



SIBO: Dysbiosis Has A New Name

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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 osteoporosis⁵
- 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 prebiotics;
- 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,

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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).

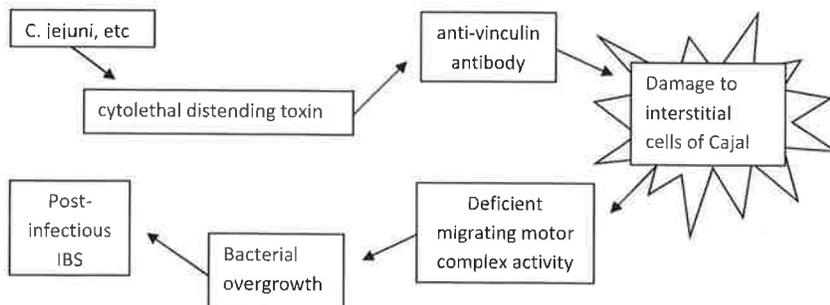
CDT toxin may destroy the interstitial cell of Cajal by stimulating the production of autoantibodies against a cytoskeletal protein known as vinculin. The antigen-antibody complexes between antivinculin antibodies and cytolytic distending toxin lead to autoimmune destruction of ICC.^{49,50}

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

SIBO Pathophysiology I

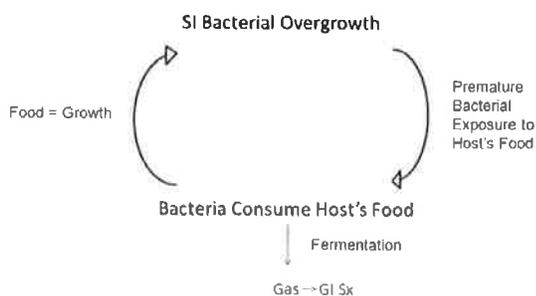
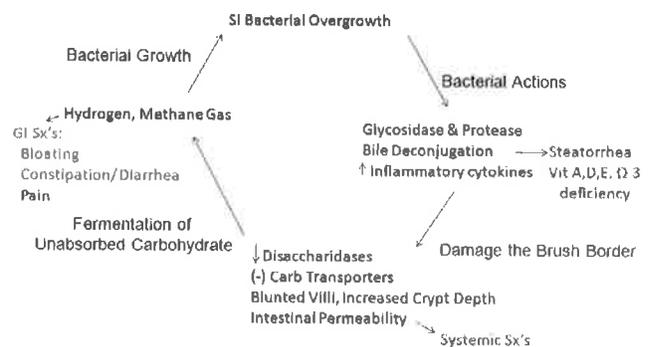


Figure 3

SIBO Pathophysiology II



SIBO

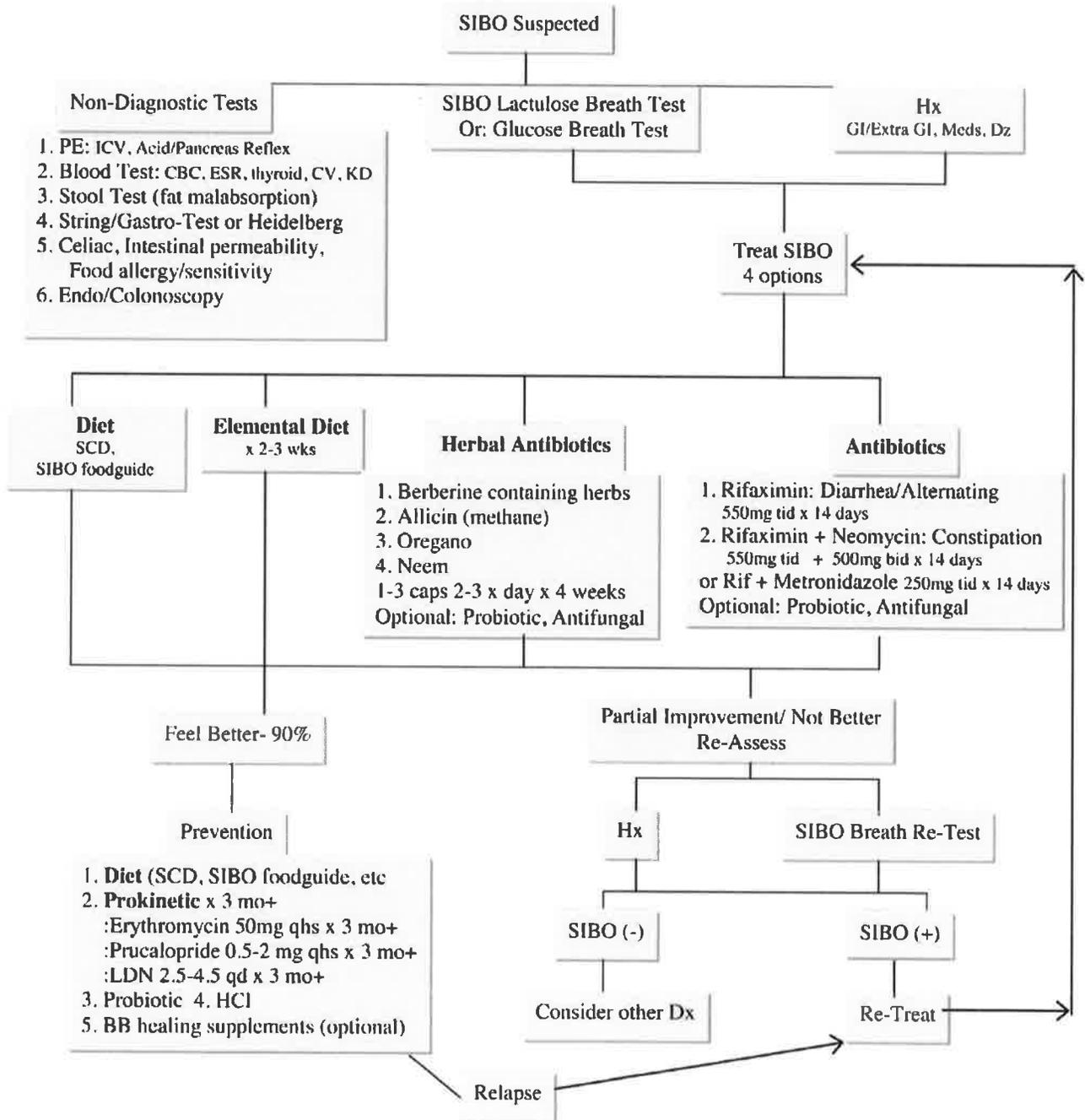
- a rise over baseline in hydrogen production of 20 parts per million (PPM) or greater within 120 minutes after ingesting the test substrate;

- 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



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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):

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.

Antibiotics

The most studied and successful prescription antibiotic for SIBO is

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- κ B 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. \times 14 days) is more effective.⁹⁹ Many gastroenterologists use metronidazole (250 mg t.i.d. \times 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

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

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 \times 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*

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. \times 14 days.^{91,92} Many physicians continue to prescribe a lower dosage of 1200 mg b.i.d. \times 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. \times 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

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.

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 breve* (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 prebiotics 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.,



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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- κ B, 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-acetyl-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 \geq 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.**

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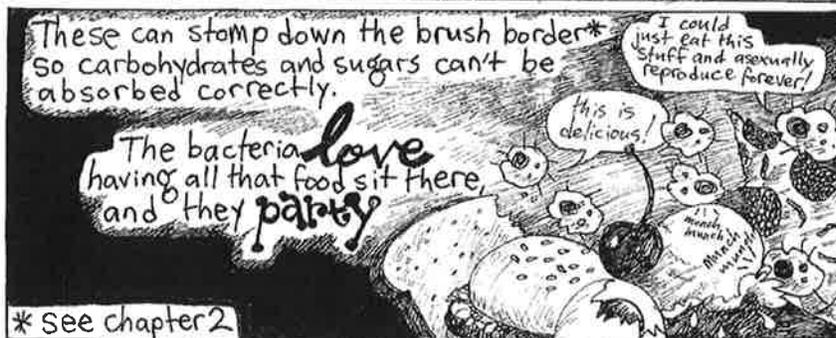
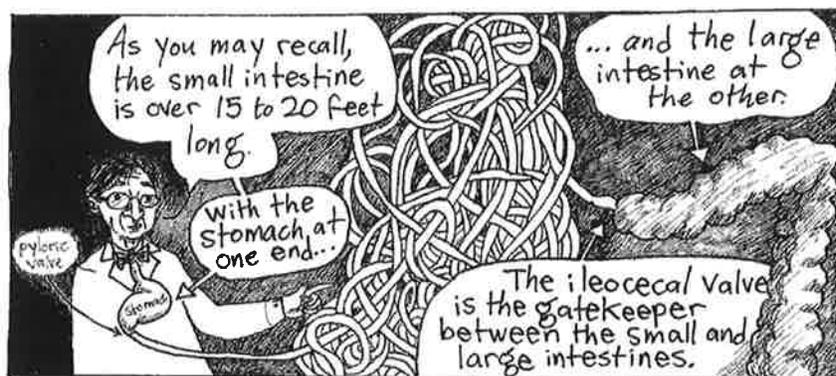
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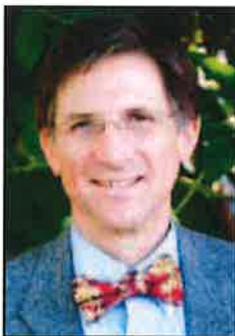
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As cofounder of the SIBO Center for Digestive Health at NCCM, Dr. Sandberg-Lewis often treats patients whose health conditions have defied diagnosis despite exhaustive medical testing. Restoring ideal digestive function and normalizing the gut microflora 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* (NCCM Press; 2009). He and his wife

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