Information about SIBO and dysbiosis in IBS, rosacea and other conditions

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Introduction
The colon is accustomed to having contact with 100 trillion bacteria yet the small intestine has very few by comparison. Complications arise when the colon type bacterial count increases in the small intestine or there is an imbalance of bacteria in the colon with harmful bacteria (dysbiosis). The natural protective mechanisms that keep the small bowel bacteria colony counts suppressed include the presence of stomach acid, normal gastrointestinal motility, digestive enzymes, mucosal immunity and the integrity of the ileocecal valve. The balance in the colon is generally kept in check by the background of healthy bacteria, mucosal integrity and normal motility (Weinstock-2011).

Small intestinal bacterial overgrowth (SIBO) is defined as the presence of more than $10^5$ colony forming units per milliliter in the jejunum with a symptoms or signs of bacterial overgrowth or malabsorption. Non-invasive diagnostic testing to determine the presence of SIBO are lactulose or glucose breath tests that determine excess products of fermentation (hydrogen or methane) from the proximal small intestine which pass into the respiratory system. This condition can result in gas, bloating, flatulence, altered bowel function and/or malabsorption of nutrients. Bloating, diarrhea, and nutrient deficiencies are induced by excess intraluminal small intestinal bacteria, which results from: (1) fermentation of nutrients producing gas, and (2) bile salt deconjugation by bacteria, leading to fat malabsorption and subsequent steatorrhea and secretory effects, causing diarrhea. Bacterial overgrowth is associated with many complex syndromes including irritable bowel syndrome, fibromyalgia syndrome, rosacea, interstitial cystitis and type III chronic prostatitis (Weinstock-2012). Furthermore, SIBO occurs in the setting of many diseases and treatment with antibiotic therapy is beneficial (Weintock-2011, Weinstock-2008, Weinstock-2009, Weinstock-2010).

Chronic SIBO can result in systemic inflammation (Lin-2004). Circulating levels of cytokines, such as TNF-α and pro-inflammatory interleukins and immune complexes are elevated in both SIBO and irritable bowel syndrome (Hughes-2013). Net effects of damaged tight junctions of intestinal mucosal cells include stimulation of the inflammatory network and activation of lymphocytes and mast cells locally and systemically. With increased intestinal permeability there is translocation of
lipopolysaccharides (the outer covering of Gram-negative bacteria) into the damaged mucosal lining and can this increase systemic inflammation.

Gastrointestinal (GI) dysfunction is defined as a GI condition with abnormal metabolic function, motility, structure, infection, or inflammation. There are many systemic symptoms and signs (extra-intestinal manifestations) that may be an expression of GI dysfunction. There are systemic diseases and syndromes that are triggered or influenced by primary GI disorders.

Classic examples of extra-intestinal manifestations include fever and joint pain during a flare of Crohn’s disease. Other extra-intestinal manifestations of inflammatory bowel disease (IBD) include various skin, eye, hepatobiliary diseases and, as recently reported, restless legs syndrome (RLS).

Celiac disease has myriad extra-intestinal manifestations owing to a variety of GI dysfunction including altered structure and absorption, increased intestinal permeability, and bacterial overgrowth. Associated autoimmune phenomena include thyroid and neurological diseases. Additional extra-intestinal manifestations include decreased fertility, low intrauterine weights and, surprisingly, recurrent urinary tract infections.

Irritable bowel syndrome (IBS) patients often have extra-intestinal manifestations and IBS is associated with a variety of syndromes. GI dysfunction that is responsible for this includes altered visceral hypersensitivity, inflammation and bacterial overgrowth. General pelvic pain and urologic disturbances are common in IBS. More than 25% of women with IBS have interstitial cystitis (IC). Many women also have fibromyalgia syndrome (FMS). Although it is well known that fatigue is common in IBS, it is not as well recognized that sleep disturbance and RLS may be additional problems.

**Representative case history of SIBO**
The following case history illustrates what can be seen as a consequence of a foodborne illness and how gastrointestinal dysfunction may explain seemingly unrelated idiopathic syndromes. This will be extensively discussed in this chapter.

One of my patients is a 55-year-old Caucasian woman who was an ICU nurse before she became disabled from her idiopathic syndromes. She had seen 22 physicians and alternative medical caregivers to diagnose and treat her conditions, which developed after a self-limited acute, non-bloody diarrheal illness acquired at a restaurant 22 years ago. Soon after the infection she developed IBS with abdominal pain, bloating and altered bowel movements. A year later she developed fibromyalgia with chronic fatigue and ultimately muscle pain was so severe that she was unable to touch her legs. She became disabled and had to quit her job. Her fatigue worsened 8 years later when she noticed characteristic symptoms of RLS (the compelling urge to move the legs at night associated with leg discomfort). Her sleep was greatly impaired and her fatigue worsened. She fell asleep while driving and had a motor vehicle accident. Three years later she developed symptoms of the painful bladder syndrome (a form of interstitial cystitis) with urinary frequency and urgency, pelvic pain and pain with intercourse.
The patient finally was tested for SIBO with a lactulose breath test. She noted rapid and sustained clinical improvement in all of her symptoms after use of a non-absorbable broad-spectrum antibiotic followed by intestinal permeability and prokinetic therapy.

**Gastrointestinal dysfunction: extra-intestinal effects**
Altered genetic background or phenotype may result in GI dysfunction in several ways. Specific HLA genome subtypes are found in celiac disease and result in predisposition for the disease. A variety of genetic markers have been found in Crohn’s disease patients, as discussed in Dr. Gerald Mullin’s text book published in 2010. The impact of various stimuli including inflammation and dysbiosis can lead to a variety of diseases or syndromes based on the phenotypic genetic makeup.

Inflammation and infection of the intestinal lining can lead to increased intestinal permeability by damage to the tight junctions of mucosal cells. Stimulus to the inflammatory network and activation of lymphocytes and mast cells locally and systemically are the net effects. Release of various cytokines can lead to increase of corticotrophin-releasing hormone, which can affect central nervous system, hypothalamic-pituitary-adrenal (HPA) axis, and the peripheral nervous system. Translocation of bacteria or the lipopolysaccharides (outer covering of gram negative bacteria) into a damaged mucosal lining can alter the HPA axis.

There is a complex system of the emotional motor system and the interplay of stress, cytokines, cortisol, neurological and neuroendocrine responses.

Neuromuscular disorders of the esophageal body, lower esophageal sphincter, stomach and small intestine are important in the pathophysiology of many GI and systemic disorders. If small intestinal motility is disturbed and the ability to “sweep” pathogenic organisms away from the upper gastrointestinal tract is impaired, then SIBO can occur.

GI and respiratory viral infections (enterovirus and adenovirus) can trigger a number of gastrointestinal disorders (e.g. celiac disease, Crohn’s disease, IBS). Altered immune mechanisms triggered by an abnormal gene in Crohn’s disease can be a setup for an infection such as intramucosal *E. coli*, which may exacerbate the disease process. Histological studies have shown differences in adherence and invasion of bacteria into intestinal mucosa of patients with Crohn’s disease and this may be on the basis of altered immunity.

The phenomenon of post-enteric infections causing systemic diseases and syndromes is a critical concept. There are approximately 76 million episodes of food poisoning per year in the U.S. and many of the diseases and syndromes that are linked to this are poorly documented. The well-publicized tainted food products in the past few years have included beef, cheese, lettuce, peanut butter, spinach, sprouts, tomatoes and a variety of canned food. Hundreds of thousands of pounds of beef have been recalled because of concerns about *E. coli* and *Salmonella*. Data from the CDC show that foodborne illnesses cause 325,000 hospitalizations and 5,000 deaths a year.
The effects of acute food poisoning can be severe and long-lasting. Of those infected with *E. coli* O517:H7, 10% develop hemolytic uremic syndrome, which can cause kidney failure and pancreatitis. After recovery, 25% of these patients will develop chronic renal disease and diabetes. The incidence of diabetes was determined from a review of 1,139 children from 13 studies (1966-1998, age 0.2-16 years) and ranged from 0 to 15%, with a pooled incidence of 3.2%.

Reactive arthritis can start six months or longer after a bout of *Salmonella*, *Shigella* and *Yersinia*. There may be eye inflammation and urethritis as part of the classic triad of Reiter's syndrome. One of the most severe post-enteric complications usually acquired from infected poultry is *Campylobacter*-associated Guillain-Barré syndrome. Antibodies against *Campylobacter* create an autoimmune syndrome with ascending paralysis. Subsequent gastrointestinal dysmotilities have been reported as well.

There are, however, several good studies that have determined the risk of developing post-infectious irritable bowel syndrome (Pi-IBS). This ranges between 7 to 34% after a bacterial infection (see the table below).

### Incidence of Post Infectious - IBS (Pi-IBS)

<table>
<thead>
<tr>
<th>Author</th>
<th>Follow-Up period(s)</th>
<th>Number with acute diarrhea</th>
<th>% of patients with acute diarrhea who developed IBS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marshall 2005</td>
<td>2-3 yr</td>
<td>1137</td>
<td>34</td>
</tr>
<tr>
<td>Mearin 2005</td>
<td>1 yr</td>
<td>271</td>
<td>10</td>
</tr>
<tr>
<td>Okhuysen 2004</td>
<td>6 mo</td>
<td>60</td>
<td>10</td>
</tr>
<tr>
<td>Neal 1997 &amp; 2003</td>
<td>6 mo</td>
<td>357</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>6 yr</td>
<td>192</td>
<td>7</td>
</tr>
<tr>
<td>Thornley 2000</td>
<td>6 mo</td>
<td>93</td>
<td>9</td>
</tr>
<tr>
<td>Gwee 1999</td>
<td>3 mo</td>
<td>100</td>
<td>22</td>
</tr>
<tr>
<td>McKendrick 1994</td>
<td>1 yr</td>
<td>38</td>
<td>31</td>
</tr>
</tbody>
</table>

**Increased intestinal permeability**

There are many barriers and defensive mechanisms by which the intestinal tract mucosa can be exposed to antigens, bacteria and chemicals and yet still be selective about what is absorbed and secreted. Bacterial overgrowth and enteric infections are two major insults to the gut that result in increased permeability. There can be a viscous cycle with the bacteria triggering release of TNF-alpha with subsequent increase in intestinal permeability which increases more TNF-alpha production. An intact gut barrier is required to monitor and keep toxins, allergens and bacteria from invading the mucosa. The gut barrier is a complex system and depends on anatomic tight junctions, immune function, antimicrobial chemicals and digestive enzymes.

Protection requires an intact immunological and micro-anatomical defense system. Healthy commensal bacteria play a role in this process. The "leaky gut" has been described as a breach in the integrity of the gut that may be a result of genetic...
weakness in combination with stress factors. These stress factors include severe illness, non-steroidal anti-inflammatory drugs and a shift of bacteria into the small intestine. Abnormal gut changes such as ulcerated mucosa in Crohn’s disease are obvious disruptions of the defense system and create increased intestinal permeability. Less obvious changes occur as a delayed effect after an enteric infection.

The concept of increased intestinal permeability has received a bad image in the conventional medical community owing to overuse of the word “leaky gut”, unfamiliarity with intestinal integrity and questionable claims touting the benefits of various modalities to correct the “leaky gut.” Only recently have investigators found that there really is a leaky gut but it is often not the colon—it is primarily a problem of the small intestine. Perhaps the small intestine needs a “cleanse,” not the colon. With a compromised gut barrier, bacteria can attach to the lining and translocation of the bacteria or bacterial byproducts into the mucosa can occur. When the outer coating of gram negative bacteria is shed, these lipopolysaccharides induce an imbalance of the hypothalamic-pituitary-adrenal axis. This, along with cytokines that occur in bacterial overgrowth, can lead to chronic fatigue and depression. Finally, larger food particles can be absorbed and acts as allergens. This process may explain some of the food allergies and nonspecific food reactions (“sensitivities”) that are increasingly seen. There has been a two-fold increase in the prevalence of peanut allergies alone in the U.S. during the last decade. A study of subjects with food sensitivities versus controls looked at lactulose/mannitol ratio detection as a measurement of intestinal permeability. There was a significant difference between those with food allergy, food hypersensitivity and no food reactions. Another potential complication of food antigens is triggering autoimmune diseases.

**SIBO mechanisms, causes and diagnosis**

There are several natural protective mechanisms that keep the small bowel bacteria at low colony counts. The colon is used to having trillions of coliform bacteria. The distal ileum is adept at maintaining balance with thousands of bacteria but complications arise when the coliform count grows. To keep bacterial counts down, one has to have normal gastric acid levels to reduce swallowed bacteria, normal digestion to reduce nutrition provided for bacteria, normal small bowel motility to sweep the bacteria out every 90 minutes while fasting as part of the migrating motor complex, normal immunity, and an intact ileocecal valve to act as a barrier and prevent reflux of stool/bacterial contents from the large intestine.

The party line is that SIBO is defined as a disruption or increase of the normal small bowel bacterial population that can result in gas, bloating, flatulence, altered bowel function and/or malabsorption of nutrients. Bloating, diarrhea and nutrient deficiency are induced by excess intraluminal small intestinal bacteria which results from: 1) fermentation of nutrients producing gas and 2) bile salt deconjugation by bacteria leading to fat malabsorption and subsequent steatorrhea and secretory effects, causing diarrhea. Deconjugation of the hydrophilic components decreases absorption because of loss of the water-soluble state which is involved in fat absorption.
Diagnostic tests for SIBO are either direct invasive studies with bacterial cultures via nasal jejunal tubes or indirect techniques using breath testing with either glucose or lactulose. With chronicity, weakness and weight loss from villous atrophy and/or malabsorption secondary to the effects of bile salt deconjugation will become evident. Advanced cases may have peripheral edema from hypoalbuminemia and pallor from anemia (B12 deficiency, chronic disease and in some cases iron deficiency, for which achlorhydria is the most common explanation). In advanced stages, cachexia and other changes of vitamin and nutrient deficiency may become evident.

Small intestinal pseudo-obstruction, scleroderma and post-surgical states including achlorhydria after gastric surgery are among the most well-known causes for SIBO. The most common reason for SIBO is poor motility of the small intestine, which allows for overgrowth of the colon-type bacteria that are normally present in low colony counts in the small intestine. This allows for undigested nutrients to enhance bacterial growth. Many systemic diseases and conditions cause SIBO. Lack of adequate production of gastric acid or gastrointestinal motility disorders in elderly asymptomatic people have also been a commonly recognized phenomenon allowing for SIBO. The elderly may also have impaired mucosal immunity, leading to SIBO, as is seen in more serious disorders such as chronic lymphocytic leukemia, IgA deficiency and T-cell disorders. Other classic examples of SIBO include pancreatic insufficiency, abnormal small intestinal mucosal disorders including celiac disease and Crohn's disease, as shown in the table below.

**Standard SIBO Conditions**

<table>
<thead>
<tr>
<th>Scleroderma</th>
<th>Achlorhydria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small intestinal pseudo-obstruction</td>
<td>Diabetes</td>
</tr>
<tr>
<td>Pancreatic insufficiency</td>
<td>Radiation enteritis</td>
</tr>
<tr>
<td>Jejunal diverticulosis</td>
<td>Immunodeficiency: CLL, IgA deficiency, T-cell deficiency</td>
</tr>
<tr>
<td>Post-surgical anatomy: Billroth, Blind-loop, ICV resection, J-pouch</td>
<td>Celiac and Crohn's disease</td>
</tr>
</tbody>
</table>
Studies suggesting a relationship of SIBO to IBS are shown in the following table.

<table>
<thead>
<tr>
<th>Lesser Known and New SIBO Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic renal failure</td>
</tr>
<tr>
<td>Cirrhosis</td>
</tr>
<tr>
<td>Chemotherapy</td>
</tr>
<tr>
<td>Acromegaly</td>
</tr>
<tr>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Chronic fatigue syndrome</td>
</tr>
</tbody>
</table>

Frequency of small intestinal bacterial overgrowth in irritable bowel syndrome patients as determined by a positive breath test (note glucose has a lower sensitivity than lactulose)

<table>
<thead>
<tr>
<th>Author</th>
<th>Substrate</th>
<th># Subjects</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>McCallum, 2005</td>
<td>Glucose</td>
<td>143</td>
<td>38.5</td>
</tr>
<tr>
<td>Lupascu, 2005</td>
<td>Glucose</td>
<td>65</td>
<td>30.7</td>
</tr>
<tr>
<td>Nucera, 2005</td>
<td>Lactulose</td>
<td>98</td>
<td>65</td>
</tr>
<tr>
<td>Walters, 2005</td>
<td>Lactulose</td>
<td>39</td>
<td>10</td>
</tr>
<tr>
<td>Noddin, 2005</td>
<td>Lactulose</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>Nucera, 2004</td>
<td>Lactulose</td>
<td>200</td>
<td>75</td>
</tr>
<tr>
<td>Pimentel, 2000 -3</td>
<td>Lactulose</td>
<td>313</td>
<td>57, 76, 84</td>
</tr>
<tr>
<td>Weinstock, 2006</td>
<td>Lactulose</td>
<td>254</td>
<td>63</td>
</tr>
</tbody>
</table>

The exciting new area of SIBO is the recognition that the condition causes more than just have problems with gas and diarrhea. Chronic asymptomatic SIBO can cause systemic inflammation. Visceral hypersensitivity has been linked to post-infectious IBS and is possibly due to chronic inflammation, which has been seen in the colonic mucosa. An important discovery in 2013 by Dr. Pimentel (presented at the American College of Gastroenterology Conference in October 2013) was the finding that post-infectious IBS was associated with an autoimmune antibody called anti-vinculin. He previously showed in the animal model, that infection by *Campylobacter* will result in SIBO, increased anti-vinculin antibody and reduction of the number of nerves innervating the small intestine. This association was explored further in patients with post-infectious IBS. They too had an increased level of anti-vinculin antibodies. Thus, there is now evidence that some IBS patients have an autoimmune disease causing...
SIBO. Approximately 20% of all IBS patients remember having an acute infection prior to the onset of their chronic symptoms.

Several investigators have shown an increase in inflammatory cells in patients with IBS and post-infectious IBS, including ileal mast cells, colon mast cells and submucosal and paraneuronal lymphocytes. Barbara et al. showed that the closer mast cells were to the colonic nerves, the more pain the patients experienced. There were increased levels of tryptase and histamine in the tissue as well, which suggested that inflammation plays a role in visceral hypersensitivity. There are a variety of stimuli to mast cells that may factor into this phenomenon. SIBO may cause visceral hypersensitivity by the above mechanisms and be a consequence of post-infectious IBS.

SIBO may explain other syndromes by the presence of systemic low-grade inflammation and increased intestinal permeability. Circulating levels of cytokines such as TNF-alpha and pro-inflammatory interleukins are elevated in SIBO and in IBS. This critical concept may tie together dysbiosis in the gut and unexplained syndromes and diseases. Intestinal permeability may allow for allergens to be a trigger for some disorders.

The obvious consequence of bacterial fermentation is production of gas. A variety of gases that develop in the gut expand the diameter of the gut and are absorbed through the mucosa, travel in the bloodstream and then are excreted through the pulmonary system and come out the mouth. In each step there are complications. The general expansion of the gut causes discomfort by triggering stretch receptors. Specific characteristics of each gas pose their own hazard, as shown below.

- Hydrogen and methane excess
  - Bloating (IBS)
- Methane excess
  - Altered motility (constipation)
  - Bloating (IBS)
- Hydrogen sulfide production
  - Increased nociception (IBS, chronic pelvic pain disorders)
- Other gases
  - Bad odor (breath, flatus, urine, sweat)

Overall excess production of gases in the small intestine leads to abdominal bloating and distension (see figure below). This is most often caused by excess hydrogen production by bacterial fermentation. Simple lactose maldigestion is well-known to cause hydrogen and lactic acid production with subsequent bloating and diarrhea. Hydrogen breath testing is useful in identifying patients with IBS who are affected by
SIBO, but other exhaled gases may have diagnostic benefit as well.

Early studies of the association of methane production and altered motility looked at orocecal and whole gut transit and found that each was significantly delayed if methane excretion occurred early on in the lactulose breath test (LBT). Abnormal methane production was showed to be strongly associated with constipation-predominant IBS. Methane was detected in 50 (17%) of 296 patients with IBS, compared with 2 (3%) of 78 patients with IBD ($P < .01$). Subsequently, a study of 87 patients showed that, of the 20 that had methane production, severity of constipation was double that of non-methane-producing IBS subjects. A correlation was found between the degree of methane production on the breath test and the severity of constipation. Studies with infusion of methane into the small intestine of dogs have shown that gut transit was reduced by 70%.

In an observational study of 254 patients with IBS who were administered LBT, 120 patients (47%) had elevated hydrogen levels, 27 patients (11%) had elevated methane levels, and 14 patients (6%) had elevated levels of both gases. Methane production was associated with patients with IBS-C.

**General treatment of SIBO**

The basis for SIBO treatment goes back to the understanding that most cases of SIBO are caused by poor motility of the small intestine, which then allows for bacterial overgrowth and subsequent damage to the intestinal lining. The three-pronged concept of long-term treatment is eradication, protection, and, when indicated, stimulation. Antibiotic treatment is the mainstay of treatment and usually requires a broad-spectrum antibiotic to be effective. Treatment with quinolones, amoxicillin, tetracycline and metronidazole is somewhat effective but can develop bacterial resistance and antibiotic-
associated diarrhea. Rifaximin offers a unique profile for SIBO: 1) broad-spectrum activity, 2) non-absorbable moiety, 3) bile solvency, thus increasing activity in the small intestine, and 4) low likelihood of long-term resistance. It has been effective in patients with SIBO, IBS with SIBO and scleroderma. Rifaximin has shown efficacy in the treatment of SIBO and its efficacy in the treatment of IBS and functional bowel syndrome has been evaluated in several studies, as summarized in the table below. The latest double blind randomized control studies published in 2010 in 1200 patients show that rifaximin (Xifaxan) is effective in patients with IBS diarrhea and alternating types (Pimentel, et al., Gastroenterology May 2010).

Nucera looked at a large group of patients who were treated with weekly courses of combination antibiotics every month for 4 months. There was a significant improvement in the breath tests using lactulose, lactose and fructose. Laurentino showed that increasing the dose of rifaximin from 800 mg/day/week to 1,200 mg/day/week resulted in double the improvement in reversing the breath test. The UCLA group has subsequently reported that reversing the breath test is critical in symptom resolution. Furthermore, Pimentel’s study in 2005 showed that a 10-day course of 1,200 mg/day of rifaximin resulted in 10 weeks of improvement of IBS symptoms. Patients experienced a 36% mean improvement from baseline in the severity of IBS symptoms at 10 weeks post-treatment, compared with a mean improvement of 21% among 44 patients who received placebo ($P = .02$). The dose of rifaximin in Sharara’s study was 800 mg/day for 10 days: global symptomatic response was achieved in 41% of 37 patients, compared

<table>
<thead>
<tr>
<th>Author</th>
<th>Yr</th>
<th>Patients</th>
<th>Type</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nucera</td>
<td>'04</td>
<td>IBS-SIBO (n=200)</td>
<td>Open label; Rfx + paramomycin</td>
<td>87-100% effective in treating SIBO by reversing 3 sugar BT’s</td>
</tr>
<tr>
<td>Lauritano</td>
<td>'05</td>
<td>IBS-SIBO (n=90)</td>
<td>Dose-ranging</td>
<td>Dose response with Rfx</td>
</tr>
<tr>
<td>Lupascu</td>
<td>'05</td>
<td>IBS-SIBO (n=80)</td>
<td>Abx comparison; open label</td>
<td>1 wk of Rfx vs. metro/levoquin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>12/20 vs. 14/20 H2 BT normalized</td>
</tr>
<tr>
<td>Pimentel</td>
<td>'05</td>
<td>IBS-SIBO (n=87)</td>
<td>R/DB/PC</td>
<td>Statistical sig. vs. placebo; duration of response over 2 months for 10-day Rx</td>
</tr>
<tr>
<td>Sharara</td>
<td>'06</td>
<td>IBS (n=70)</td>
<td>R/DB/PC</td>
<td>Statistically sig. vs. placebo</td>
</tr>
<tr>
<td>Sharara</td>
<td>'06</td>
<td>Fx-SIBO (n=54)</td>
<td>R/DB/PC</td>
<td>Numerically diff. vs. placebo</td>
</tr>
<tr>
<td>Weinstock</td>
<td>'06</td>
<td>IBS-SIBO (n=254)</td>
<td>Observational</td>
<td>60% mod-greatly improved</td>
</tr>
<tr>
<td>Weinstock</td>
<td>'06</td>
<td>Fx-SIBO (n=85)</td>
<td>Observational</td>
<td>63% mod-greatly improved</td>
</tr>
</tbody>
</table>
with 6 (18%) of 33 patients who received placebo \( (P = .04) \). After 10 days post-
treatment, 10 (27%) of 37 patients in the rifaximin group maintained their symptomatic
response, compared with 3 (9%) of 33 patients in the placebo group \( (p=0.05) \).
Furthermore, in an open-label, observational study, a 10-day course of rifaximin 1,200
mg/day, as part of a comprehensive treatment regimen including tegaserod and
probiotic therapy, improved IBS symptoms in 60% of 81 patients.

Other antibiotics have been used for the treatment of SIBO and IBS. A retrospective
chart review of 98 patients with IBS who received antibiotic therapy showed that 58
(69\%) of 84 patients who received at least one course of rifaximin experienced clinical
response, compared with 9 (38\%) of 24 patients who received neomycin \( (p<0.01) \) and
27 (44\%) of 61 patients who received other antibiotics (e.g. Augmentin and doxycycline;
\( P < .01 \)). Naturopathic and integrative medical doctors often use concentrates of natural
herbs that kill excess gut bacteria. These can be purchased on the Internet without a
prescription and are often less expensive than pharmaceutical antibiotics (and do not
pose a risk of antibiotic-induced diarrheal diseases). Another published SIBO treatment
is a two week course of an elemental diet which is obtained by prescription.

The second phases of SIBO therapy can help maintain symptomatic improvement. In
the past, long-term tegaserod (a serotonin agonist) was given in an attempt to improve
the phase III abnormality of the migrating motor complex found in patients with IBS who
have SIBO. A review of IBS-SIBO patients who were treated with antibiotics and then
were given tegaserod (no longer available in the U.S.) vs. low-dose erythromycin (50
mg dose acts as a stimulant to the migrating motor complex) showed that tegaserod
decreased recurrence of IBS-SIBO symptoms at a rate twice that of erythromycin and
four times that of no medication after rifaximin alone. The problems with erythromycin
include the potential for abdominal cramps, interference with birth-control pills, and
other drug interactions including an increased risk of muscle damage with statin
medicines. Low-dose naltrexone may be an alternative to erythromycin. This anti-opioid
can stimulate the intestine and some emerging data suggests that it has anti-
inflammatory properties, which might help repair the intestinal lining. The problems with
naltrexone include general CNS stimulation: potential for jittery feeling, insomnia and
unalso dreams. It is contraindicated for people who take chronic opioids. Physicians or
patients in Canada have access to Resolor which can help improve gastrointestinal
motility.

Additional complementary approaches to supplement SIBO therapy include probiotics
and zinc. Probiotics can reduce inflammation and improve permeability problems.
Bifidobacter-based probiotic may repair small intestinal permeability and immune
defects characteristic of SIBO, IBS, and post-infectious IBS. Zinc can theoretically help
reverse defects in small intestinal permeability. Experimental evidence shows that zinc
supplementation improves intestinal permeability in toxin-induced colitis. Zinc carnosine
stimulated migration and proliferation of cells in vitro in a dose-dependent manner and
decreased gastric and small-intestinal injury (50\% reduction in villous shortening at 40
mg/ml; both \( p<0.01 \)). In volunteers, indomethacin caused a threefold increase in gut
permeability in the control arm, while no significant increase in permeability was seen
when zinc was co-administered. Probiotics alone do not cure small intestinal bacterial overgrowth.