

Uninvited Guests: The Impact of Small Intestinal Bacterial Overgrowth on Nutritional Status

by Oren Zaidel and Henry C. Lin

When large numbers of bacteria colonize the small intestine, a syndrome known as small intestinal bacterial overgrowth occurs. Nutrient malabsorption is a hallmark of the disorder and can result in a multitude of problems for the host. Understanding how these bacteria exert their deleterious effects on the host via competition for nutrients, damage of absorptive surfaces, and the production of symptoms, which reduce or alter food intake is key to diagnosing and treating the condition. New links between small intestinal bacterial overgrowth (SIBO) and disease entities such as irritable bowel syndrome (IBS) provide intriguing new insights into the pathophysiology of the syndrome.

INTRODUCTION TO SMALL INTESTINAL BACTERIAL OVERGROWTH

Small intestinal bacterial overgrowth (SIBO) is an often-neglected mechanism for impaired nutrition. This review will examine the pathogenesis of SIBO and the multifaceted impact of this condition on the nutritional status of the human host.

Normally, only small numbers of bacteria are found in the small intestine when compared with that found in the colon (1). Since the small intestine is the site of

digestion and absorption of food, bacterial flora are excluded from the small intestine to prevent unwanted competition with the host and abnormal entry of bacteria into the host. In addition, gas production from bacterial fermentation of food is minimized. SIBO is defined when colonic bacteria invade proximally into the ileum and jejunum and $>10^5$ organisms/mL of intestinal juice are present (2). The bacterial species in the small intestine in SIBO closely resemble the 300–400 species normally found in the colon. Although anatomic abnormalities and severe intestinal dysmotility are often considered to be requisite for the development of SIBO, recent discoveries linking SIBO to patients with irritable bowel syndrome suggest otherwise (3).

The dramatic changes in the bacterial flora of the small bowel that occur in SIBO have a multitude of effects on nutritional status. The bacterial flora may compete with the host for critical nutrients, alter host metabolism, directly damage the absorptive mucosa of the host, and produce gastrointestinal symptoms that reduce or alter food intake by the host.

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NORMAL ENTERIC FLORA

The stomach and small intestine contain small numbers of bacteria in healthy subjects. Jejunal cultures may not identify any bacteria in as many as 33% of healthy volunteers (4). Organisms, if present, are usually lactobacilli and enterococci species, gram-positive aerobes, or facultative anaerobes reflecting the bacterial flora of the oropharynx. Although various coliforms may be transiently present as contaminants of recently ingested food, the bacterial count tends not to exceed 10^3 organisms/mL of jejunal juice. Anaerobic *Bacteroides* species common to the colon are not found in the healthy proximal small intestine.

The terminal ileum represents a transition zone between normal colonic flora and the microorganisms found in the more proximal small intestine. Predominantly anaerobic colonic bacterial species in the colon contrast with the mostly aerobic species seen in the proximal small bowel. Concentrations of bacteria ranging from 10^5 to 10^9 organisms/mL of contents are found in the terminal ileum immediately proximal to the ileocecal valve, and include enterobacteriaceae and strict anaerobes, which normally cannot survive in the jejunum.

As one moves to the colonic side of the ileocecal valve, both the type and concentration of enteric flora dramatically changes. Concentrations of 10^9 to 10^{12} organisms/mL of colonic contents are routinely found. The flora within the lumen of the colon consists primarily of fastidious anaerobic species such as *Bacteroides*, anaerobic lactobacilli, and clostridia. With any anatomic alteration of the ileocecal valve, microorganisms in the terminal ileum resemble even more closely those usually present only in the colon.

Multiple factors defend against SIBO and determine both numbers and types of bacteria found in the small intestine. The major defensive factor is normal small intestinal motility. Other defensive mechanisms involve mucosal immunity, intestinal, pancreatic and biliary secretions, and the ileocecal valve. The cleansing action of the lumen-obliterating contractions of the phase III of the interdigestive migrating motor complex (MMC) or "intestinal housekeeper" wave limits the ability of bacteria to colonize the small intestine by sweeping the content of the small intestine toward the colon every 90–120 minutes between meals (5). When bacteria enter the gut from the mouth, many ingested bacteria are killed in the acidic environment of the stomach. Those that survive are quickly swept from

the small intestine into the colon because of the MMC. The enormous difference in the number of bacteria in the colon when compared to the small intestine is maintained by the MMC. The importance of normal small intestinal peristalsis in maintaining this balance is emphasized by the fact that SIBO has been associated with a loss or reduced frequency of cycling of the MMC (6).

Both diet and antibiotic usage further affect the normal enteric flora. The specific effects of antibiotics depend on the effect of an antibiotic on the complex interaction of host and bacterial species since anaerobes often persist despite treatment with a broad spectrum antibiotic; they stabilize the enteric flora and may prevent the proliferation of pathogenic organisms. Although certain foods are considered probiotics because of their use by gut bacteria, there is no evidence that a particular pattern of food intake causes small intestinal bacterial overgrowth.

CLINICAL CONDITIONS ASSOCIATED WITH SIBO

A variety of clinical conditions are associated with SIBO (Table 1). Surgical alteration of normal small intestinal anatomy has traditionally and frequently been associated with SIBO. Stagnant intestinal contents within fistulas, surgical enterostomies, surgically created blind loops of small intestine, and post gastrectomy surgical anatomy such as a Billroth II anastomosis resulting in stasis within the afferent limb have all been reported to have SIBO as a complication.

Since impaired interdigestive intestinal motility predisposes to an expansion of colonic bacteria into the small intestine, disease entities with impaired intestinal motility are well known to have SIBO as a complication. Examples include chronic scleroderma, intestinal pseudo-obstruction, and autonomic visceral neuropathy (e.g., secondary to diabetes). In a study of 61 patients with Crohn's disease, 15 were found to have an abnormal breath test result to suggest small intestinal bacterial overgrowth (7). Ileal dysfunction was present in 44% of the 61 patients. Bacterial overgrowth may be present even in patients without known strictures or intestinal fistulous tract. A high prevalence of bacterial overgrowth in Crohn's disease has been reported in patients with as well as without a history of intestinal surgery (8).

SIBO has been associated with chronic pancreatitis in up to 40% of patients (9). Putative mechanisms

Table 1
Conditions Associated with SIBO

Stasis

- Anatomic
 - Small bowel diverticula
 - Surgical change
 - Billroth II
 - Ileal bypass
 - Ileo-cecal valve resection
 - Strictures
 - Crohn's
 - Abnormal communication between proximal and distal gut
 - Fistulas
 - Gastrocolic
 - Jejunocolic

Motor

- Pseudoobstruction
- Diabetic neuropathy
- Scleroderma
- Disordered MMC

Decreased acid

- Chronic atrophic gastritis
- Acid suppressing meds

Miscellaneous

- Pancreatitis
- Cirrhosis
- Immune deficiency
- Malnutrition

behind this association include decreased intestinal motility as a result of narcotic pain medication, or the disease itself, or inflammatory/obstructive changes to the proximal small intestine resulting from pancreatic enlargement. Based on animal studies, since pancreatic secretions may also have some degree of antibacterial effect (10,11), patients with reduced pancreatic secretion may be at risk for SIBO.

Multiple studies have demonstrated a relationship between the presence of SIBO and liver disease (12,13) as well as complications of liver disease such as spontaneous bacterial peritonitis (14). In particular, SIBO has been demonstrated in patients with NASH and even cirrhosis. Successful eradication of overgrowth has even been associated with histologic regression of liver disease (15).

Recent studies have shown a link between SIBO and irritable bowel syndrome (IBS). In a recent randomized, double blind, placebo controlled study of 101 patients with IBS, 83% were found to have an abnormal Lactulose Hydrogen Breath Test (LBT), suggesting the presence of SIBO, compared with 20% in sex matched controls. The causative role of SIBO in IBS was supported by the response of patients to antibiotic treatment. If antibiotic treatment succeeds in normalizing the breath test to demonstrate eradication of SIBO, IBS patients reported 75% improvement in symptoms. Thus, SIBO may be found even in patients without abnormal intestinal anatomy or severely impaired intestinal motility.

NUTRITIONAL SUPPORT IN SIBO

Nutritional support is a major part of the therapeutic regimen in SIBO. This may be needed despite complete eradication of overgrowth because of mucosal damage that may persist even after treatment. Fluid, nutritional support, and replacement of vitamin deficiencies (particularly fat soluble vitamins) are part of the initial management strategies in SIBO. While nutritional repletion is ongoing, efforts must be focused on eradication of overgrowth, usually with a combination of antimicrobial therapy (Table 2) and pharmacological agents designed to restore normal small intestinal motility.

In rare circumstances, TPN may be of use in providing nutrition to the severely malnourished patient. However, it is also fraught with infectious, metabolic, and gastrointestinal complications such as small intestinal dysmotility. For example, delays in gastric emptying have been noted in patients receiving TPN (16). Also, in rat models, TPN has been associated with breakdown of intestinal mucosal barrier function and bacterial translocation (17,18). As a result, TPN may actually promote conditions favorable for the development of SIBO.

Table 2
Antibiotics commonly used in SIBO

- Metronidazole
- Ciprofloxacin
- Neomycin
- Doxycycline
- Amoxicillin/clavulanate (augmentin)

EFFECTS OF SIBO ON DIGESTION AND ABSORPTION

The adverse effects of SIBO on nutrition involve a number of factors including bacterial metabolism, injury of the mucosa of the host, and altered food intake secondary to gastrointestinal symptoms of SIBO.

One of the most common clinical manifestations of SIBO is chronic diarrhea secondary to fat maldigestion and malabsorption. This complication primarily occurs through the step of deconjugation of bile acids by intraluminal bacteria (19). Because fat solubilization and absorption require a critical concentration of conjugated bile acids for the formation of mixed micelles, when the concentration of conjugated bile acids drops below this threshold as a result of SIBO, micellar formation and fat digestion and absorption may be impaired. Through this conversion of bile acids, bacteria may indirectly damage the absorptive mucosa. Specifically, deconjugated bile acids may exert toxic injurious effects on enterocytes, so that malabsorption extends beyond fat assimilation, even carbohydrate and protein absorption may be adversely affected (20,21).

Similar to patients with maldigestion secondary to pancreatic insufficiency, the abnormal presentation of nutrients that occurs in the setting of bacterial overgrowth may lead to altered postprandial motility (22) which in turn, may worsen the patient's gastrointestinal symptoms. The change in motility and transit may be related to a displacement of nutrients from the transit control mechanism located in the proximal small intestine known as the jejunal brake (23) to the transit control located in the distal small intestine known as the ileal brake (24–26). Electron microscopic studies have confirmed such morphological damage to enterocytes in animals with SIBO, providing direct evidence that absorptive cell injury contributes to malabsorption in this condition (27).

SIBO decreases brush border enzyme activity as a result of this change and further exacerbates carbohydrate intolerance in patients (28). As carbohydrates fail to be assimilated proximally, these substrates continue to be fermented by the gut bacterial flora, and are therefore not available to the host. Mucosal injury further interferes with carbohydrate uptake.

Although hypoproteinemia maybe seen in SIBO, severe protein malnutrition is rare (29). Bacteria do compete with the host for protein substrates, much as they do with carbohydrates, producing fatty acids and ammonia.

However, bacterial products do not contribute significantly to host protein catabolism. The absorptive dysfunction and mucosal injury seen in SIBO may also contribute to decreased amino acid and peptide uptake. In addition, decreased levels of enterokinases have been demonstrated in patients with SIBO, which may impair the activation of proteases in pancreatic secretions (30). Protein-losing enteropathy has also been described in both animal and human models of SIBO.

Vitamin B₁₂ deficiency occurs in SIBO as a result of utilization of the vitamin by bacteria. When bacteria take up the vitamin, it is partially metabolized to inactive analogues, which compete with normal vitamin B₁₂ binding and absorption (31,32). Folate levels, however, are usually normal or elevated in the context of SIBO because bacteria are able to synthesize folate (33).

Through the complication of steatorrhea associated with fat maldigestion and malabsorption, SIBO is complicated by malabsorption of fat-soluble vitamins. Vitamin A, D, and E deficiencies can all be seen in SIBO. Because vitamin K is synthesized by luminal bacteria, deficiency of this vitamin is rarely seen in the context of SIBO.

CLINICAL FEATURES

Although clinical manifestations vary greatly and depend to some extent on the nature of the small intestinal abnormality causing SIBO, there are common clinical features that may be regarded as hallmarks of the disease. Vitamin deficiency, steatorrhea, diarrhea, hypoalbuminemia, and postprandial bloating are some of these.

The postprandial bloating plays a major role in that this leads to a sense of fullness and ultimately early satiety, which clearly inhibits nutrient intake. Other common postprandial symptoms include bloating, cramps, diarrhea, and nausea. In order to obtain relief from these symptoms, patients often fast. Repeated fasting to avoid symptoms further contributes to an overall decrease in caloric intake and ultimately weight loss. In contrast, some patients with SIBO report an intense preference for sweets, which may lead to weight gain.

Patients with SIBO with or without known altered anatomy may describe abdominal discomfort, bloating, and crampy periumbilical pain before diarrhea, steatorrhea, and the symptoms of anemia develop. Months and

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even years may elapse between the time a surgical procedure on the small intestine is performed and the onset of symptoms attributable to SIBO. In the context of strictures or fistulas caused by Crohn's disease of the small intestine, hypomotility caused by scleroderma, or intestinal pseudo-obstruction, the clinical features of the primary disease may completely overshadow any manifestations of intraluminal microbial proliferation. It may be difficult to determine in patients with Crohn's disease, radiation enteritis, short bowel syndrome or lymphoma the extent to which malabsorption is the result of primary disease or secondary bacterial overgrowth.

Regardless of the cause of the abnormal proliferation of bacteria within the small intestinal lumen, the consequences tend to be the same for the patient. Weight loss, post prandial bloating, and clinically apparent vitamin B₁₂ deficiency may be seen in as many as one half to three quarters of patients with SIBO. Osteomalacia and impaired night vision are often occult complications that may develop as a consequence of SIBO associated with steatorrhea. Whether due to epithelial dysfunction, bile acid deconjugation, or post-prandial bloating leading to decreased oral intake, SIBO clearly adversely affects the overall nutritional status of the patient.

While outside the scope of this review, readers are referred to the many publications available for further information on diagnosis and treatment of SIBO.

EFFECTS OF SYMPTOMS OF SIBO ON FOOD INTAKE

The impact of SIBO on malabsorption and maldigestion extends beyond the direct effects noted above. Post-prandial symptoms commonly seen in the context of SIBO discourage food intake, providing a further barrier to good nutrition. The nearly ubiquitous symptom of post-prandial bloating is often reported by SIBO patients as the reason for their decreased oral intake. Bloating occurs as a result of bacterial fermentation when increased numbers of bacteria come into contact with food in the small intestine. Abnormal products of bacterial fermentation, maldigestion, and malabsorption all contribute to the gastrointestinal symptoms of bloating, diarrhea, cramping, abdominal pain, borborygmi and nausea that are associated with the carbohydrate intolerance in SIBO. Bacteria normally derive energy from carbohydrate fermentation,

which produces hydrogen, carbon dioxide, and other gases in addition to short chain fatty acids (33).

The diarrhea experienced by patients with SIBO may be a result of excess fecal loss of water and electrolytes or the elaboration of gases produced by intraluminal bacteria. The former condition is in part due to an increased delivery to the small intestine of osmotically active carbohydrate fragments resulting not just from mucosal injury but also from disaccharidase deficiency. These mucosal disaccharidases are destroyed by proteases secreted by anaerobic bacteria present in the small intestine (34). Other byproducts of luminal bacterial metabolism such as hydroxylated fatty acids, short chain fatty acids, alcohols, and deconjugated bile acids act as secretagogues to contribute further to the diarrhea seen in SIBO. This directly results in reduced intake of essential nutrients needed for maintenance of good health. We believe this effect is of equal importance clinico-pathologically to those described above in the context of SIBO.

WHEN TO CONSIDER SIBO IN YOUR PATIENT?

SIBO should be considered in any patient who presents with diarrhea, steatorrhea, weight loss, or macrocytic anemia who complains of symptoms of bloating, cramping, or alternating bowel habits. It is important to remember that altered anatomy and severely impaired intestinal motility are not required for the development of SIBO.

While direct culture is considered "gold standard" for bacterial disorders, culturing is not an appropriate gold standard for bacterial overgrowth since the intestinal bacterial flora may be out of reach of available instrumentation. It is important to recognize that bacterial overgrowth may involve only the more distal portions of the small intestine (35). Culturing for bacterial overgrowth is characterized by its high false-negative rate (36–38) and it is poorly reproducible (39). Instead, lactulose breath test is a noninvasive test for SIBO with the advantages that include: unlimited access to bacteria along the whole gut (in contrast to glucose which only detects overgrowth of proximal small intestine); good correlation between rate of hydrogen production in the gut and rate of hydrogen excretion by the lungs (40); distinct separation of metabolic activity of bacteria from host (41).

CONCLUSIONS

With a high degree of suspicion and the use of the lactulose breath test, small intestinal bacterial overgrowth can be readily identified as a contributing factor for the patient's gastrointestinal symptoms and malnutrition. Eradicating SIBO will lead not just to dramatic improvement in symptoms, but will correct the multi-faceted adverse effect of bacterial overgrowth on nutrition. ■

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