Small Intestinal Bacterial Overgrowth

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INTRODUCTION

Gut flora are defined as natural living organisms within the gastrointestinal (GI) tract. The GI tract at birth is sterile, but bacteria in the environment as well as exposure to the birth canal, food, and caregivers quickly give rise to the gut flora. Bacteria are the primary organisms, with yeast and helminths added to the milieu depending on geographic region and prior exposures. The bacterial population numbers over 100 trillion organisms and is estimated to contain 500 to 1000 species; of these, at least 50% cannot be cultured with current technology.[1]

The environment in the mouth and upper gut allows aerobic organisms to grow, while anaerobic conditions predominate in the distal gut, enhancing coliform bacterial reproduction. The majority of bacteria form a symbiotic relationship with the host (the "good flora"), providing benefits such as development of normal gut immunology and histology, fermentation of indigestible polysaccharides, and metabolism of vitamins and drugs. This symbiotic relationship depends on a properly functioning host barrier. However, the host barrier comprises several mechanisms, including luminal mechanisms and digestive enzymes, tight junctions between epithelial cells, and the gut immune system. In addition, epithelial production of alpha defensins and mucin prevent bacteria translocation, and secretory IgA produced by the intestinal mucosa protects against bacterial invasion. In general, diseases associated with gut flora occur when the defense mechanisms break down and allow for bacterial overgrowth in the small intestine, when "bad" bacteria proliferate, or when "good" bacteria are destroyed by antibiotics. This manual discusses commensal bacteria and disorders of the balance in gut flora that lead to harmful outcomes.

BACTERIAL BALANCE

"THE GOOD" FLORA

The number of bacteria in the human gut exceeds that found in other mammals, but the diversity is less complex. The largest classes are the Firmicutes and Bacteroidetes.[1] The complexity and number of bacteria increases as one goes from the stomach to the colon (**Table 1**). Relatively few of the dietary and oropharyngeal organisms that are swallowed survive the acidity of the stomach to enter the duodenum (100/g). In the distal ileum, there is a dramatic increase in the number of bacteria (in the 10^7–10^8/g range), with the flora predominantly comprising fecal-like anaerobes. In the right colon, the bacteria count increases 3 log folds, with the same type of organisms but with more Bifidobacteria and Clostridia.

Animal studies have demonstrated several benefits of bacteria, including the development of normal immunity and gut histology.[3] In the absence of bacteria, mice lack T cells and IgA secretion. Bacteria also play an important role in energy balance.[4] Conventionally raised mice have 40% more total body fat than germ-free mice fed the same diet, as bacteria are responsible for salvaging energy from indigestible dietary polysaccharides. Stool contents obtained from normal rats transplanted to the intestine of germ-free rats rapidly increased body fat content by several mechanisms: elevations of serum glucose and insulin stimulating liver fat production; increased availability of short-chain fatty acids (SCFA); and suppression of the lipoprotein lipase inhibitor.

Bacteria also ferment insoluble fiber and nonabsorbable carbohydrates, including indigestible polysaccharides. Subsequent SCFA provide additional calories as well as important nutrition to the epithelial cells of the colon.[5] SCFA are responsible for regulating cell proliferation and vascular flow within the mucosa. When stool flow is diverted from the colon, the colonic lining may become inflamed.[6]

Bacteria also play an important role in metabolic processes. *Clostridium* and *Escherichia coli* hydrolyze conjugated bile acids, allowing dietary fat and fat-soluble vitamins to be processed and absorbed.[7] This process is adversely affected by bacterial overgrowth or imbalance (dysbiosis) in the small intestine. Bacteria also metabolize dietary vitamin K from leafy vegetables and convert it to an absorbable K2 form. This process is also dependent on the presence of bile salts and results in improved bioavailability. Drugs and other unnatural

Table 1. Dominant Gut Bacteria and Typical Colony Counts

Stomach: $0–10^2$	
	Lactobacillus, Candida, Streptococcus, Helicobacter pylori, Peptostreptococcus
Duodenum and jejunum: 10^2	
	Streptococcus, Lactobacillus
Proximal ileum: 10^3	
	Streptococcus, Lactobacillus
Distal ileum: $10^7–10^8$	
	Clostridium, Bacteroides, coliforms
Colon: $10^{11}–10^{12}$	
	Bacteroides, Bi*fidobacterium, Clostridium coccodesm, Clostridium leptum, Fusobacterium*

Adapted with permission from Sartor BR. Therapeutic manipulation of the enteric microflora in inflammatory bowel diseases: antibiotics, probiotics, and prebiotics. Gastroenterology 2004;2004;16:1620–33. **[au: Is this adapted from a table in the Sartor article, or is it from the text? If from a table, what page is the table on?]**

compounds may be metabolized by bacteria in various ways. The inflammatory bowel disease (IBD) drugs sulfasalazine and balsalazide are made bioavailable by bacterial enzymes. Estrogens are also affected by bacterial enzyme conjugation.

Bowel movement form and activity are dependent on bacteria, as bacteria account for 50% to 80% of stool weight and bulk. There are 10^9 to 10^{11} bacteria per mL of stool. Finally, immune tolerance, defense, and cytoprotection rely on the presence of bacteria in the gut. Early exposure to bacteria such as nonpathologic forms of *E. coli* allows humans to build up tolerance to pathogenic *E. coli*. The balance of protective versus harmful enteric bacteria determines whether there is mucosal homeostasis or inflammation.

In addition to healthy commensal bacteria, the human gut flora can include small quantities of "bad" bacteria, noninvasive yeast, and helminths (**Table 2**). Yeast generally does not play a role in disease below the level of the esophagus and mouth. The variety of flora is partially dependant on the degree to which the society is hygienic. In agrarian cultures, helminth infestation is common, and is most often asymptomatic. Some specific immune benefits from helminths should be noted. Helminths induce mucosal T cells to make regulatory cytokines, including interleukin (IL)-4, transforming growth factor-beta, and IL-10.[8] Worms also induce various regulatory-type T-cell subsets in the gut that limit effector T-cell growth and impede release of IL-12, interferon-γ, and tumor necrosis factor-alpha (TNF-α).[9]

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ALTERED FLORA AND/OR BALANCE

Table 2. Gut Bacteria Categories and Characteristics

	Characteristics	Examples
"Good" bacteria	Protective, anti-inflammatory	Lactobacilli, Bifidobacteria, nonpathogenic *Escherichia coli*, *Streptococcus thermophilus*
"Bad" bacteria	Injurious, proinflammatory	*Bacteroides vulgatus*, *Enterococcus faecalis*, *E. coli*–enteroinvasive, *Klebsiella*
"Ugly" bacteria	Toxic, invasive	*Clostridia difficile*, *Camphylobacter*, *E. coli*, *Salmonella*, *Shigella*

Normally, the bacteria that may tilt the inflammatory activity into a disease state are kept in check by good flora, immunity, and intestinal integrity. Small intestinal dysfunction, mucosal damage, and potential systemic inflammation will occur due to imbalance, especially with overgrowth of coliforms. Altered microecology in combination with phenotypic predisposition may result in various diseases. Genetic alterations decrease immune barriers and affect how bacteria increase proinflammatory immune cells and responsiveness in IBD.[10] There is also a higher incidence of a proinflammatory state in the irritable bowel syndrome (IBS) with decreased IL-10 production and increased TNF-α production.[11] The following are 4 examples where either imbalance or the wrong type of bacteria are injurious.

Antibiotic-Associated Diarrhea

Most mild cases of antibiotic-associated diarrhea (AAD) are due to functional disturbances of intestinal carbohydrate or bile acid metabolism, allergic and toxic effects of antibiotics on intestinal mucosa, or pharmacologic effects on motility.[12] *Clostridium difficile* accounts for 10% to 20% of all cases of AAD. Other infectious organisms include *Clostridium perfringens*, *Staphylococcus aureus*, *Klebsiella oxytoca*, *Candida*, and *Salmonella*.[13]

Enteroinvasive Bacteria in Crohn's disease

Increased harmful bacteria (*Bacteroides*, invasive *E. coli*, and enterococci) and decreased levels of beneficial bacterial species (*Bifidobacterium* and *Lactobacillus*) have been suggested to trigger new cases and relapses of IBD.[2] A study of adherent-invasive *E. coli* (AIEC) in 63 patients with Crohn's disease that defined invasion as living organisms in intestinal cells found AIEC in 21% of chronic lesions in Crohn's patients but in only 6% of resected ileum specimens from non-Crohn's patients.[14]

Obesity

Recognition that certain bacteria may be more efficient in assisting in energy recovery of indigestible foods suggests that an imbalance of these bacteria may

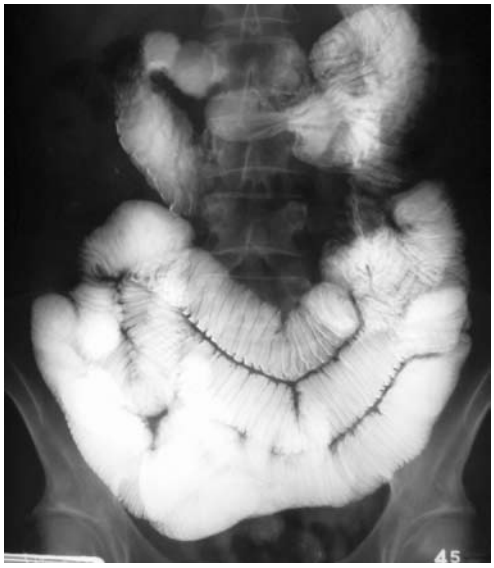

Figure 1. Radiograph of the small bowel showing areas of dilation.

be a cause of obesity.[15] Methane-producing bacteria, especially *Methanobrevibacter smithii*, lower the partial pressure of hydrogen by utilizing hydrogen and carbon dioxide after degradation of polysaccharides, allowing for further degeneration of polysaccharides and ability to provide more calories. This newly described role of bacterial flora in the etiology of obesity in man is a controversial but exciting development.

Irritable Bowel Syndrome

Fecal DNA testing studies have demonstrated high variation in bacterial counts from stool from IBS patients.[16] Another study reported less *Lactobacillus* in IBS-diarrhea (IBS-D) patients versus IBS-constipation (IBS-C) patients and controls and higher concentrations of *Veillonella* in IBS-C patients than in controls.[17] The important role of small intestinal bacteria in IBS will be reviewed later.

"THE UGLY" FLORA

C. difficile commonly colonizes infants without harm, and 4% and 7% of adults carry *C. difficile* as nonpathologic organisms. A recent study suggested that dense colonization of the intestine by enterococci may be associated with *C. difficile* colonization.[18] Only when the balance changes so that normal bacteria are reduced in numbers by antibiotic use do these organisms proliferate and cause disease. A significant number of flares of IBD appear to be triggered by *C. difficile* and can start spontaneously.[19]

The typical diarrhea-inducing invasive bacteria, noninvasive bacteria, viruses, and other pathogens are acquired from animals but use humans as temporary hosts and act as vectors for infections to others. Parasites, protozoans, and invasive helminths can also be temporary flora leading to disease.

SMALL INTESTINE BACTERIAL OVERGROWTH

CASE PRESENTATION

A 62-year-old woman presents with a 2-year history of diarrhea and bloating. She reports that she experiences postprandial distension, which is not improved by flatus or stool passage. She has lost 15 lb [**au: over 2 years?**]. Recently, she has had difficulty swallowing solid food and has experienced heartburn and Raynaud's phenomenon.

On physical examination, the patient is thin, pale, and slightly short of breath. Her height is 5 ft 3 in, weight is 99 lb, blood pressure is 160/100 mm Hg, and pulse is 100 bpm. She has a small mouth with skin crevices at the angles. Pulmonary and cardiac examinations are normal. She has mild diffuse distension and tympany. Bowel sounds are intermittent and loud. There is mild abdominal tenderness in the mid abdomen. Rectal examination shows loose guaiac-negative stool.

Laboratory testing reveals a serum albumin level of 3.1 U/L. Hemoglobin is 10.1 g/dL with a mean corpuscular volume of 110 μm^3. The levels of vitamin B_{12} and vitamin D are low. Radiography shows several areas of dilated small bowel (**Figure 1**). Upper endoscopy reveals reduced motility of the esophagus and a 2-cm long stricture, which responds well to dilatation.

- **What conditions can account for this patient's presentation?**

CLINICAL FEATURES

Scleroderma is the most logical diagnosis as indicated by [**au: Please indicate what findings point to a diagnosis of scleroderma.**]. ~~It is important to elicit symptoms involving the skin, especially inflammation and skin tightness or hardening. These skin changes can be widespread, but most commonly affect the fingers, feet, face, and neck. Laboratory tests should include antinuclear, anticentromere, and anti-Scl 70 antibodies. Small bowel follow through barium study, chest radiograph, and pulmonary function tests should be ordered. Nutritional and hematologic assessment is essential. Upper endoscopy to exclude a stricture is indicated.~~ [**au: Ok to delete this since the focus of this article is not scleroderma?**] In addition, the likely cause of this patient's diarrhea is bacte- **Will fix BB**

rial overgrowth secondary to scleroderma as suggested by [**au: Please say explicitly what findings point to bacterial overgrowth.**] ~~In light of the above analysis, confirmation of suspected bacterial overgrowth was not felt to be required to diagnose and treat the patient's diarrhea.~~ Small intestinal bacterial overgrowth (SIBO) may be defined as a disruption or increase of the normal small bowel bacterial population that can result in altered bowel function, bloating, flatulence, and/or malabsorption of nutrients. With chronicity, weakness and weight loss will become evident. Advanced cases may have peripheral edema from hypoalbuminemia. Pallor from anemia due to vitamin B_{12} deficiency, anemia of chronic disease, and, in some cases, iron deficiency (most often attributed to achlorhydria) may be present. Anemia in scleroderma may be due to gas bleeding from vascular malformations. In advanced stages, cachexia and other changes of vitamin and nutrient deficiency may become evident. Symptoms and nutrient deficiency are induced by excess intraluminal small intestinal bacteria, which cause fermentation of nutrients, producing gas, and excessive bile salt deconjugation, leading to fat malabsorption and secretory effects causing diarrhea. Bacterial consumption of vitamins including vitamin B_{12} also occurs.

- **What tests are used to diagnose bacterial overgrowth?**

DIAGNOSIS

The diagnostic level of bacterial overgrowth has been defined as a culture greater than 10^5 aerobic or 10^3 anaerobic colony-forming units (CFU) per mL of small intestinal fluid.[53] It has been argued that there is no gold standard for SIBO since the general definition is a syndrome and testing has not been properly evaluated.[54] Bacterial overgrowth, or dysbiosis, with transition of the bacterial content of the proximal small intestine whereby excessive bacteria adversely affect nutrient absorption and/or cause clinical symptoms may be adequate diagnostic criteria.

Direct Method: Culture

Small bowel fluid aspiration via nasoduodenal or nasojejunal catheters may be used to obtain specimens for culture.[53] Accuracy of the culture of anaerobic bacteria to media is likely altered by exposure to air during transit. Sampling errors need to be addressed since the presence of excess bacteria may vary in areas of the bowel.[55] Such variations may occur when only parts of the small intestine are affected with a motility disorder or when there is a partially obstructed condition such as a blind loop. Jejunal cultures catheters do not pass beyond the proximal jejunum and are plagued by the problems of oral and upper GI tract contamination and the difficulty of culturing bacteria.

Indirect Method: Breath Testing

There is no source of hydrogen gas production in humans other than bacterial metabolism of carbohydrates. With bacterial fermentation, hydrogen and other gases are released and then absorbed through the mucosa. Gases are transported to the alveoli by the circulation and then released into the airways. Breath tests provide indirect evidence of bacterial overgrowth. The test entails administering a sugar substrate and measuring gases after a specific period of time has elapsed. Diagnostic criteria have varied substantially in the literature. Most investigators have concluded that a rise of hydrogen and/or methane over 20 parts per million before 90 minutes is abnormal. Others sample the gases for 3 hours. The older requirement to detect separate small intestinal and colonic peaks is no longer necessary.

The sensitivity and specificity of the breath test for SIBO is dependent on the substrate used. The sensitivity and specificity of the glucose breath test (GBT) range between 60% and 90%.[56] Glucose is absorbed in the first 3 feet of the small intestine and thus cannot be used to evaluate the mid-jejunum and beyond. Glucose underestimates the incidence of bacterial overgrowth by one half as compared with an abnormal lactulose breath test (LBT) in IBS patients.[47,51,52] Lactulose is more sensitive but it is less specific since it is not absorbed from the gut; thus, the entire bacterial flora is sampled. Variability in transit of lactulose and hence sampling by colonic bacteria reduce the sensitivity. In 2 comparative studies of the LBT and culture, LBT had a sensitivity of 16.6% and 68% and a specificity of 44% and 70%, respectively.[57,58] These studies had several faults, particularly patient selection. Many patients had gastric resections which would have blocked the access of lactulose to the afferent loop. Large studies of the normal population are limited. A study of the LBT that used controls showed abnormal results in 3 of 15 controls (versus 93 of 111 IBS patients).[52] In a study of GBT in patients with IBS, 4 of 102 controls had abnormal results.[48] [**au: Do you have any specific recommendations on approach to testing in SIBO?**]

Effects of Gases Created by Bacterial Overgrowth

Overall excess production of gases in the small intestine leads to abdominal bloating and distension, most often due to excess hydrogen production by bacterial fermentation.[59] Early studies showed that excess methane production during breath testing correlated with delayed orocecal and whole gut transit. Abnormal

Table 3. Small Intestinal Bacterial Overgrowth Disorders

Classic conditions	**Recently reported**
Small intestinal pseudoobstruction	Celiac disease
Scleroderma	Chronic kidney disease
Achlorhydria	Postinfectious rritable bowel syndrome
Crohn's disease	Irritable bowel syndrome
Diabetes	Fibromyalgia
Cirrhosis	Chemotherapy
Radiation enteritis	Acromegaly
Jejunal diverticulosis	Hypothyroidism
Post-surgical	**Latest reports**
Billroth	Interstitial cystitis
Blind-loop	Restless legs syndrome
Ileocecal valve resection	
J-pouch	
Immunodeficiency	
CLL	
IgA deficiency	
T-cell deficiency	

methane production is associated with IBS-C and correlates with the severity of IBS.[60,61] Infusion of methane into dog's small intestines reduced gut transit by 70%.[62] Hydrogen sulfide can act as a neuronal transmitter, activating extrinsic sensory nerves, and it contracts the detrusor muscle in interstitial cystitis.[63,64] It may have a role in pouchitis and can produce a rotten egg smell in breath,[65] flatus, urine and skin. During bacterial fermentation, hydrogen is converted to either methane by methanogenic microbes or hydrogen sulfide by sulfate-reducing bacteria in the right colon.[66] The body is equipped with an efficient detoxification system[67] that rapidly reduces the concentration of hydrogen sulfide from parts per million to parts per billion. Hydrogen sulfide is oxidized to thiosulfate in the right colon. Hydrogen sulfide is also removed by first pass metabolism in the liver. If there is a location and volume shift in the sulfate-reducing bacteria to the small intestine, then hydrogen sulfide excess may predominate and cause symptoms. There are other gases that are not as well characterized but contribute to the bad odor of both the flatus and the breath.

Impairment of gas transit in IBS patients appears to differ from that in controls, which could lead to trapping of gas in the small intestine.[68] Bloating and gas are the most common IBS complaints and affect the quality of life for many patients.[69] Many gastroenterologists still feel that this is related to visceral hypersensitivity and relaxation of the abdominal wall despite recent evidence from plethysmography.[70] Two studies have shown that excretion of intestinal gas is increased in IBS patients. A chamber study showed that the maximum rate of excretion of hydrogen and methane after a standardized meal was 4 times that of controls.[59] Another study compared bowel gas volume in 30 IBS patients and 30 controls. Bowel gas volume scores as determined by digitized radiography were significantly higher in IBS compared with controls regardless of the bowel habit pattern.[71]

- **What conditions are associated with SIBO?**

CONDITIONS COMPLICATED BY SIBO

Scleroderma is one of several well-known causes of SIBO (**Table 3**). Lack of acid or motility disorders in elderly, asymptomatic people is a frequently recognized phenomenon (**Figure 2**).[24–26] Classic conditions associated with SIBO as well as recently reported associated conditions will be discussed in the following sections.

Restless Legs Syndrome

Restless legs syndrome (RLS) occurs in 10% of the population. RLS is either idiopathic or secondary to over 20 conditions and is related to central nervous system iron deficiency with altered dopamine interaction in the substantia nigra. Various degrees of peripheral iron deficiency are found in patients. Many of the secondary RLS disorders also have bacterial overgrowth and/or inflammation. One study showed that the prevalence of RLS in scleroderma was 22%.[104] Research by this author showed increased prevalence in Crohn's disease and celiac disease. A pilot study showed an excellent response in RLS symptoms to rifaximin antibiotic therapy in 13 SIBO patients, 12 with IBS and 1 with recurrent small bowel obstructions.[27] Other conditions with bacterial overgrowth that have a high prevalence of RLS include fibromyalgia, end-stage renal disease, diabetes, and chronic liver disease.

Celiac Disease

Ten of 15 celiac patients with persistence of gastrointestinal symptoms after gluten withdrawal had SIBO, and rifaximin reversed all symptoms in these patients.[28] Another study showed that the majority of celiac disease patients unresponsive to dietary therapy had SIBO.[29]

End-Stage Renal Disease

The only study of SIBO in ESRD evaluated 12 patients with and 10 patients without GI symptoms.[30] Neuropathic changes on small intestinal manometry were found frequently in association with GI symptoms. More patients with SIBO lacked phase III activity. Jejunal aspi-

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rates, however, did not correlate with motility pattern. Overall, 8 of 22 patients had more than 10^5 CFU/mL by jejunal aspirates.

Fibromyalgia

Fibromyalgia was recently reported to be associated with SIBO.[31] This association is particularly important due to the frequent association with IBS and the difficulty in treating this syndrome. Hydrogen production on the LBT was compared in 111 patients with IBS and 42 patients with fibromyalgia. In this study, 20% (3 of 15) of controls had an abnormal LBT compared with 84% (93 of 111) of patients with IBS and 100% (42/42) of patients with fibromyalgia. The degree of somatic pain correlated with hydrogen levels.

Interstitial Cystitis

IBS patients often have interstitial cystitis (IC), a disabling syndrome of pelvic pain, urgency, and frequency with evidence of immune activation and bladder hypersensitivity. Increased intestinal permeability, immune activation, and visceral hypersensitivity may have roles in the pathophysiology of IC.[32] A recent study of IC patients with chronic active GI symptoms showed that 17 of 21 patients (81%) had an abnormal LBT and that open-label antibiotic treatment with rifaximin was effective.[33]

Postinfectious IBS

It is conservatively estimated that between 20% and 30% of all cases of IBS are secondary to postinfectious causes (Eammon Quiggley, MD, personal communication, 2007). In several case series, between 7% and 33% of normal persons developed IBS after having acute infectious gastroenteritis.[34–36] Post-infectious IBS (Pi-IBS) is having a profound effect on the way that IBS is viewed. Whether Pi-IBS triggers bacterial overgrowth through altered motility or whether Pi-IBS causes inflammation with subsequent visceral hypersensitivity continues to be debated. Studies have shown a diminished migrating motor complex wave in IBS patients with SIBO.[37] It is likely that in some patients time is required for bacterial counts to increase between developing the infection and the motility disorder. Thus, subsequent symptoms may not be well connected to that patient's recall of the initial insult. Conversely, in IBS patients who have abnormal breath tests reflective of SIBO, 20% recall a distinct onset of the symptoms that commenced after a diarrheal illness.

Risk factors for developing Pi-IBS include female sex, severity and length of the diarrhea, absence of vomiting, and increased stress at the time of the infection.[34,38] *Campylobacter* followed by *E. coli*, *Shigella*, and *Salmonella* have the highest risk of Pi-IBS. Viral gastroenteritis also has a significant risk of Pi-IBS.[39] In a study of 197 persons exposed to norovirus at a meeting, 77% had an acute diarrheal illness. In the people who never had IBS, 21 of 89 developed Pi-IBS after gastroenteritis. Recently, trichinella has been shown to cause Pi-IBS.[40]

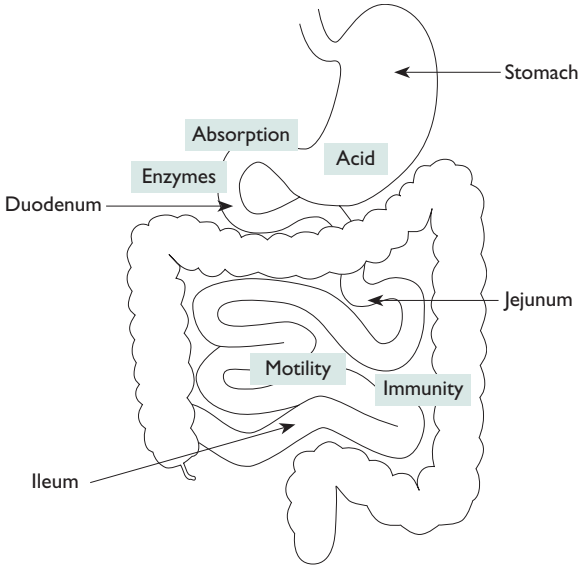

Figure 2. Natural defenses that prevent small intestinal bacterial overgrowth (SIBO). The key factors in preventing overgrowth are shown in the circles. Motility of the small intestine is the most important and is frequently compromised in diseases classic for SIBO.

A study of Pi-IBS due to *Campylobacter* involving 31 patients demonstrated increased permeability at 0, 6, and 12 weeks.[41] Retesting in 10 patients 1 year later showed abnormal permeability as well as increased lymphocytes and enterochromaffin cells deposits and elevated IL-6 levels. Further studies using chromium-ETDA 24-hr urine collection showed that permeability was abnormal in Pi-IBS-D and general IBS-D patient groups compared to IBS-C and controls.[42] Mechanisms underlying these changes are shown in **Figure 3** [**au: Briefly discuss these mechanisms here and delete Figure 3 to save space?**].[43,44]

Two animal studies have demonstrated motility, hypersensitivity, and bacterial overgrowth disorders after enteric infections. A motility disorder was demonstrated following trichinella infection, which leads to innate bacterial overgrowth and inflammation (**Table 4**).[43] The trichinella study also showed how transient gut inflammation causes hyperalgesia, which is the hallmark of the pain disorder associated with IBS. The second study shows how *Campylobacter* infection can cause SIBO.[44] Half of 60 rats received *Campylobacter jejuni* by oral in-

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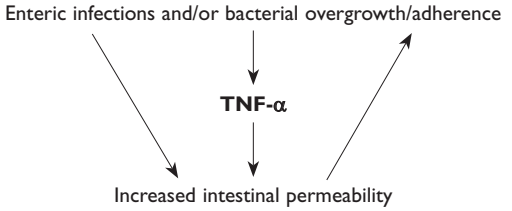

Figure 3. Inflammatory mechanism of pathophysiology of small intestinal bacterial overgrowth. Bacterial overgrowth damages the epithelial lining and stimulates production of tumor necrosis alpha, which decreases the tight junctions between cells, leading to increased intestinal permeability. Increased permeability may in turn allow for increased adherence by bacteria.

stallation. Three months later, 57% of the infected rats had loose stool versus 7% of the sham-treated animals. Segmental resection with PCR evaluation of bacterial contents showed that 27% of the infected rats had diagnostic PCR changes of SIBO.

Large published studies show a relationship of SIBO to IBS (**Table 5**). Studies that have looked for direct evidence of bacterial overgrowth by jejunal aspirate studies have had contrasting results. One found that only 4% of 162 patients had abnormal cultures; however, 43% of the IBS patients in this report had more than 5000 coliforms versus 12% of controls ($P = 0.002$).[45] The other culture study found that 12% of 33 IBS patients had colony counts exceeding 10^5 CFU/mL.[46]

- **What medical therapy might be used for this patient's diarrhea?**
- **What other therapy and specific nutrients might be warranted?**

MANAGEMENT

[au: Does this discussion of management pertain to SIBO in general?]

Prokinetic Therapy

Motility therapy is essential in treating SIBO, but often has limited success. In some early cases **[au: of SIBO or scleroderma?]**, there may be response to cisapride (presently available with a compassionate drug protocol). Erythromycin is another option for stimulating migrating motor complexes as well as propulsive motions in the intestine. Erythromycin mimics the actions of motilin, a digestive hormone that stimulates small bowel muscular activity. Low-dose octreotide can be of some help in patients with pseudoobstruction and might help this patient.[20] Prokinetic treatment usually fails in advanced scleroderma.

Antibiotic Therapy

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Table 4. Abnormal Phase III Migrating Motor Complex Leads to Small Intestine Bacterial Overgrowth

Poor clearance and growth of innate SB bacteria
Adherence and translocation of bacteria
Increased intestinal permeability
Inflammatory mediators—cytokines
Inflammatory cells

Initially, a 7- to 10-day course of an antibiotic [**au: for SIBO or in scleroderma?**] repeated every 4 to 5 weeks is administered. In severe cases [**au: of SIBO or in scleroderma?**], different antibiotics are often given as a rotation 1 week at a time followed by a rest period of 3 weeks. Reversing the results of breath tests is a quantifiable means to determine treatment success (**Table 6**). Recent studies have shown that rifaximin has high efficacy in SIBO conditions.[21,22] A 1-week study comparing rifaximin 1200 mg, metronidazole 750 mg, ~~levoquinalone~~ levofloxacin 750 mg, and combination ~~levaquinolone~~ levofloxacin and metronidazole showed similar breath test normalization in 60% to 70% of the patients treated with rifaximin and ~~levaquinalone~~ levofloxacin with or without metronidazole compared to 39% for metronidazole alone [**au: Should this be "levofloxacin" rather than "levoquinolone"?**].[23] Rifaximin is a nonsystemic antibiotic with broad-spectrum antibacterial activity against enteric pathogens.[74] The minimal bioavailability (< 0.4%) of rifaximin restricts its activity to the GI tract and limits the potential occurrence of systemic adverse events, pseudomembranous colitis, and drug-drug interactions.[75]

Two studies of neomycin therapy in IBS patients with abnormal LBT results showed statistical improvement: 46 achieved a 35% reduction from baseline in severity of IBS symptoms, compared with a 15% reduction in 47 who received placebo ($P < 0.01$).[52] Similar success was seen in IBS-C.[72] Successful antibiotic treatment of IBS symptoms correlates with normalization of LBT results. This is an important concept in the treatment of SIBO since there is no gold standard for diagnosing SIBO. In a retrospective study of 50 patients with positive LBTs who had been administered rifaximin, 31 patients (62%) achieved clinical improvement.[73] Post-treatment LBTs were normal in 81% of the patients who responded to rifaximin, compared with 16% of patients who did not respond ($P < 0.001$). A retrospective chart review of 98 patients with IBS who received antibiotic therapy (median duration of patient time in clinical treatment, 11 months) reported that 58 (69%) of 84 patients who received at least 1 course of rifaximin experienced clinical response as compared with 9 (38%)

Table 5. Indirect Evidence of Small Intestinal Bacterial Overgrowth by Breath Testing in Irritable Bowel Syndrome

Author	Substrate	N	Prevalence (%)
McCallum[47]	Glucose	143	38.5
Lupascu[48]	Glucose	65	30.7
Nucera[49]	Lactulose	98	65
Nucera[50]	Lactulose	200	75
Pimentel[51]	Lactulose	202	78
Pimentel[52]	Lactulose	111	84

Table 6. Efficacy of Antibiotics in the Treatment of Small Intestinal Bacterial Overgrowth

Antibiotic	Reversal of Breath Test,%
Neomycin	25
Doxycycline	30–40
Quinolones	60–70
Metronidazole	20–40
Rifaximin	70
Chlortetracycline	27
Amoxicillin clavulanate	30–40

of 24 patients who received neomycin ($P < 0.01$) and 27 (44%) of 61 patients who received amoxicillin clavulanate or doxycycline ($P < 0.01$).[76] In a randomized, double-blind, placebo-controlled trial, 15 of 37 (41%) IBS patients who received rifaximin 800 mg/day for 10 days achieved global symptomatic response compared with 6 of 33 (18%) who received placebo ($P = 0.04$).[77] After 10 days post-treatment, 27% of the patients in the rifaximin group maintained their symptomatic response as compared with 9% in the placebo group ($P = 0.05$). In a second randomized, double-blind, placebo-controlled trial, 43 IBS patients who received rifaximin 1200 mg/day for 10 days experienced a 36% mean improvement from baseline in the severity of IBS symptoms at 10 weeks post-treatment as compared with a mean improvement of 21% among 44 patients who received placebo ($P = 0.02$).[78] Bloating was significantly improved in the rifaximin group compared with the placebo group ($P = 0.01$).

Nutritional Therapy

Essential nutritional interventions in SIBO include increasing caloric intake with oral protein supplementation, use of medium-chain triglyceride oil to provide essential fatty acids, and administering vitamins, including fat-soluble vitamins. Intramuscular supplementation of vitamin B_{12} is required to prevent onset of neurologic complications. Ultimately, patients with severe cases of scleroderma will develop nutritional failure leading to total parenteral nutrition.

~~CASE CONTINUED~~

~~On the next office visit, the patient complains of fatigue, difficulty sleeping, and the uncontrollable urge to move her legs while lying in bed. She has a creepy crawly feeling only at those times. During these episodes, she has to get out of bed to walk around to get relief because the feeling is so uncomfortable.~~

Promotility Agents

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Promotility agents play a role in preventing recurrence of bacterial overgrowth after eradication of SIBO.[79,80] Tegaserod is no longer available, but other medications that improve intestinal motility (eg, erythromycin) may have clinical benefit in maintaining resolution of IBS associated with SIBO.[81] **[au: Should this paragraph be merged with the Prokinetic Therapy section above?]**

PROBIOTIC THERAPY

Probiotics have been used after antibiotic treatment of SIBO with success.[82] Probiotics are defined as organisms that provide health benefits to the host more than is derived from their nutritional properties (**Table 7**). There is some evidence that the organism does not need to be living to promote beneficial intestinal activity. Cellular and animal studies have shown improvement in maintaining the tight junctions of intestinal cells, and this has been shown in a stressed rat model and in human intestinal cells exposed to inflammatory cytokines and invasive *E. coli*.[83–85] Several types of *Lactobacilli*, a variety of Bifidobacteria, *E. coli* Nissle (in Germany), and *Saccharomyces boulardii* (a yeast) are commonly used as probiotics.

EFFICACY IN IBS

A small placebo-controlled, 8-week study of probiotic mixture VSL #3 (a mixture of 4 strains of *Lactobacillus*, 3 strains of *Bifidobacterium*, and 1 strain of *Streptococcus*) demonstrated no benefit in bloating, pain, bowel frequency, or other GI symptoms in 25 patients with IBS-D.[86] However, a randomized, double-blind, placebo-controlled trial of a European probiotic mixture reported that 41 patients who received the probiotics achieved a 42% median reduction from baseline in IBS symptom severity as compared with 6% in 40 controls ($P = 0.015$).[87] A randomized, double-blind, placebo-controlled trial of

Table 7. Mechanisms of Actions of Probiotics

Inhibition of bad bacteria by:
Decreasing acid levels in gut
Secretion of bacterial killing proteins
Resisting colonization
Blocking binding to gut lining
Improvement in lining barrier by:
Producing SCFA
Increasing mucus production
Altering immune function by:
Increasing interleukin-10 and decreasing TNF
Increasing IgA production

Bifidobacterium infantis demonstrated that after 4 weeks 90 women with IBS who received the probiotics reported significant relief from baseline in abdominal pain, bloating, and bowel dysfunction compared with 92 controls ($P \leq 0.05$).[88]

EFFICACY IN CROHN'S DISEASE

Interpretation of probiotic studies in IBD can be challenging due to the use of concomitant medicines and small numbers in the patient groups. In a study that examined *E. coli* Nissle for maintenance of steroid-induced remission of Crohn's colitis, the relapse rate was 33% in 11 treated patients versus 63% in 12 placebo patients.[89] *S. boulardii* plus 2 g mesalazine was better than 3-g monotherapy for maintaining remission in 32 patients, with remission rates of 37% versus 6%.[90] *Trichuris suis* has been studied in patients with active Crohn's disease. Patients ingested 2500 live ova every 3 weeks for 24 weeks, and disease activity was monitored with the Crohn's Disease Activity Index (CDAI): 23 patients (79.3%) responded with a significant decrease in the CDAI, and 21 of 29 (72.4%) remitted (CDAI < 150).[91]

EFFICACY IN ULCERATIVE COLITIS

The utility of *E. coli* Nissle in ulcerative colitis has been reported in 3 studies with 200 patients and appears to have similar efficacy to mesalazine in the maintenance of remission: 30% in each group relapsed.[92] VSL#3 has been evaluated in many studies and has been recently reviewed.[93] A randomized study showed that VSL#3 in combination with balsalazide versus 5-ASA monotherapy resulted in faster remission and a trend towards better symptom and sigmoidoscopy scores at 8 weeks.[94] *S. boulardii* was studied in a 4-week open-label manner and induced remission in 17 of 21 patients with mild to moderate UC.[95] *Trichuris suis* was studied in a randomized, double-blind, placebo-controlled trial of 54 patients with active ulcerative colitis. Improvement occurred in 13 of 30 patients (43.3%) with ova treatment compared with 4 of 24 placebo patients (16.7%; $P = 0.04$).[96]

Two studies have shown efficacy of VSL#3 in treatment of pouchitis after antibiotic use.[97,98] Another study showed prevention of pouchitis versus placebo after surgery.[99] A randomized study did not show statistical improvement.[100]

EFFICACY IN *C. DIFFICILE* DISEASE

Meta-analysis of the role of probiotics in AAD and *C. difficile* disease was recently carried out.[101] Data from 25 randomized controlled trials showed that 3 types of probiotics (*Saccharomyces boulardii*, *Lactobacillus rhamnosus* GG, and probiotic mixtures) significantly reduced AAD. From 6 trials, probiotics had significant efficacy for CDD, but only *S. boulardii* was effective for *C. difficile* disease. *S. boulardii* versus placebo was evaluated in the prevention of AAD in 269 children.[102] Patients who received *S. boulardii* treatment had a lower prevalence of diarrhea than those receiving placebo: 9 of 119 (8%) versus 29 of 127 (23%). A significant decrease in recurrences of *C. difficile* disease was observed in adults treated with high-dose vancomycin (2 g/day) plus *S. boulardii* (16.7%) as compared with those who received high-dose vancomycin and placebo (50%; $P = 0.05$).[103]

SUMMARY

Bacteria aid body function and health in many ways. Disturbance of the bacterial balance and/or overgrowth caused primarily by motility disorders of the small intestine is being investigated as a way to explain previously misunderstood syndromes. Future manipulation of gut flora may play a role in treating obesity. Refinement of probiotics may help a variety of diseases. The use of probiotics or nutrition to potentiate the growth of good bacteria may play an important role in the future but has yet to undergo good placebo-controlled studies.

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