

Principles of Integrative Gastroenterology

Systemic Signs of Underlying Digestive Dysfunction and Disease

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Key Concepts

- Many idiopathic syndromes overlap and are caused by underlying gut dysfunction
- Acute and chronic GI infections trigger chronic systemic diseases by several mechanisms, including small intestinal bacterial overgrowth (SIBO), inflammation and autoimmune phenomenon
- SIBO underlies many poorly understood syndromes, including irritable bowel syndrome (IBS), restless legs syndrome (RLS), fibromyalgia syndrome (FMS), rosacea and interstitial cystitis (IC)
- Increased intestinal permeability and inflammation are complications of SIBO
- Increased intestinal permeability may explain food allergies and the increased involvement of diseases with eosinophils and mast cells (e.g. asthma)
- SIBO treatment is effective treatment for IBS and SIBO-related syndromes

Introduction

Gastrointestinal (GI) dysfunction is defined as abnormal metabolic function, motility, structure, infection, or inflammation and there are many systemic symptoms and signs (extraintestinal manifestations) that may be an expression of such dysfunction. Classic examples of extraintestinal manifestations include the fever and joint pain that occur during a flare of Crohn's disease, as well as various skin, eye and hepatobiliary diseases associated with inflammatory bowel disease (IBD). While these examples are correlated with overt GI illness, the underlying cause of many extraintestinal manifestations can also be attributed to underlying systemic inflammation resulting from asymptomatic gut dysfunction, primarily intestinal permeability. Two predominant causes of this breach in the integrity of the intestines are small intestinal bacterial overgrowth and post-infectious enteric illness. Throughout this chapter we will primarily explore the consequences of SIBO and its relationship to systemic conditions. The prevalence of these disorders and a review of integrative modalities to their treatment will be discussed.

Text Box

Common Extraintestinal Manifestations of GI Dysfunction
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Celiac Disease

- Autoimmune phenomena including thyroid and neurological diseases
- Decreased fertility
- Low intrauterine weights
- Recurrent urinary tract infections.

Irritable bowel syndrome (IBS)

- General pelvic pain and urologic disturbances
- **More than 25% of women with IBS have interstitial cystitis (IC).**
- Fibromyalgia syndrome (FMS)
- Fatigue
- Sleep disturbance
- RLS

Other diseases triggered or influenced by primary GI disorders:

- Sclerosing cholangitis can result from chronic IBD
- Asthma, hoarseness and chronic cough can be caused by silent gastroesophageal reflux disease (GERD)
- Many conditions are triggered by small intestinal bacterial overgrowth (SIBO), including interstitial cystitis.

Increased intestinal permeability

There are many barriers and defensive mechanisms by which the intestinal tract mucosa can be exposed to antigens, bacteria and chemicals, yet still be selective about what is absorbed and secreted. This protection requires an intact immunological and microanatomical defense system; a process in which healthy commensal bacteria play a role. Therefore, **bacterial overgrowth and enteric infections** are two major insults to the gut that result in increased permeability, as is shown below in Figure 1.

Genetics, Inflammation and Intestinal Permeability

Altered genetic background or phenotype may result in GI dysfunction in several ways. First, specific HLA genome subtypes are found in celiac disease and result in predisposition for the disease. Furthermore, a variety of genetic markers have been found in Crohn's disease patients, as discussed in Chapters [xxxxx, Galland, Dean]. Lastly, in both celiac disease and Crohn's disease, a genetically-determined increased intestinal permeability may be a harbinger of clinical disease. Based on the phenotypic genetic makeup, the impact of various stimuli, including inflammation and dysbiosis, can lead to a variety of diseases or syndromes.

Inflammation and infection of the intestinal lining can lead to increased intestinal permeability by damaging the tight junctions of mucosal cells. The net effects are the stimulation of the inflammatory network and activation of lymphocytes and mast cells

locally and systemically. This stimulation results in the release of various cytokines which can lead to an increase of corticotropin-releasing hormone, which can affect the central nervous system (CNS), the hypothalamic-pituitary-adrenal (HPA) axis, and the peripheral nervous system. Additionally translocation of bacteria or the lipopolysaccharides (outer covering of gram negative bacteria) into a damaged mucosal lining can alter the HPA axis.

The complex system of the emotional motor system (EMS) and the interplay of stress, cytokines, cortisol, neurological and neuroendocrine responses are shown in Figure 2.

Infections Triggerring Digestive Disease and Systemic Illness

GI and respiratory viral infections (enterovirus and adenovirus) can trigger a number of gastrointestinal disorders (e.g. celiac disease, Crohn's disease, IBS) and systemic diseases. There are 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). Likewise, an existing GI condition can be worsened by a subsequent viral infection. For example, 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.¹ Histological studies have shown differences in adherence and invasion of bacteria into intestinal mucosa of patients with Crohn's disease and this may also be based on altered immunity.²

The phenomenon of post-enteric infections causing systemic diseases and syndromes is a critical concept because, of the approximately 76 million episodes of food poisoning per year in the U.S., many of the diseases and syndromes that are linked to food poisoning are poorly documented.³ 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.^{4,5} 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. However, the subsequent manifestations are not as well publicized.

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.⁶ After recovery, 25% of these patients will develop chronic renal disease and diabetes.⁷ 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%.⁸

Other systemic illnesses that can result from acute food poisoning include reactive arthritis which can start six months or longer after a bout of Salmonella, Shigella and Yersinia. Eye inflammation and urethritis are 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.⁹ Antibodies against campylobacter create an autoimmune syndrome with ascending paralysis. Subsequent gastrointestinal dysmotilities have been reported as well.¹⁰

Small intestinal bacterial overgrowth (SIBO)

The colon is accustomed to having trillions of coliform bacteria but complications arise when the coliform count grows in the small intestine.

Text box. There are several natural protective mechanisms that keep the small bowel bacteria at low colony counts including the presence of stomach acid, gastrointestinal motility, digestive enzymes, mucosal immunity and the integrity of the ileocecal valve.

To minimize bacterial counts in the small intestine (SI), one has to:

- maintain physiologic gastric acid production to reduce swallowed bacteria
- control the ingestion and have proper digestion of starches (ie legumes) to limit the nutrition necessary for bacterial growth
- retain normal small bowel motility (as driven by the migrating motor complex in the fasting state) to sweep the bacteria toward the colon,
- preserve an intact ileocecal valve to act as a physical barrier (between the SI and colon) to prevent the reflux of stool/bacterial contents from the large intestine.

These natural defenses are shown in Figure 3.

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 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. Deconjugation of the hydrophilic components decreases absorption from the loss of the water-soluble state which is involved in fat absorption. The change in bacteria and the effect of undigested starches are shown in Figure 4.

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.

Chronic asymptomatic SIBO can result in systemic inflammation.¹¹ Circulating levels of cytokines such as TNF- α and proinflammatory interleukins are elevated in SIBO.¹² Recent evidence indicates that low-grade SIBO may present with virtually no GI symptoms but may affect the body in profound ways because of the systemic inflammation it causes. This may explain many syndromes and symptoms associated with chronic fatigue syndrome, rheumatoid arthritis, fibromyalgia, interstitial cystitis, restless legs syndrome and rosacea (table 3). SIBO may also explain other syndromes due to the presence of systemic low-grade inflammation and increased intestinal permeability.

Causes of SIBO:

SIBO occurs when the normal protective mechanisms that maintain bacterial balance are interrupted. The most common causes of SIBO are poor motility of the small intestine allowing for overgrowth of coliform-type bacteria, pancreatitis which allows for undigested nutrients to enhance bacterial growth, and gastroparesis.

Gastrointestinal Motility and SIBO

Neuromuscular disorders of the esophageal body, lower esophageal sphincter, stomach and small intestine are important in the pathophysiology of many GI and systemic disorders. Functional disorders such as IBS, GERD and non-ulcer dyspepsia are in part caused by disordered gastrointestinal motility. When small intestinal motility is disturbed and the ability to “sweep” pathogenic organisms away from the upper gastrointestinal tract is impaired, the risk of SIBO is increased. There is a growing prevalence of SIBO in IBS patients and as the SIBO resolves the IBS symptoms improve—this will be discussed in detail in this chapter.

Other gastrointestinal motility disorders that can contribute to SIBO are small intestinal pseudoobstruction, scleroderma and post-surgical states. The latter is among the most well known causes of SIBO and is due to the decreased motility and achlorhydria after certain gastrointestinal surgical procedures including, but not limited to, gastric-bypass surgery and Whipple’s type surgical procedures. Additionally, gastrointestinal motility disorders or lack of adequate production of gastric acid with subsequent ingestion of live bacteria has been commonly recognized as contributing to SIBO.^{13, 14, 15} Other classic examples of SIBO include pancreatic insufficiency, abnormal small intestinal mucosal disorders including celiac disease and Crohn’s disease, as shown in table 2. below. Finally, many systemic diseases and conditions can also cause SIBO – see tables 2,3 below.

Text box. SIBO has been reported in as many as 84% of patients meeting diagnostic criteria for IBS.^{16, 17, 18, 19} Other studies confirm a relationship of SIBO to IBS as shown in table 4.^{20, 21, 22, 23, 24, 25}

Intestinal Gas and the Diagnosis of SIBO.

The obvious consequence of bacterial fermentation is the production of gas. The variety of gases that develop in the gut expand its diameter causing abdominal bloating, distention and discomfort from the triggering of stretch receptors (see figure 5 below). This bloating is most often caused by excess hydrogen production from bacterial fermentation.²⁶ Simple lactose maldigestion is well known to cause hydrogen and lactic acid production with subsequent bloating and diarrhea. 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.²⁷ Hydrogen breath testing in particular is useful in identifying patients with IBS who are affected by SIBO, but other exhaled gases may have diagnostic benefit as well.²⁸

Specific characteristics of each gas pose their own hazard. The production of hydrogen sulfide can cause increased nociception as found in IBS, IC and CP. Excess

hydrogen and methane result predominantly in bloating (as seen in IBS), while excess methane also results in altered motility manifested primarily as constipation.

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). As a result, abnormal methane production was shown to be strongly associated with constipation-predominant IBS.²⁹ 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.³⁰ A correlation was found between the degree of methane production on the breath test and the severity of constipation. Infusion of methane into the small intestine has shown that gut transit can be reduced by up to 70%.³¹ **Thus, methane as a by-product of fermentation itself can slow intestinal transit.**

Therapy for Small Intestinal Bacterial Overgrowth.

The basis for SIBO treatment is 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. Antibiotic treatment is the mainstay of treatment and requires a broad-spectrum antibiotic to be effective. Treatment with quinilones, amoxicillin, tetracycline and metronidazole is somewhat effective but can cause bacterial resistance and antibiotic-associated diarrhea.

Rifaximin Therapy for SIBO

Rifaximin offers a unique profile for SIBO with its broad-spectrum activity, non-absorbable moiety, bile solvency (thus increasing activity in the small intestine) and low likelihood of long-term resistance.³² It has been shown to be effective in patients with SIBO, IBS with SIBO and scleroderma.^{33, 34, 35} The efficacy of Rifaximin in the treatment of SIBO, IBS and functional bowel syndrome has been evaluated in several studies, as summarized in table 5. below.³⁶

Nucera et al looked at a large group of patients who were treated with weekly courses of combination antibiotics every month for 4 months.³⁷ There was a significant improvement in the breath tests using lactulose, lactose and fructose. Laurentino et al 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.³⁸ The UCLA group has subsequently reported that reversing the breath test is critical in symptom resolution.³⁹

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 ($P = .02$).⁴⁰ 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 with 6 (18%) of 33 patients who received placebo ($P = .04$).⁴¹ 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 ($p=0.05$).

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.⁴² Our own experience shows that effective antibiotic therapy (LBW) along with high doses of Coenzyme Q10, (GM) reduces the severity of fatigue in IBS patients with SIBO.

Studies have also been done comparing the effectiveness of other antibiotics used in the treatment of SIBO compared to Rifaximin. 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; $P < .01$).⁴³

Combination Promotility Antibiotic Therapy for SIBO

Given that disturbances in gastrointestinal motility are key to the development of SIBO (via impaired “sweeping” of bacteria in the upper digestive tract), treatment with promotility agents are paramount to the therapy of this condition. 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.⁴⁴ 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.⁴⁵ 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 when used concurrently with statin medications.

Low-dose naltrexone may be used as 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 feelings, insomnia and unusual dreams). It is contraindicated for people who take chronic opioids.

Alternative Approaches for the Treatment of SIBO (Figure 7.).

The following are possible alternative treatments for SIBO:

- Probiotics can reduce inflammation and improve permeability problems.^{46 47 48} Specifically, Bifidobacteria-based probiotic may repair small intestinal permeability and immune defects characteristic of SIBO, IBS, and post-infectious IBS.^{49 50 51}
- Zinc can theoretically help reverse defects in small intestinal permeability.⁵² Experimental evidence shows that zinc supplementation improves intestinal permeability in toxin-induced colitis.⁵³ Zinc carnosine (ZnC) 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 $p < 0.01$).⁵⁴ In volunteers, indomethacin caused a threefold increase in gut permeability in the control arm, while no significant increase in permeability was seen when ZnC was co-administered.

- Medical foods containing glutamine or aloe (either individually or in combination) are used by many practitioners to facilitate intestinal permeability resolution after therapy of SIBO.
- Antimicrobial herbal preparations have been used by the author (G. Mullin) to resolve SIBO that is **refractory** to Rifaximin and triple antibiotics (Clindamycin, Neomycin, Flagyl). Examples of products used by the author (GM) with success include:
 - Dysbiocide (Biotics Research Laboratories)
 - FC Cidal (Biotics Research Laboratories)
 - Candibactin AR (Metagenics)
 - Candibactin BR (Metagenics)*2 tablets/capsules before breakfast and 2 tablets/capsules before bed on an empty stomach for 30 days.
- The role of diet therapy during the treatment of SIBO cannot be emphasized enough. Individuals need to be counseled to avoid fructose, fructans and poorly digestible starches such as beans (see appendix).
- Since immune GI dysfunction plays a role in IBS, there are additional alternative approaches to SIBO treatment, including:
 - Probiotics administered post-treatment, once SIBO is resolved
 - Elimination diet to avoid allergens which can trigger immune and inflammatory responses
 - Avoiding food products (ie undigestible starches) that can ferment in the small intestine and facilitate the growth of the gut microbiota (appendix)
 - Hypnotherapy to downregulate the stress response on the immune system and the gut lining
 - Acupuncture to facilitate GI motility via resetting the migrating motor complex to sweep intestinal bacteria in an antegrade manner
 - Immune enhancers such as:
 - Arabinogalactans (raises mucosal sIgA levels)
 - *Sacromyces boulardii* (raises mucosal sIgA levels)
 - IgG2000 (raises mucosal sIgA levels)
 - Colustrum (rich in preformed antibodies)
 - Behavioral therapy to attenuate the stress response, reset pain thresholds and lower neuroendocrine and inflammatory markers.

Systemic Consequences of SIBO-Induced Gut Injury

Chronic fatigue syndrome

CFS is an idiopathic complex illness characterized by heightened reactive oxygen metabolites along with mitochondrial defects that lead to aberrant fatty acid and energy metabolism. Research also indicates that CFS patients are under increased oxidative

stress, have a type 2 helper-cell-dominant cytokine profile, frequently report allergies, have altered essential fatty acid (EFA) status and may have malabsorption of certain micronutrients.⁵⁵ Gastrointestinal links to chronic fatigue syndrome (CFS) include marked alterations in microbial flora, including lowered levels of bifidobacteria and SIBO.⁵⁶ Lactic acid bacteria (LAB) found in probiotics have the potential to influence the immune system in CFS patients by supporting T helper-cell-1-driven cellular immunity and may decrease allergies.

Systemic inflammation induced by SIBO could be responsible for alterations in the hypothalamic pituitary adrenal axis causing the fatigue found in the irritable bowel syndrome. Interestingly, IBS has also been associated with CFS and SIBO independently (Figure 2).^{57, 58, 59} Preliminary data by Pimentel et al showed that SIBO was common in CFS (77% of 31 patients) and there was improvement in tender points and depression (but not in fatigue scores) when antibiotics improved SIBO.⁶⁰

Restless legs syndrome (RLS)

The prevalence of RLS is estimated at 10% of the general population and it results in sleep disorders and a poor quality of life⁶¹ from the compelling urge to move the legs at night, often with discomfort. RLS is a central nervous system disorder that is either idiopathic (primary) or secondary to a number of conditions including GI dysfunction. Possible mechanisms of action in RLS include; iron deficiency, inflammation and/or SIBO.

In virtually all forms of RLS (primary, familial and secondary), there is central nervous system iron deficiency.^{62, 63} Additionally, RLS patients often have varying degrees of asymptomatic peripheral iron deficiency.^{64, 65} A chronic inflammatory state caused by SIBO⁶⁶ could be related to RLS by affecting hepcidin production directly⁶⁷ and indirectly⁶⁸ decreasing peripheral and central nervous system iron uptake and transportation.^{69, 70} Recognition that iron deficiency is an integral part of the pathophysiology of RLS is generally limited by gastroenterologists. The future understanding of iron metabolism and the role of SIBO and systemic inflammation are exciting. The role for modulation of dysbiosis will be determined with double-blind, placebo-controlled studies, which are in progress.

Textbox.

Theory for SIBO causing RLS and Central Iron Deficiency

- SIBO → increases small bowel permeability which leads to:
 - Adherent bacteria and translocation of LPS
 - TNF-alpha & interleukins levels are increased
 - Cytokines increase liver production of hepcidin
 - Decreases iron absorption from gut and release from reticuloendothelial system
 - May decrease transit of iron into brain

Factors that are associated with secondary RLS include elderly status, diabetes, end-stage renal disease, fibromyalgia, rheumatoid arthritis and Parkinson's syndrome. Furthermore, all of these conditions have also been associated with SIBO. Secondary RLS has also been associated with gastrointestinal conditions such as gastric resection, chronic liver disease, IBS associated with SIBO, celiac disease and Crohn's disease.^{71, 72, 73, 74, 75} Patients with scleroderma also have a reported increased incidence of RLS, although in this single study the patients did not have symptoms of end-stage SIBO.⁷⁶

Treatment of Secondary RLS

Medical trials for RLS have been recently reviewed extensively and are summarized in the table 6.⁷⁷ Magnesium, folic acid and exercise are frequently used in practice but are considered to be investigational. The efficacy of oral iron is also considered investigational, however, its efficacy appears to depend on the iron status of subjects. Intravenous iron is likely efficacious for the treatment of RLS secondary to end-stage renal disease but investigational in RLS subjects with normal renal function.⁷⁸

Most physicians who treat RLS feel that the first approach after iron treatment is to initiate dopamine agonists.⁷⁹ Ropinirole is marginally better than placebo. Augmentation and a wide array of side effects of dopamine agonists have led to interest in finding therapeutic alternatives.⁸⁰

Antibiotics for RLS

Two pilot studies have evaluated the effect of rifaximin for the treatment of RLS. The first prospective clinical trial of 13 IBS patients with both SIBO and RLS reported that 77% of patients (10/13) had $\geq 80\%$ long-lasting improvement of RLS symptoms following open-label treatment with rifaximin 1,200 mg/day for 10 days followed by motility and probiotic therapy.⁸¹ The next study included patients with primary RLS who had a positive lactulose breath test for SIBO. The mean baseline IRLS score was 23.1.⁸² Open-label treatment with rifaximin 1,200 mg/day/10 days followed by 400 mg/every other day/20 days resulted in a decrease in the IRLS score by 10.7 in 9 of 14 patients. Two of the five RLS non-responders had improvement with a second course of rifaximin when combined with metronidazole and a third patient improved when she was later diagnosed with celiac disease and placed on a gluten-free diet and iron supplementation.

Alternative Therapies for RLS

The common approaches used for many conditions include herbs, vitamins and/or minerals, acupuncture, botulinum toxin, *hyperbaric therapy and *chelation therapy. Small studies have suggested improvement from magnesium although scientific studies of magnesium in RLS have been non-supportive.^{83, 84, 85} Acupuncture has been studied in 14 studies but only 2 were judged worthy of comment based on the design, and there is insufficient evidence to support the use of acupuncture in RLS.⁸⁶ Intramuscular botulinum injections have shown success in 3 patients.⁸⁷ Finally, pneumatic sequential compression devices on RLS symptoms showed success in 6 of 10 patients.⁸⁸ Small open-label studies with RLS are problematic since the placebo response is so high.

**have not been reported in the literature.

Restless Leg Syndrome (RLS), Celiac and Crohn's Disease

- The relationship between restless legs syndrome (RLS) and celiac disease has recently been reported.⁸⁹
- RLS was found to be a frequently associated condition in 85 celiac patients: the incidence was 35.5% and the prevalence was 24.7%, compared to spouse control group of 9.5%.
- Neurologic complications have only recently been reported in Crohn's disease.
- The incidence of RLS was 42.7% in a large number of Crohn's disease patients from three academic centers and one large community practice.⁹⁰
- The prevalence of RLS in Crohn's disease was 30.2%, compared to a prevalence of 8.4% in the sex-matched spouse control group.

Interstitial cystitis (IC)

Interstitial cystitis (also known as painful bladder syndrome) is an idiopathic syndrome characterized by symptoms of urinary frequency, urinary urgency, pain with bladder filling, pelvic pain and dyspareunia. There is a significant overlap of interstitial cystitis (IC) with food allergies, autoimmune disease and IBS. GI dysfunction may play a role in IC since food triggers, mast cells, neural cross talk and SIBO have been implicated in the pathophysiology. A connection to SIBO has been proposed and a

positive therapeutic study using SIBO open-label antibiotic therapy was reported.^{91, 92} The potential interactions of mast cells, inflammatory mediators and the peripheral nervous system are shown in Figure 7.

Text box.

Possible role of SIBO and IC pathophysiology

- Hydrogen sulfide
 - Contracts detrusor muscle
 - Activates extrinsic sensory nerves
- Mast cell deposition in bladder
 - Degranulation triggered by LPS
 - Involvement shown by elevated urine tryptase levels
- Substance P staining nerve fibers near mast cells in bladder and colon
- IL-6 elevated in urine

Attene-Ramos 2006.
Chahl 2004.
Patacchini 2004.
Patacchini 2005.

Role of Food Allergies

Shorter et al determined the prevalence of the effect of food substances on painful bladder syndrome/interstitial cystitis symptoms.⁹³ Of the surveyed patients with IC, 90.2% indicated that the consumption of certain foods or beverages caused symptom exacerbation. Patients who reported that specific foods worsened symptoms tended to have more severe IC symptom scores. The most frequently reported foods causing symptom exacerbations were coffee, tea, soda, alcoholic beverages, citrus fruits and juices, artificial sweeteners and hot pepper.

Gut Permeability, Inflammation and Pelvic Pain

The link between chronic pelvic pain, dyspareunia and functional digestive diseases (ie IBS) has been long established.⁹⁴ Since SIBO, chronic inflammation, altered

HPA axis and systemic proinflammatory cytokines are implicated in the pathogenesis of IBS, an experimental study was undertaken to investigate the mechanism of development of pelvic pain.⁹⁵ One study explored in an animal model of IBS whether pelvic pain could develop remotely from the original site of inflammation. These investigators confirmed that there is organ cross talk (between the intestine and vagina) as well as modulation of pain responses by visceral inputs distinct from the inflamed site. Thus, SIBO/IBS can manifest in other organ systems distant from the site of pathology via the common mucosal immune system (see Hanaway chapter).

Rosacea

Systemic inflammation caused by GI dysfunction may be an explanation for rosacea, which is a common idiopathic disease that presents with transient or persistent facial erythema, telangiectasia, edema, papules and pustules usually confined to the central portion of the face.⁹⁶ In the past, genetic, environmental, vascular and inflammatory factors, and microorganisms such as skin bacteria, including *Demodex folliculorum*, and gastric infections with *Helicobacter pylori* have been considered as etiologic factors.

Rosacea and Digestive Disorders

Text box Rosacea has been associated with gastritis and hypochlorhydria; many people have nonspecific gastrointestinal symptoms.

Helicobacter pylori

The role of *Helicobacter pylori* has often been a subject of investigation with studies showing conflicting results. A small study investigated ocular rosacea, and clinical and serological evidence of *H. pylori* infection showed significant improvement of rosacea symptoms with ocular disease responding better than cutaneous rosacea.⁹⁷ An older study from Poland on the treatment of *H. pylori* infection in 60 patients with rosacea having erythema and flushing on the face with visible papules and pustules was compared to 60 age- and gender-matched patients without any skin diseases.⁹⁸ The effect of treatment on plasma interleukin (IL)-8 and tumor necrosis factor alpha (TNF-alpha) was also determined after 1 week of omeprazole 20 mg, clarithromycin 500 mg, and metronidazole 500 mg, all twice daily. The *H. pylori* prevalence in rosacea patients was about 88%, compared to 65% in control patients. There was twice the incidence among rosacea patients of a more virulent form of *H. pylori* (cytotoxin-associated gene A [CagA] positive). After antibiotics, 51 out of 53 treated rosacea patients became Hp negative. Within 2 to 4 weeks, the symptoms of rosacea disappeared in 51 patients, markedly declined in one and remained unchanged in one other subject. Plasma TNF-alpha and IL-8 were reduced significantly after the therapy in both groups of patients (72% and 65%, respectively).

Textbox.

There may be differences in populations around the world and it is possible that rosacea could be considered as one of the major extragastric symptoms of *H. pylori* infection cytotoxins and cytokines.

SIBO

Italian investigators recently discovered the link between rosacea and small intestinal bacterial overgrowth.⁹⁹ Of 113 consecutive rosacea patients, 52 had a positive breath test (vs. 3 of 60 controls). After SIBO eradication by rifaximin, as determined by reversal of the breath test, cutaneous lesions cleared in 20 of 28 and greatly improved in 6 of 28 patients, whereas patients treated with placebo remained unchanged (18/20) or worsened (2/20) ($P < 0.001$) (see figure below).

The patients who were given placebo were subsequently switched to rifaximin. In these patients, SIBO was eradicated in 17 of 20 cases. Fifteen of these patients had a complete resolution of rosacea. Thirteen of 16 patients with negative breath tests for SIBO remained unchanged, and this result differed from SIBO-positive cases ($P < 0.001$). Eradication of SIBO induced an almost complete regression of their cutaneous lesions for at least 9 months.

The authors of the study suggested that chronic systemic inflammation causes inflammation of the skin. Figure 8. shows the clinical outcome in SIBO-positive and SIBO-negative rosacea patients treated with rifaximin.

Sidebars

1. Myth: syndromes are all “in your head” and are due to “stress”
2. Restless legs syndrome is caused by central nervous system iron deficiency and altered dopamine interactions. Evidence for the role of small intestinal bacterial overgrowth is growing.
3. The real name for “leaky gut” is increased intestinal permeability.

Chapter summary

1. Integrity of the gut mucosa is essential for good health.
2. Imbalance of bacteria plays a role in many disorders.
3. A shift of colonic type bacteria into the small intestine results in inflammation as well as fermentation with subsequent gas production.
4. Treatment with special antibiotics, motility medicine and probiotics may provide benefits to those suffering from “syndromes.”
5. Syndromes do not exist in a vacuum. The high prevalence of these idiopathic conditions in the population, and the overlapping of symptoms from one condition to another, suggest that a central cause could be a significant factor (Figure 9.).

Figures and Tables.

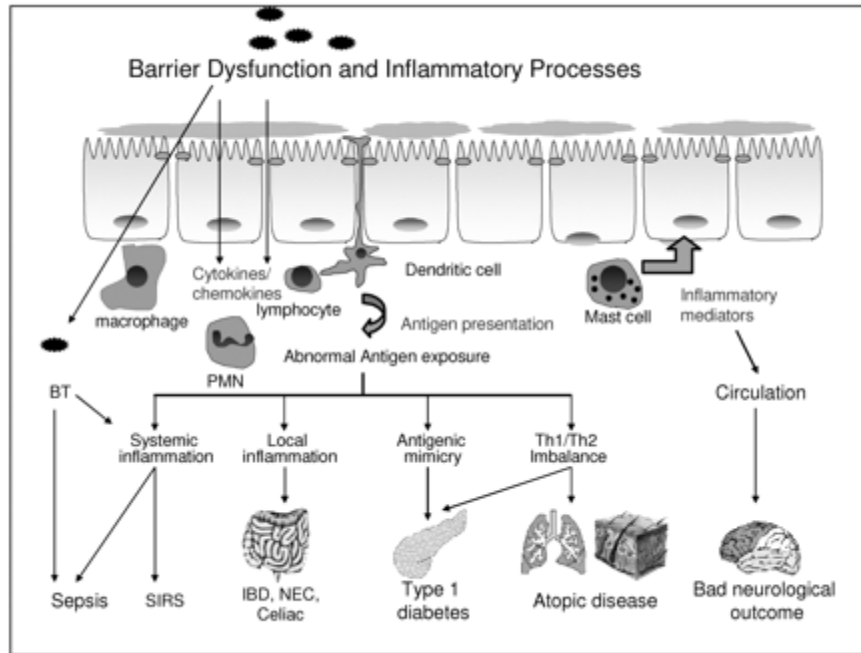
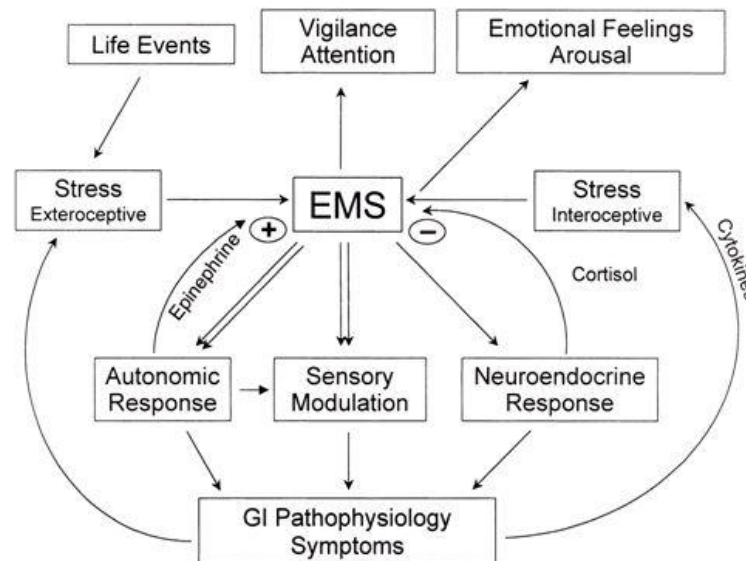


Figure 1. Intestinal Barrier Dysfunction and Systemic Inflammation. An intact gut barrier is necessary to monitor and keep toxins, allergens and bacteria from invading the mucosa. The gut barrier is a complex system and depends on anatomic tight junctions, immune function, antimicrobial chemicals and digestive enzymes. Disruptions in barrier dysfunction lead to heightened immune activation in the gut which leads to circulation of cytokines and a systemic inflammatory response.¹⁰⁰ Pathogenic microbes and intestinal barrier dysfunction may cause an inflammatory response by interacting and activating lymphocytes, mast cells, and dendritic cells that mediate release of inflammatory mediators. Also abnormal antigen exposure may lead to diseases characterized by local inflammation (such as IBD, NEC, and celiac), antigenic mimicry (such as type 1 diabetes), imbalance Th1/Th2 (atopic disease), and systemic inflammation (eg, systemic inflammatory response syndrome, sepsis, bad neurologic outcome). Reprinted from Liu Z, Li N, Neu J. Tight junctions, leaky intestines, and pediatric diseases. *Acta Paediatr.* 2005;94:386–393, with permission from Blackwell Publishing. IBD, inflammatory bowel disease; NEC, necrotizing enterocolitis; SIRS, systemic inflammatory response syndrome. The “leaky gut” has been described as a breach in the integrity of the gut (specifically the small intestine) that may be a result of genetic weakness combined with stress factors¹⁰¹ including illness, nonsteroidal 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, while less obvious changes can occur as a delayed effect after an enteric infection.^{102, 103}

Intestinal permeability can result in many systemic from the permeation of food antigens as well as neuroendocrine imbalances (see Figure 2) driven by bacterial byproducts. In the face of a compromised gut barrier, bacteria can attach to the gut lining resulting in translocation of the bacteria, or bacterial byproducts, into the mucosa. When the outer coating of gram negative bacteria is shed, these lipopolysaccharides induce an

imbalance of the hypothalamic-pituitary-adrenal axis.^{104, 105} This, along with cytokines that occur in bacterial overgrowth, can lead to chronic fatigue and depression.¹⁰⁶

Compromised integrity of the small intestine allow for larger food particles that are the byproducts of incomplete digestion to cross an impaired intestinal barrier, acting systemically as allergens. This process may explain some of the food allergies and nonspecific food reactions (“sensitivities”) that are increasingly seen. For example, one study of subjects with food sensitivities versus controls looked at lactulose/mannitol ratio detection as a measurement of intestinal permeability.¹⁰⁷ The results demonstrated a significant difference in small intestinal permeability between those with food allergy, food hypersensitivity and no food reactions (see chapters xxx and xxx by Turnbull, Hanaway, respectively).



Mayer, E. A. et al. Am J Physiol Gastrointest Liver Physiol 280: G519-G524 2001

Figure 2. Interplay of the emotional motor system (EMS) and gastrointestinal pathophysiology (with permission of EA Mayer Am J Gastrointestinal Liver Physiology 2001;288:G519-524.) . Stress, abuse and emotional feelings influence bowel symptoms via activation of the brain’s central circuitry called the emotional motor system (EMS) to produce autonomic and neuroendocrine responses. Bowel symptoms then cause more distress triggering the release of mediators (cytokines, cortisol, and adrenaline) which act on the EMS producing a feed-forward cycle of bowel symptoms and emotional distress.

Natural defense factors that prevention of small intestinal bacterial overgrowth are shown within the circles.

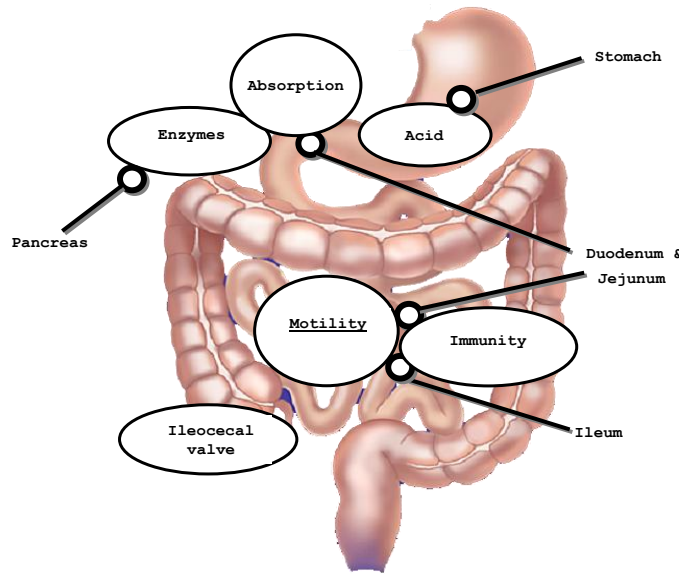


Figure 3. Host Defenses Against Small Intestinal Bacterial Overgrowth. The upper gastrointestinal tract is sparsely populated with gut coliforms. The protective mechanisms for maintaining relative gut sterility include: stomach acid, proper absorption of fermentable carbohydrates, gastric, intestinal and pancreatic enzymes, gastrointestinal motility, mucosal immunity and an intact (competent) ileocecal valve which serves as a barrier between the terminal ileum and colon.

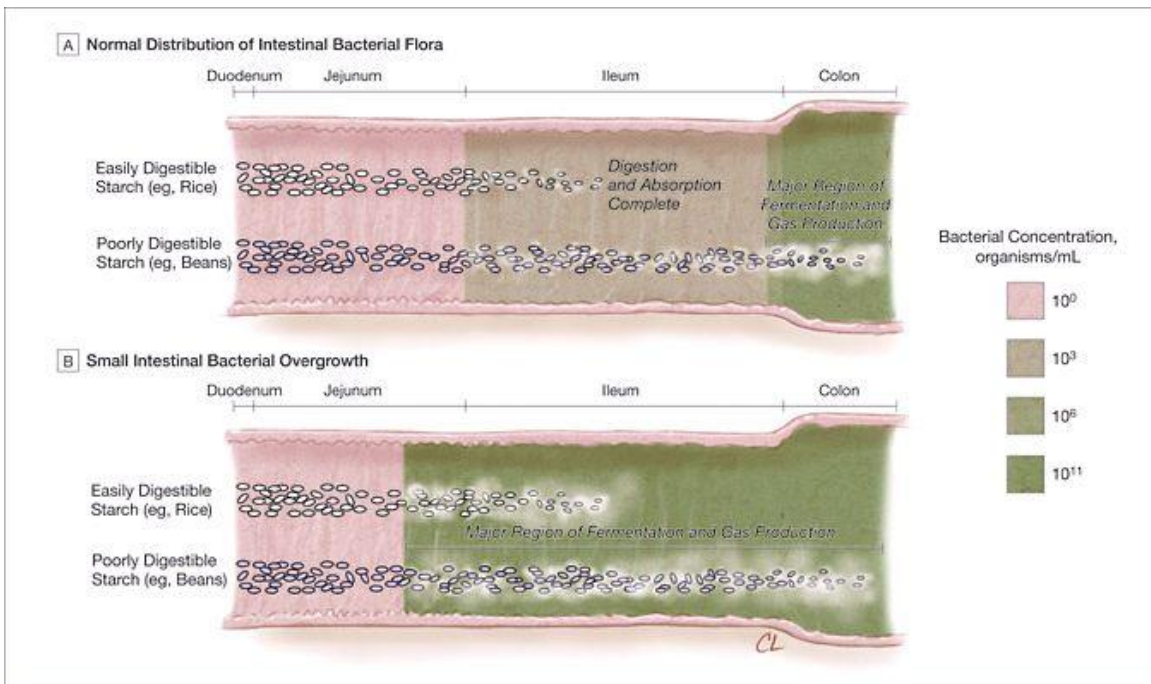


Figure 4. Small Intestinal Bacterial Overgrowth. In A) there is a normal distribution of intestinal bacteria that does not ferment poorly digestible starches such as beans until they reach the large intestine. In B) there is small intestinal bacterial overgrowth where the easily (rice) and poorly (beans) digestible carbohydrates are fermented in the small intestine by the bacteria due to their overpopulation.

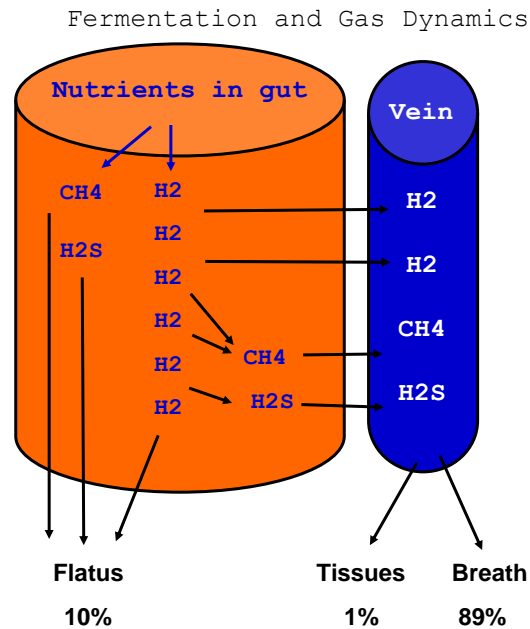


Figure 5. Fermentation and Gas Dynamics. Undigested starches are fermented by gut coliforms into hydrogen, methane and other gases. These gases equilibrate and are absorbed into the blood stream which diffuse through pulmonary capillaries and are excreted in the breath. This allows for the detection of intestinal gases as byproducts of fermentation of undigestible starches by breath testing.

IBS Pathophysiology-CAM Therapy

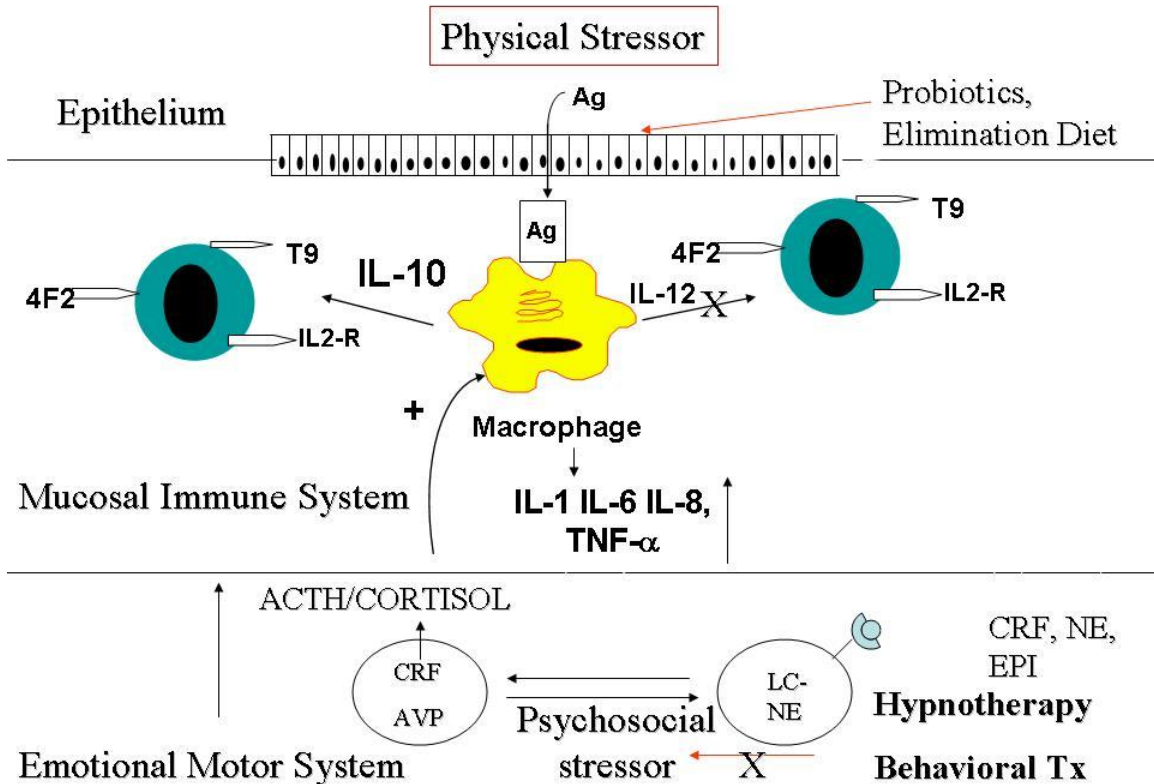
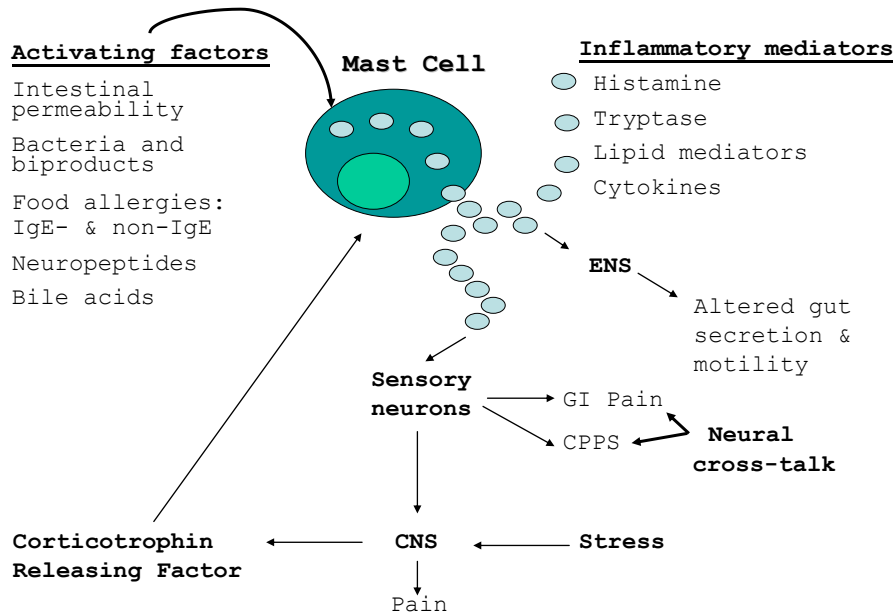
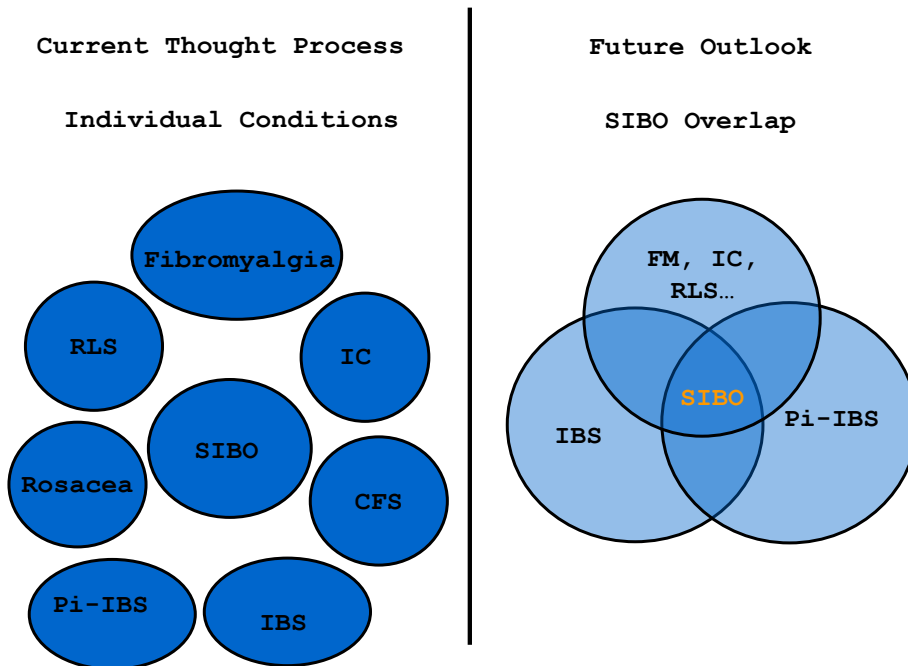


Figure 6. Role of Alternative Strategies in the Treatment of SIBO-IBS. Dysbiosis of the gut can initiate and drive a proinflammatory process that results in systemic neuroendocrine stress factors to be elaborated. Impairments in the emotional motor system of the brain drive the distorted mind-body processes via altered gut motility, hormones and sympathetic nervous system overdrive. Treatment of SIBO-IBS can be targeted at 1) ameliorating dysbiosis by eradication of SIBO with antibiotics and/or herbal therapies followed by inoculation with probiotics 2) repair of the injured gut epithelium by providing nutrients such as glutamine, aloe vera, zinc carnosine 3) elimination diet that is low in poorly digestible starches that feed bacteria (ie legumes) and eliminates allergens (which cause impairments in gut integrity and chronic intestinal injury) 4) resetting the aberrant mind-body connection by ameliorating the distortion in the emotional motor response (stress reduction, breathing exercises, affirmations, music therapy, Tai Chi, yoga, meditation, hypnotherapy, acupuncture, cognitive behavioral therapy, integrative psychotherapy).



Adapted from Barbara; Neurogastroenterol Motil 2006 and Pezzone; Gastroenterology 2005.

Figure 7. Factors involved in the pathogenesis of Interstitial Cystitis. The translocation of gastrointestinal bacterial byproducts across a leaky-defective barrier can trigger a mast-cell centered immune-inflammatory response throughout the common mucosal immune system, including the bladder. Localized production of inflammatory mediators (histamine, tryptase, cytokines, prostaglandins) sensitize the pain response.



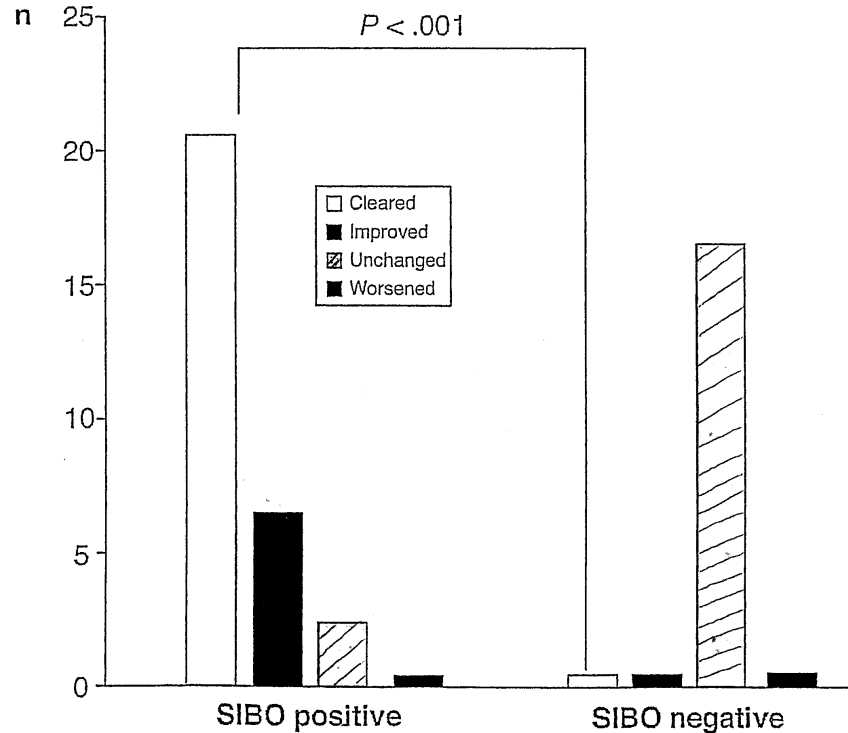


Figure 8. Clinical outcome in SIBO-positive and SIBO-negative patients treated with rifaximin. All SIBO-eradicated patients have been followed for at least 9 months. Cutaneous lesions were kept in remission without any other therapy in all but two patients, in whom papulopustules recurred after several months when they proved to be G-BT positive again. After SIBO eradication, rosacea lesions cleared. OCTT proved significantly more delayed in patients with SIBO (150 minutes; 25th–75th percentiles, 142.5–165) than in controls (105 minutes; 25th–75th percentiles, 90–135) ($P < .001$). Last, in 7 patients with both SIBO and Hp infection, cutaneous lesions fully cleared after rifaximin administration before commencing the anti-Hp therapy.¹³⁴

Figure 9. SIBO as the Root Cause of Functional Digestive Conditions with Systemic Manifestations. The irritable bowel syndrome (IBS) has many associated systemic manifestations such as chronic fatigue syndrome (CFS), fibromyalgia, restless leg syndrome (RLS), interstitial cystitis (IC) and skin rashes such as Rosacea. In current conventional medical practice, these “conditions” are viewed separate from concurrent digestive disorders. The results of standard medical therapy for these “conditions” are often unsatisfactory. As reviewed in the text, research ties the association of these “conditions” to an underlying causality to small intestinal bacterial overgrowth (SIBO). IBS, RLS, CFS, IC and Rosacea have been linked to the presences of SIBO. Successful treatment of SIBO with antibiotics results in the resolution of thses “conditions.”

Table 1. Incidence of Post-Infectious IBS.

Incidence of Post Infectious-IBS (Pi-IBS)

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

Table 2. Common Causes of SIBO.

Standard SIBO Conditions

Scleroderma	Achlorhydria
Small intestinal pseudo-obstruction	Diabetes
Pancreatic insufficiency	Radiation enteritis
Jejunal diverticulosis	<i>Immunodeficiency:</i> CLL, IgA deficiency, T-cell deficiency
<i>Post-surgical anatomy:</i> Billroth, Blind-loop, ICV resection, J-pouch	Celiac and Crohn's diseases

Table 3. Lesser Known Causes of SIBO.

Lesser Known and New SIBO Conditions

Chronic renal failure	Rheumatoid arthritis
Cirrhosis	Irritable bowel syndrome
Chemotherapy	Fibromyalgia
Acromegaly	Interstitial cystitis
Hypothyroidism	Restless legs syndrome
Chronic fatigue syndrome	Rosacea

Table 4. Prevalence of small intestinal bacterial overgrowth in IBS patients as determined by a positive breath test for bacterial overgrowth.

Prevalence of small intestinal bacterial overgrowth in IBS patients as determined by a positive breath test for bacterial overgrowth.

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

Table 5. Rifaximin therapy for IBS-SIBO.

Rifaximin therapy: IBS/Fx-SIBO				
Author	Yr	Patients	Type	Efficacy
Nucera	'04	IBS-SIBO (n=200)	Open label; Rfx + paramomycin	87-100% effective in treating SIBO by reversing 3 sugar BT's
Lauritano	'05	IBS-SIBO (n=90)	Dose-ranging	Dose response with Rfx
Lupascu	'05	IBS-SIBO (n=80)	Abx comparison; open label	1 wk of Rfx vs. metro/levoquin 12/20 vs. 14/20 H2 BT normalized
Pimentel	'05	IBS-SIBO (n=87)	R/DB/PC	Statistical sig. vs. placebo; duration of response over 2 months for 10-day Rx
Sharara	'06	IBS (n=70)	R/DB/PC	Statistically sig. vs. placebo
Sharara	'06	Fx-SIBO (n=54)	R/DB/PC	Numerically diff. vs. placebo
Weinstock	'06	IBS-SIBO (n=254)	Observational	60% mod-greatly improved
Weinstock	'06	Fx-SIBO (n=85)	Observational	63% mod-greatly improved

Table 6. Medical therapy for restless legs syndrome

Dopaminergic agents
 Neuroleptics
 Anti-seizure medications
 Narcotics
 Benzodiazepines
 Iron
 Investigational
 Rifaximin antibiotic therapy
 Magnesium
 Acupuncture
 Botox injections

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