol*. 2008;69:15–28.
66. Prizont R. Glycoprotein degradation in the blind loop syndrome: identification of glycosidases in jejunal contents. *J Clin Invest*. 1981 Feb;67(2):336–344.
67. Lauritano EC, Valenza V, Sparano L, et al. Small intestinal bacterial overgrowth and intestinal permeability. *Scand J Gastroenterol*. 2010 Sep;45(9):1131–1132.
68. Resnick C. Nutritional protocol for the treatment of intestinal permeability defects and related conditions. *Nat Med J*. March 2010.
69. Lactulose solution USP label. Pharmaceutical Assoc. Inc. Greenville, SC 29605.
70. Pimentel M. Report from the multinational irritable bowel syndrome initiative 2012. *Gastroenterology*. 2013 Jun;144(7):e1–e5.
71. Eisenmann A et al. Implementation and interpretation of hydrogen breath tests. *J Breath Res*. 2008 Dec;2(4):046002.
72. Costa MB. Evaluation of small intestine bacterial overgrowth in patients with functional dyspepsia through H2 breath test. *Arq Gastroenterol*. 2012 Dec;49(4):279–283.
73. Pimentel M. Lecture at the SIBO Symposium. Portland OR; 2014.
74. Ibid.
75. Attaluri A. Methanogenic flora is associated with altered colonic transit but not stool characteristics in constipation without IBS. *Am J Gastroenterol*. 2010 Jun;105(6):1407–1411.
76. Quigley EM, Quera R. Small intestinal bacterial overgrowth: roles of antibiotics, prebiotics, and probiotics. *Gastroenterology*. 2006 Feb;130(2 Suppl 1):S78–S90.
77. Quin Tron Instrument Company Inc. Quin Tron catalog and information. 2012:22.
78. Pimentel. *New IBS Solution*. 2006.
79. Gottschall. *Breaking the Vicious Cycle*. 1994.
80. Siebecker A. SIBO Specific Diet food guide. Available at http://www.siboinfo.com/uploads/5/4/8/4/5484269/sibo_specific_diet_food_guide_sept_2014.pdf.
81. Ong DK. Manipulation of dietary short chain carbohydrates alters the pattern of gas production and genesis of symptoms in irritable bowel syndrome. *J Gastroenterol Hepatol*. 2010 Aug;25(8):1366–1373.
82. Nieves R, Jackson RT. Specific carbohydrate diet in treatment of inflammatory bowel disease. *Tenn Med*. 2004 Sep;97(9):407.
83. Choung RS. Clinical predictors of small intestinal bacterial overgrowth by duodenal aspirate culture. *Aliment Pharmacol Ther*. 2011 May;33(9):1059–1067.
84. Shepherd SJ. The role of FODMAPs in irritable bowel syndrome. *Curr Opin Clin Nutr Metab Care*. 2014 Nov;17(6):605–609.
85. Staudacher HM, Whelan K, Irving PM, Lomer MC. Comparison of symptom response following advice for a diet low in fermentable carbohydrates (FODMAPs) versus standard dietary advice in patients with irritable bowel syndrome. *J Hum Nutr Diet*. 2011 Oct;24(5):487–495.

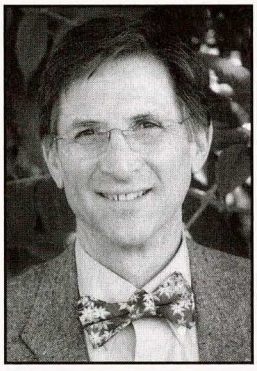
➤



SIBO

86. Pimentel M, Constantino T. A 14-day elemental diet is highly effective in normalizing the lactulose breath test. *Dig Dis Sci.* 2004 Jan;49(1):73–77.
87. Ibid.
88. Logan AC, Beaulne TM. The treatment of small intestinal bacterial overgrowth with enteric-coated peppermint oil: a case report. *Altern Med Rev.* 2002 Oct;7(5):410–417.
89. Chedid V. Herbal therapy is equivalent to rifaximin for the treatment of small intestinal bacterial overgrowth. *Glob Adv Health Med.* 2014 May;3(3):16–24.
90. Scarpignato C, Pelosini I. Experimental and clinical pharmacology of rifaximin, a gastrointestinal selective antibiotic. *Digestion.* 2006;73 Suppl 1:13–27.
91. Lombardo L, Increased Incidence of Small Intestinal Bacterial Overgrowth During Proton Pump Inhibitor Therapy. *Clin Gastroenterol Hepatol.* 2010 June; 8(6):504–508.
92. Pimentel M, Lembo A. TARGET Study Group. Rifaximin therapy for patients with irritable bowel syndrome without constipation. *N Engl J Med.* 2011 Jan 6;364(1):22–32.
93. Scarpellini E et al. Rifaximin treatment for small intestinal bacterial overgrowth in children with irritable bowel syndrome. *Eur Rev Med Pharmacol Sci.* 2013 May;17(10):1314–1320.
94. Muniyappa P et al. Use and safety of rifaximin in children with inflammatory bowel disease. *J Pediatr Gastroenterol Nutr.* 2009 Oct;49(4):400–404.
95. Scarpignato C. Pelosini I. Experimental and clinical pharmacology of rifaximin, a gastrointestinal selective antibiotic. *Digestion.* 2006;73 Suppl 1:13–27.
96. Debbia EA, Maioli E, Roveta S, Marchese A. Effects of rifaximin on bacterial virulence mechanisms at supra- and sub-inhibitory concentrations. *J Chemother.* 2008 Apr;20(2):186–194.
97. Yang J, Lee HR, Low K, Chatterjee S, Pimentel M. Rifaximin versus other antibiotics in the primary treatment and retreatment of bacterial overgrowth in IBS. *Dig Dis Sci.* 2008 Jan;53(1):169–174
98. Mencarelli A. Inhibition of NF-κB by a PXR-dependent pathway mediates counter-regulatory activities of rifaximin on innate immunity in intestinal epithelial cells. *Eur J Pharmacol.* 2011 Oct 1;668(1–2):317–324.
99. Low K, Hwang L, Hua J, Zhu A, Morales W, Pimentel M. A combination of rifaximin and neomycin is most effective in treating irritable bowel syndrome patients with methane on lactulose breath test. *J Clin Gastroenterol.* 2010 Sep;44(8):547–550.
100. Furnari M, Clinical trial: the combination of rifaximin with partially hydrolysed guar gum is more effective than rifaximin alone in eradicating small intestinal bacterial overgrowth. *Aliment Pharmacol Ther.* 2010 Oct;32(8):1000–1006.
101. Bang C. Biofilm formation of mucosa-associated methanoarchaeal strains. *Front Microbiol.* 2014 Jul 8;5:353.
102. Pimentel M, Morales W. Low-dose nocturnal tegaserod or erythromycin delays symptom recurrence after treatment of irritable bowel syndrome based on presumed bacterial overgrowth. *Gastroenterol Hepatol (N Y).* 2009 Jun;5(6):435–442.
103. Pimentel M. An evidence-based treatment algorithm for IBS based on a bacterial/SIBO hypothesis: Part 2. *Am J Gastroenterol.* 2010 Jun;105(6):1227–1230.
104. Pimentel M, Morales W. Low-dose nocturnal tegaserod or erythromycin delays symptom recurrence after treatment of irritable bowel syndrome based on presumed bacterial overgrowth. *Gastroenterol Hepatol (N Y).* 2009 Jun;5(6):435–442.
105. Ochoa-Cortes F. Potential for developing purinergic drugs for gastrointestinal diseases. *Inflamm Bowel Dis.* 2014 Jul;20(7):1259–1287.
106. Braden B. Clinical effects of STW 5 (Iberogast) are not based on acceleration of gastric emptying in patients with functional dyspepsia and gastroparesis. *Neurogastroenterol Motil.* 2009 Jun;21(6):632–638, e25.
107. Rösch W. A randomised clinical trial comparing the efficacy of a herbal preparation STW 5 with the prokinetic drug cisapride in patients with dysmotility type of functional dyspepsia. *Z Gastroenterol.* 2002 Jun;40(6):401–408.
108. Raedsch R. Assessment of the efficacy and safety of the phytopharmacon STW 5 versus metoclopramide in functional dyspepsia–a retrospective cohort study. *Z Gastroenterol.* 2007 Oct;45(10):1041–1048.
109. Leichtle K. Experience reports of the application of Iberogast in children. Research report. Steigerwald: Arzneimittelwerk; 1999.
110. Gundermann KJ, Vinson B, Hänicke S. Die funktionelle Dyspepsie bei Kindern – eine retrospektive Studie mit einem Phytopharmakon. *Päd.* 2004;10:1–6.
111. Ploesser J, Weinstock LB, Thomas E. Low dose naltrexone: side effects and efficacy in gastrointestinal disorders. *Int J Pharm Compd.* March 2010.
112. Pimentel M, Morales W. Low-dose nocturnal tegaserod or erythromycin delays symptom recurrence after treatment of irritable bowel syndrome based on presumed bacterial overgrowth. *Gastroenterol Hepatol (N Y).* 2009 Jun;5(6):435–442.
113. Pimentel M, Morales W. Low-dose nocturnal tegaserod or erythromycin delays symptom recurrence after treatment of irritable bowel syndrome based on presumed bacterial overgrowth. *Gastroenterol Hepatol (N Y).* 2009 Jun;5(6):435–442.
114. Manabe N, Rao AS, Wong BS, Camilleri M. Emerging pharmacologic therapies for irritable bowel syndrome. *Curr Gastroenterol Rep.* 2010 Oct;12(5):408–416.
115. Pimentel. *New IBS Solution.* 2006.
116. Lauritano EC. Small intestinal bacterial overgrowth and intestinal permeability. *Scand J Gastroenterol.* 2010 Sep;45(9):1131–1132.
117. Riordan SM et al. Luminal bacteria and small-intestinal permeability *Scan J Gastroenterol.* 1997 Jun;32(6):556–563.
118. Pimentel. *New IBS Solution.* 2006.
119. Gibson PR, Shepherd SJ. Evidence-based dietary management of functional gastrointestinal symptoms: The FODMAP approach. *J Gastroenterol Hepatol.* 2010 Feb;25(2):252–258. Review.
120. Pimentel. *New IBS Solution.* 2006.
121. Bowman G. The gut, the brain and the functional GI disorders. Functional Gastroenterology Seminar: Level 1. Winter 2010:19.
122. Bouhnik Y. Bacterial populations contaminating the upper gut in patients with small intestinal bacterial overgrowth syndrome. *Am J Gastroenterol.* 1999 May;94(5):1327–1331.
123. Gabrielli M. Bacillus clausii as a treatment of small intestinal bacterial overgrowth. *Am J Gastroenterol.* 2009 May;104(5):1327–1328.
124. Soifer LO, Peralta D, Dima G, Besasso H. Comparative clinical efficacy of a probiotic vs. an antibiotic in the treatment of patients with intestinal bacterial overgrowth and chronic abdominal functional distension: a pilot study. *Acta Gastroenterol Latinoam.* 2010 Dec;40(4):323–327.
125. Schiffrin EJ, Parlesak A, Bode C, et al. Probiotic yogurt in the elderly with intestinal bacterial overgrowth: endotoxaemia and innate immune functions. *Br J Nutr.* 2009 Apr;101(7):961–966.
126. Ruland J. Return to homeostasis: downregulation of NF-κB responses. *Nat Immunol.* 2011 Jun 19;12(8):709–714. doi:10.1038/ni.2055.
127. Al-Sadi RM, Ma TY. IL-1beta causes an increase in intestinal epithelial tight junction permeability. *J Immunol.* 2007 Apr 1;178(7):4641–4649.
128. Csaki C, Mobasheri A. Synergistic chondroprotective effects of curcumin and resveratrol in human articular chondrocytes: inhibition of IL-1beta-induced NF-kappaB-mediated inflammation and apoptosis. *Arthritis Res Ther.* 2009;11(6):R165.
129. Kharazian D. *The Digestion Sessions* [webinar series]. 2014.
130. Taneja I. Yogic versus conventional treatment in diarrhea-predominant irritable bowel syndrome: a randomized control study. *Appl Psychophysiol Biofeedback.* 2004 Mar;29(1):19–33.
131. Kharazian. *Digestion Sessions.* 2014.

◆



Dr. Steven Sandberg-Lewis is a practitioner of naturopathic gastroenterology. He has been in practice for 36 years, the first 18 years in private practice. In 1996 he joined the full-time faculty of the National College of Natural Medicine (NCNM) in Portland, Oregon. He engages in patient care four days per week and is a professor of gastroenterology. He is a frequent presenter at educational seminars around the US and Canada.

In 2013 he was listed among "Top Docs" in *Portland Magazine*. His articles on hiatal hernia and SIBO won first prize in the *Townsend Letter's* Best of Naturopathic Medicine in 2009 and 2013. His piece on proton pump inhibitors was an honorable mention in 2011.

As cofounder of the SIBO Center for Digestive Health at NCNM, Dr. Sandberg-Lewis often treats patients whose health conditions have defied diagnosis despite exhaustive medical testing. Restoring ideal digestive function and normalizing the gut microflora have earned the center a reputation for success in helping many who previously suffered digestive diseases without hope of cure.

Sandberg-Lewis is the author of the textbook *Functional Gastroenterology: Assessing and Addressing the Causes of Functional GI Disorders* (NCNM Press; 2009). He and his wife and son have also written a comic book explanation of SIBO for patients. The textbook and comic are both available at www.ncnm.edu/bookstore.

Allison Siebecker, ND, MSOM, LAc, is a graduate of the National College of Natural Medicine. Dr Siebecker is the cofounder and medical director of the SIBO Center for Digestive Health at NCNM Clinic in Portland, Oregon, where she specializes in the treatment of SIBO. She is instructor of advanced gastroenterology at NCNM, is the author of the educational website siboinfo.com, and is writing a book synthesizing the SIBO data into one source. In 2005 and 2013, she received the Best in Naturopathy award from the *Townsend Letter* for her articles "Traditional Bone Broth in Modern Health and Disease"(2005) and "Small Intestine Bacterial Overgrowth: Often Overlooked Cause of IBS" (2013).