Small Intestinal Bacterial Overgrowth: Roles of Antibiotics, Prebiotics, and Probiotics

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Small intestinal bacterial overgrowth is common in intestinal failure. Its occurrence relates to alterations in intestinal anatomy, motility, and gastric acid secretion. Its presence may contribute to symptoms, mucosal injury, and malnutrition. Relationships between bacterial overgrowth and systemic sepsis are of potential importance in the intestinal failure patient because the direct translocation of bacteria across the intestinal epithelium may contribute to systemic sepsis: a phenomenon that has been well established in experimental animal models. The accurate diagnosis of bacterial overgrowth continues to present a number of challenges in clinical practice and especially so among patients with intestinal failure. The management of patients with bacterial overgrowth remains, for the most part, primarily empiric and comprises antibiotic therapy and correction of any associated nutritional deficiencies. Although evidence from experimental animal studies consistently indicates that probiotics exert barrier-enhancing, antibacterial, immune-modulating, and anti-inflammatory effects, which all could be benefits in small intestinal bacterial overgrowth and intestinal failure, their role in human beings remains to be evaluated adequately.

The human gastrointestinal microflora is a complex ecosystem of approximately 300–500 bacterial species; indeed, the number of bacteria within the gut is about 10 times that of eukaryotic cells in the human body. In the healthy host, enteric bacteria colonize the alimentary tract soon after birth and the composition of the intestinal microflora remains relatively constant thereafter. Because of peristalsis and the antimicrobial effects of gastric acid, the stomach and proximal small intestine contain relatively small numbers of bacteria in healthy patients; jejunal cultures may not detect any bacteria in as many as 33%. When bacterial species are present, they usually are lactobacilli, enterococci, oral streptococci, and other gram-positive aerobic or facultative anaerobes reflecting the bacterial flora of the oropharynx; coliforms rarely exceed 10^5 colony-forming units (CFUs)/mL in jejunal juice. The microbiology of the terminal ileum represents a transition zone between the jejunum, containing predominantly aerobic species, and the dense population of anaerobes found in the colon. Bacterial colony counts may be as high as 10^9 CFU/mL in the terminal ileum immediately proximal to the ileocecal valve, with a predominance of gram-negative organisms and anaerobes. On crossing into the colon, the concentration and variety of enteric flora changes dramatically (Figure 1). Concentrations as high as 10^{12} CFU/mL may be found; comprised mainly of anaerobes such as Bacteroides, Porphyromonas, Bifidobacterium, Lactobacillus, and Clostridium, with anaerobic bacteria outnumbering aerobic bacteria by a factor of 100–1000:1 (Table 1).

The normal enteric bacterial flora influences a variety of intestinal functions. Unabsorbed dietary sugars are salvaged by bacterial disaccharidases, converted into short-chain fatty acids, and used as an energy source by the colonic mucosa. Vitamins and nutrients such as folate and vitamin K are produced by enteric bacteria. The relationship between the host’s immune system and non-pathogenic flora is important in protecting the host from colonization by pathogenic species. Bacterial metabolism of some medications (such as sulfasalazine) within the intestinal lumen is essential for the release of their active moieties.

The bacterial flora provides regulatory signals that condition the development and function of the gut. The critical role of the indigenous flora is shown most clearly by studies of intestinal morphology and function in germ-free animals. In the small-bowel mucosa of germ-free animals, villi are longer and more uniform and crypts are shorter than those in normal animals. Digestive enzyme activity and local cytokine production are reduced and the development of the mucosa-associated or gut-associated lymphoid tissues, lamina propria cellularity, and mucosal vascularity all are impaired. Motility also is affected in germ-free animals, the migrating motor complex being less evident. On the other hand, there

**Abbreviations used in this paper:** CFU, colony-forming unit; SIBO, small intestinal bacterial overgrowth; TPN, total parenteral nutrition.

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is an increase in enterochromaffin cell density and in the caloric intake necessary to sustain body weight.\textsuperscript{4}

The delicate balance between host and environment is central to intestinal homeostasis. The intestinal epithelium is exposed on a daily basis to the bacterial antigens of the commensal microflora that in turn induce a state of controlled inflammation. This physiologic response to bacterial antigens is not harmful to the host and generates both the induction of immune tolerance and the secretion of immunoglobulin A (IgA). Oral tolerance is defined strictly as the suppression of cellular and/or humoral immune responses to an antigen by prior oral administration of the same antigen.\textsuperscript{5} The development of tolerance to an antigen (including bacterial antigens) represents a response, mediated by antigen-presenting cells and generated by T lymphocytes, resulting in an anti-inflammatory or suppressive response to these antigens.\textsuperscript{6} In disease states, a proinflammatory response to these luminal antigens leads to the development of such disorders as celiac sprue and inflammatory bowel disease. Not surprisingly, therefore, oral tolerance is impaired in germ-free animals. Intercellular signaling is critical to the maintenance of the physical integrity and function of the epithelial barrier; in this dynamic process the epithelium responds to signals from both the lumen and gut-associated lymphoid tissue, the frontier of the systemic immune response. Enterocytes, specialized epithelial cells (M cells), antigen-presenting cells (dendritic cells), and Paneth cells play a key role in this interplay between the host and the luminal environment.\textsuperscript{6}

**Small Intestinal Bacterial Overgrowth: Definition, Pathogenesis, and Prevalence**

Traditionally, small intestinal bacterial overgrowth (SIBO) has been defined in quantitative terms. This definition, however, varies according to both the site of sampling and our ability to culture the contaminating species. Nevertheless, SIBO usually is defined as an overgrowth of more than $10^{5}$ CFU/mL of bacteria in the proximal small bowel.\textsuperscript{7,8} Other investigators have entertained the diagnosis of SIBO in the presence of lower colony counts ($>10^{3}$ CFU/mL), provided that the species of bacteria isolated in the jejunal aspirate is one that normally colonizes the large bowel or the same species is absent from saliva and gastric juice.\textsuperscript{8} Contaminating flora in SIBO commonly feature both oropharyngeal and colonic-type bacteria, including *Streptococci* (71%), *Escherichia coli* (69%), *Staphylococci* (25%), *Micrococi* (22%), and *Klebsiella* (20%).\textsuperscript{9} In 1 study of 26 patients with SIBO, Riordan et al\textsuperscript{10} documented colonic-type flora (*Enterobacteriaceae, Bacteroides, or Clostridium*) in

<table>
<thead>
<tr>
<th>Anaerobes</th>
<th>\textsuperscript{10^{9}-10^{12}}</th>
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<tbody>
<tr>
<td><em>Bacteroides</em></td>
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<td><em>Bifidobacterium</em></td>
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<td><em>Clostridium</em></td>
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<td><em>Eubacterium</em></td>
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<td><em>Lactobacillus</em></td>
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<td><em>Peptostreptococcus</em></td>
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<td><em>Peptococcus</em></td>
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<td><em>Porphyromonas</em></td>
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<td><em>Ruminococcus</em></td>
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<td>Facultative anaerobes</td>
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<tr>
<td><em>Enterococcus</em></td>
<td>\textsuperscript{10^{4}-10^{10}}</td>
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<tr>
<td><em>E coli</em></td>
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<td>Enterobacteriaceae other than <em>E coli</em></td>
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<tr>
<td><em>Staphylococcus</em></td>
<td>\textsuperscript{10^{4}-10^{9}}</td>
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20 patients and an exclusively oropharyngeal flora (Streptococcus mitis, Staphylococcus aureus, Lactobacillus spp, and yeasts) in 6 patients. It should be stressed that differentiation between oropharyngeal and colonic flora may be difficult because essentially the same genera (although not species) normally colonize both sites.

In the intact intestine, SIBO is prevented by the actions of gastric acid, pancreatic enzyme activity, small intestinal motility, and the ileocecal valve. One or more of these mechanisms often is compromised in patients with intestinal failure. In a rat model, Nieuwenhuijs et al reported that the migrating motor complex, often referred to as the housekeeper of the gut, was critical to the prevention of bacterial overgrowth in the upper small bowel. Disruption of the migrating motor complex appears to be the main factor leading to the development of SIBO in patients with radiation enteropathy and acute pancreatitis. Although motor adaptation does occur in the shortened intestine, motility remains abnormal and may contribute to overgrowth. Although the ileocecal valve forms a physical barrier to reflux of colonic material from the colon into the small bowel, results from both experimental animal models and human studies have failed to identify a major effect on either bacterial translocation or SIBO after resection of the valve. These findings would lend support to the hypothesis that specialized motor patterns in the distal ileum, and not the valve itself, are the critical elements in sustaining the propulsive functions of this region.

SIBO is common among disorders that may result in intestinal failure and in the shortened intestine per se. Husebye et al reported that 39% of their patients with radiation enteropathy had SIBO detected by a 14C D-xylose breath test; 50% of these patients had negative jejunal cultures. SIBO also is frequent in Crohn's disease and especially so among those who have undergone surgery; in 1 study SIBO was identified by a breath test in 30% of Crohn's disease patients with a history of prior intestinal surgery in comparison with 18% in patients who did not undergo surgery. Others identified SIBO in 62.5% of a group of patients with scleroderma. In both clinical and experimental surgical series, the prevalence of SIBO in the short-bowel syndrome has varied considerably, depending on whether or not the colon remained in continuity, the terminal ileum or the ileocecal valve had been resected, or whether or not distal intestinal obstruction was present.

**Diagnosis**

Although aspiration and direct culture of jejunal contents are regarded by many as the gold standards for the diagnosis of SIBO, these methods have several limitations, such as the potential for contamination by oropharyngeal bacteria during intubation, and the fact that bacterial overgrowth may be patchy and thus missed by a single aspiration. Overall, the reproducibility of jejunal aspiration and culture has been reported to be as low as 38%, in comparison with 92% for breath tests, although the latter possesses high false-positive rates. In addition, intubation methods may be regarded as cumbersome and invasive for patients with nonspecific symptoms or for those who may require repeated testing; proximal sampling, however, may be achieved more readily at endoscopy. For this reason, a variety of noninvasive diagnostic tests have been devised for the diagnosis of SIBO; these are based largely on the excretion in exhaled breath of hydrogen generated by the metabolism of carbohydrate by luminal bacteria. In these breath tests, the diagnosis of SIBO is established when the exhaled breath H2 level increases by more than 10 parts per million greater than baseline on 2 consecutive samplings or if the fasting breath hydrogen level exceeds 20 parts per million. In patients with SIBO and an intact intestine, a peak occurs within 1 hour and is less prominent than the normal colonic peak. Even though double peaks (SIBO and colonic peaks) have been defined previously as representing an abnormal lactulose breath test, they also may result from rapid orocecal transit, resulting in the premature delivery of fermentable substrate to cecal bacteria. Indeed, the reliability of these diagnostic techniques has been criticized in patients with intestinal failure, and especially those with short-bowel syndrome, because of the rapid intestinal transit that accompanies these disorders. For this reason, the combination of lactulose breath test with scintigraphy has been advocated and although this approach may increase test specificity to 100%, sensitivity remains low at 38.9%.

Although bacterial overgrowth undoubtedly is common in intestinal failure, its diagnosis may be difficult. For example, the interpretation of breath tests may be complicated in patients with short bowel syndrome because of carbohydrate malabsorption and a resultant premature delivery of unabsorbed carbohydrate to the colon where it will undergo fermentation. It also must be borne in mind that false-negative or flat responses to lactulose administration may be found among those whose bacterial flora has been altered by antibiotic therapy or diarrhea or in whom motility disorders coexist; situations commonly present in patients with intestinal failure. Finally, between 15% and 27% of the population do not generate hydrogen after the ingestion of lactulose but instead produce methane; the measurement of hydrogen alone clearly will underestimate the prevalence of
SIBO among such individuals. In contrast, the combined measurement of hydrogen and methane will permit the detection of those who harbor *Methanobrevibacter smithii.* However, in support of a role for bacterial overgrowth in symptom pathogenesis, studies have reported a parallel improvement in gastrointestinal symptoms and breath tests after antibiotic therapy among intestinal failure patients with previously positive breath tests.22,24

An alternative approach to the diagnosis of SIBO is a therapeutic trial of antibiotic therapy. Initial studies using this strategy suggested that patients with SIBO should show a symptomatic response within 1 week of therapy with tetracycline administered in a dose of 250 mg 4 times a day.12 More recent studies have indicated that as many as 60% will not respond to this particular regimen; other antibiotics (detailed later) may prove more effective although few, if any, have been assessed critically in this context. Nevertheless, given the technical and interpretative difficulties described earlier that are associated with current diagnostic techniques, it should come as no surprise that many advocate the therapeutic trial as a viable alternative to diagnostic testing.32 As more options in terms of poorly or nonabsorbable antibiotics become more available, the therapeutic trial is a reasonable approach to the management of suspected SIBO in many circumstances.

**Consequences of SIBO**

**Morphologic and Metabolic Effects**

SIBO may influence gut function through direct and indirect mechanisms. Deconjugation of bile acids in the proximal small bowel will disrupt fat digestion and lead to the production of lithocholic acid, which is absorbed poorly and may be directly toxic to enterocytes.33 Although in all but the most severe cases light microscopy of the intestine shows a normal villous pattern,10 more detailed studies of morphology and enzyme content may show subtle changes. Direct mucosal injury also may result from bacterial adherence or increased conversion, by enterotoxins, of the enzyme xanthine dehydrogenase to xanthine oxidase. Indirectly, morphologic changes may occur secondary to cobalamin deficiency.34 Regardless of the mechanism, enterocyte injury leads to both a loss of activity of brush-border disaccharidases and altered permeability, the latter predisposing to the development of a protein-losing enteropathy.35,36 Indeed, increased intestinal permeability has been well documented in SIBO in the absence of villous atrophy and independent of B12 deficiency.36 Bacteria may compete with the host for protein and lead to the production of ammonia.37 In the context of an impaired mucosal barrier, encephalopathy may result, as suggested by the recently reported case of recurrent encephalopathy in an intestinal transplant recipient, which resolved after resection of an intestinal stricture38 and presumably led to the eradication of SIBO. Moreover, short-bowel syndrome patients, especially those with an intact colon, may suffer D-lactic acidemia and encephalopathy on administration of enteral nutrition as a result of the production of D-lactic acid by gram-positive anaerobes.39,40 Pneumatosis intestinalis also has been observed in the context of SIBO, both in association with, and in the absence of, intestinal obstruction.

**Nutritional Consequences**

Fat malabsorption may lead to steatorrhea and deficiencies in fat-soluble vitamins. Carbohydrate malabsorption caused by SIBO can contribute to diarrhea as a result of metabolism of malabsorbed carbohydrates by bacteria to form short-chain organic acids that, in turn, increase the osmolarity of intestinal fluid. Although some degree of hypoproteinemia is common, severe malnutrition is rare in SIBO in the absence of other intestinal disease. Cobalamin (vitamin B12) deficiency occurs commonly in SIBO as a result of use of the vitamin by anaerobic bacteria; the only bacteria that can use vitamin B12 once coupled to intrinsic factor. Levels of both folate and vitamin K, however, usually are normal or increased in the context of SIBO as a result of bacterial synthesis of these vitamins. The clinical and nutritional consequences of SIBO in short-bowel syndrome depend on the clinical context; in the patient with a remnant that is marginal for independent existence or in whom adaptation has been compromised,41 the superimposition of SIBO may prove nutritionally devastating.

**Immunologic Effects**

Not surprisingly, SIBO may exert immune effects. Riordan et al12 and Kett et al15 found that, in their patients with SIBO, luminal concentrations of IgA2, IgM, and interleukin-6, but not interferon-γ and tumor necrosis factor-α, were increased significantly in the proximal small intestine, particularly when the overgrowth included colonic-type bacteria. The same investigators also evaluated mucosal immunity and morphology in SIBO and described increased lamina propria immunoglobulin IgA plasma cell counts in all patients and higher intraepithelial lymphocyte counts in those with a colonic-type overgrowth. Lamina propria T- and B-cell populations were unaltered.10,44 Of interest, given reported overlap between SIBO and celiac sprue, increased luminal levels of IgA antigliadin antibodies were
documented in 6 of 17 patients with SIBO in 1 study. Whether these antibodies are an epiphenomenon or may have some relevance to the pathogenesis of mucosal injury in SIBO, or may explain some cases of latent or unresponsive sprue, remains to be determined. SIBO also may be associated locally with defective complement activation and with decreased circulating levels of IgG3.

Bacterial Translocation and Sepsis

The possible contribution of SIBO to bacterial translocation and sepsis is a key issue in intestinal failure, a disorder in which sepsis is an important cause of morbidity and mortality. Bacterial translocation is defined as the passage of viable bacteria from the gastrointestinal tract to extraintestinal sites such as the mesenteric lymph node complex, liver, spleen, kidney, and bloodstream. Although the traditional definition of bacterial translocation has been based on the culture of viable bacteria from mesenteric lymph nodes, more recent studies have shown that intestinal bacterial translocation can be detected by polymerase chain reaction, which recognizes bacterial DNA alone. Moreover, Albillos et al reported that, in their cirrhotic patients, endotoxin from nonviable bacteria promoted many of the pathophysiologic mechanisms previously attributed to the translocation of live bacteria.

Experimental animal models have shown that bacterial translocation may be promoted by mucosal inflammation, intestinal obstruction, ischemia and hypoperfusion injury, acute pancreatitis, liver disease, premature birth, burns, and trauma. In SIBO, increased intestinal permeability and impaired host immune defense are considered to be the primary mechanisms that promote bacterial translocation. However, experimental and human studies have failed to confirm a relationship between bacterial translocation and intestinal permeability. These observations instead imply a role for a distinct, presumably transcellular, mechanism of transport for bacteria across the intestinal barrier. Although the degree of translocation of bacteria is related directly to their concentration in the small intestine and cecum, it is evident that rates of translocation for the various constituents of the indigenous flora vary considerably, with Pseudomonas aeruginosa, Klebsiella pneumoniae, E coli, and Proteus mirabilis showing the greatest aptitude for traversing the intestinal epithelium. In healthy individuals, bacterial translocation and transference occur continuously; translocated bacteria and their particulate products being phagocytosed by the gut-associated lymphoid tissue. However, when the intestine is diseased or anatomically changed, as is the case in most patients with intestinal failure, the host could, in theory, be overwhelmed by the sheer concentration of organisms that may translocate from the contaminated intestine.

The term gut-derived sepsis is used to describe a state of systemic inflammation and organ dysfunction associated with severe catabolic stress; it has been hypothesized that this syndrome is initiated and perpetuated by the intestinal microflora. Although the gut plays a role in the development of sepsis syndrome and multiple organ failure, recent studies have shown that gut-derived bacteremia, even when caused by potent nosocomial pathogens, is an event of low proinflammatory potential and is, of itself, an insufficient stimulus for the systemic inflammatory response and organ failure state typically seen after severe and prolonged catabolic stress. This is not to dismiss a role for the intestinal flora but to state that their role in the pathophysiology of this syndrome may have more to do with bacteria-induced alterations in the immune function of the gut and consequent interactions between the gut-associated immune tissue and the rest of the body, rather than to direct translocation. With regard to the former, the ability of certain components of the flora to produce immunosuppressant or immunomodulatory effects in the mucosa through the induction of expression of appropriate cytokines and chemokines, whereas other bacterial species are potent inducers of inflammatory responses, has been well described in a number of models.

Central venous catheter infection is the most prevalent infectious complication among patients with intestinal failure on total parenteral nutrition (TPN). Although catheter sepsis often is associated with the isolation of enteric organisms, skin commensals also are prevalent. Moreover, the presence of enteric organisms in the bloodstream does not necessarily impugn bacterial overgrowth and translocation; diarrhea, so common in this population, may lead to the colonization of skin by enteric flora.

The enteric flora also may play a role in the pathogenesis of the liver abnormalities that frequently complicate parenteral nutrition–dependent intestinal failure, such as nonalcoholic fatty liver disease. Indeed, tumor necrosis factor α, whose release may be triggered by translocating bacteria, has been implicated in the pathogenesis of nonalcoholic fatty liver disease. Furthermore, endogenous production of ethanol and lipopolysaccharides by intestinal bacteria may activate hepatic macrophages, leading to the release of hepatotoxic factors such as tumor necrosis factor α. These observations may have therapeutic implications given the recent observation, in both an experimental animal model and an uncontrolled human study, that the administration of probi-
otics and prebiotics may ameliorate the hepatic injury associated with nonalcoholic fatty liver disease and the earlier observation of the amelioration of this syndrome in intestinal failure by the administration of antibiotics.69

Management of SIBO in Intestinal Failure

Surgical Approaches

Clearly, the primary goal of therapy in intestinal failure and SIBO should be the treatment or correction of any underlying disease or defect when possible. Unfortunately, for many patients with intestinal failure, reversibility simply is not possible. Of the various surgical approaches advocated to improve digestive function in the short-bowel syndrome, such as the creation of reversed bowel segments, intestinal tapering and lengthening, or the construction of valves or recirculating loops, few, if any, have been shown to confer long-term benefit.70 Indeed, some may result in short-term impairments in motor and absorptive function.71 Many promote stasis and, therefore, may lead to bacterial overgrowth.

Intestinal transplantation is the one therapeutic option that could restore intestinal function entirely to the patient with intestinal failure. Rejection and sepsis, often inextricably linked, remain the major causes of morbidity and mortality among graft recipients. Enteric flora are implicated frequently; it has been suggested, for example, that rejection-induced changes in intestinal permeability promote bacterial translocation, thus leading to systemic sepsis.73 Here again, bacterial contamination, if present, could set the stage for the precipitation of sepsis.

Nutritional Support

SIBO is an important determinant of nutritional status in intestinal failure. Kaufman et al74 found that bacterial contamination was one of the predictors of failure to wean children with short-bowel syndrome off TPN; among 7 patients who remained dependent on TPN, all had SIBO whereas only 23 of 42 children who were weaned successfully from TPN had evidence of overgrowth. It must be conceded, however, that because overgrowth is more likely among those with the shortest intestinal remnants, this latter factor, rather than SIBO, may have been the determinant of inability to come off TPN. The management of the patient with SIBO, in any context, must include the correction of any nutritional deficiencies. Among those with intestinal failure this usually is achieved by TPN; among those being weaned from TPN, or who acquire less than 75% of their nutritional requirements from TPN, the addition of supplemental fat-soluble vitamins, vitamin B12, and certain minerals may be indicated in the presence of SIBO.

Prokinetic Therapy

For those in whom intestinal stasis is present and especially in whom intestinal dysmotility is a prominent factor, as in chronic intestinal pseudo-obstruction, prokinetic agents would appear to offer considerable therapeutic potential. Although there is some evidence for efficacy for prokinetics, such as cisapride and erythromycin in particular, in chronic intestinal pseudo-obstruction the ability of these agents to reduce bacterial contamination in this disorder has been studied scarcely. In 1 small study, the somatostatin analog, octreotide, which induces migrating motor complex–like activity in the small intestine, was shown to reduce symptoms and breath-hydrogen excretion in patients with scleroderma; a subsequent study in an experimental animal model failed to replicate this effect. This may be explained by the observation that the net effect of this agent in human beings is to delay and not accelerate transit. Both animal and human studies, however, have shown the ability of cisapride to reduce bacterial overgrowth in another context: chronic liver disease. This agent, however, no longer is available.

Antibiotic Therapy

The objective of antibiotic therapy in SIBO is not so much to eradicate the bacterial flora but rather to modify it in a manner that results in symptomatic improvement. Although ideally the choice of antimicrobial agent should reflect in vitro susceptibility testing, this usually is impractical because many different bacterial species, with different antibiotic sensitivities, typically coexist. Therefore, antibiotic treatment remains primarily empiric. Effective antibiotic therapy must cover both aerobic and anaerobic enteric bacteria. Various regimens have been proposed and are listed in Table 2. Bouhnik et al9 showed that amoxicillin–clavulanic acid and cefoxitin were effective against more than 90% of isolated species in SIBO, indicating that they were suitable candidates for first-line therapy. Although in general a single short (7- to 10-day) course of an antibiotic may improve symptoms for up to several months in between 46%–90% and render breath tests negative in 20%–75% of patients with SIBO, in general, those in whom SIBO complicates intestinal failure may prove more refractory to antibiotic therapy and may require either repeated (eg, the first 5–10 days of every month) or continuous courses of antibiotic therapy. For the latter, rotating antibiotic
Table 2. Antibiotic Therapy for SIBO

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<tr>
<th>Antibiotic</th>
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<tr>
<td>Amoxicillin–clavulanic acid (500 mg 3 times/day)</td>
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<tr>
<td>Ciprofloxacin (250 mg 2 times/day)</td>
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<tr>
<td>Chloramphenicol (250 mg 4 times/day)</td>
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<tr>
<td>Doxycycline (100 mg 2 times/day)</td>
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<tr>
<td>Metronidazole (250 mg 3 times/day)</td>
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<tr>
<td>Neomycin (500 mg 4 times/day)</td>
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<tr>
<td>Norfloxacin (800 mg/day)</td>
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<tr>
<td>Tetracycline (250 mg 4 times/day)</td>
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</tr>
<tr>
<td>Trimethoprim-sulfamethoxazole (1 double-strength tablet 2 times/day)</td>
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<tr>
<td>Rifaximin (1200 mg/day)</td>
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regimens are recommended to be avoided. Decisions on management should be individualized and consider the risks of long-term antibiotic therapy such as diarrhea, *Clostridium difficile* infection, intolerance, extent of systemic absorption and bacterial resistance, and cost. For these reasons, norfloxacin, amoxicillin–clavulanic acid, and metronidazole are excellent options. Despite their narrow antibacterial spectrum, fluoroquinolones are effective against overgrowth by aerobanaerobic rods, thus supporting the hypothesis that anaerobic growth in the proximal intestine is, in turn, regulated by the aerobic flora. In 1 of only a few randomized studies of antibiotic therapy for bacterial overgrowth in short-bowel syndrome patients, Attar et al. found both norfloxacin and amoxicillin–clavulanic acid to be effective in improving diarrhea and reducing breath-hydrogen excretion. It was interesting to note, however, that despite this excellent symptomatic response, not all patients normalized breath hydrogen excretion. Among patients with short-bowel syndrome, antibiotic therapy may fail completely, indicating a need for alternative strategies in this clinical context. Antibiotic therapy also may prove effective in the prevention or therapy of complications of SIBO such as liver disease and D-lactic acidosis.

Whether antibiotic therapy, or even bowel decontamination, can prevent overgrowth, translocation, and related sepsis after intestinal transplantation remains to be defined. Selective decontamination, an approach that attempts to suppress gram-negative and pathogenic flora and fungi by using antibiotic and antifungal combinations, has been used in an attempt to prevent sepsis of gastrointestinal origin in relation to neutropenia, critical illness, cirrhosis, liver failure, pancreatitis, and transplantation. Although this approach has resulted in the expected bacteriologic changes, the impact on the prevalence of clinical infections has been more variable and concerns also have been raised regarding the potential for the development of rebound colonization and antibiotic resistance. Although this approach has not been tested in a prospective or randomized manner in the context of intestinal failure, it would appear to be a reasonable strategy in those in whom symptoms and signs can be attributed to SIBO and in whom monotherapy has failed.

Prebiotics and Synbiotics

Prebiotics are defined as nondigestible but fermentable foods that beneficially affect the host by selectively stimulating the growth and activity of 1 species, or a limited number of species, of bacteria in the colon. Compared with probiotics, which introduce exogenous bacteria into the human colon, prebiotics stimulate the preferential growth of a limited number of health-promoting commensal flora, especially, but not exclusively, lactobacilli and bifidobacteria. Success is dependent on both the initial concentration of indigenous probiotic species and intraluminal pH. The oligosaccharides in human breast milk are considered the prototypic prebiotics because they facilitate the preferential growth of bifidobacteria and lactobacilli in the colon in exclusively breast-fed neonates.

Of the many prebiotics that are available, the only ones for which sufficient data have been generated to allow consideration of their potential for classification as functional food ingredients are the inulin-type fructans, which are linked by 1-2 bonds that limit their digestion by upper-intestinal enzymes, and fructo-oligosaccharides (Table 3). Both are present in significant amounts in many edible fruits and vegetables including wheat, onion, chicory, garlic, leeks, artichokes, and bananas. Because of their chemical structure, prebiotics are not absorbed in the small intestine but are fermented in the colon by endogenous bacteria to act as energy and metabolic substrates, with lactic and short-chain carboxylic acids as the end products of fermentation. Evidence for efficacy of prebiotics, whether administered alone or in conjunction with a probiotic (a combination referred to as a synbiotic), in human disease is scanty and few large randomized controlled trials are extant in the literature. There are little or no data on their use in either intestinal failure or SIBO.

Table 3. Prebiotic Oligosaccharides

<table>
<thead>
<tr>
<th>Oligosaccharide Type</th>
<th>Example</th>
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<tbody>
<tr>
<td>Fructo-oligosaccharides</td>
<td>Fructo-oligosaccharides</td>
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<tr>
<td>Galacto-oligosaccharides</td>
<td>Galacto-oligosaccharides</td>
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<td>Isomalto-oligosaccharides</td>
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<td>Inulin</td>
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<td>Lactulose</td>
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<td>Lactosucrose</td>
<td>Lactosucrose</td>
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<tr>
<td>Soybean oligosaccharides</td>
<td>Soybean oligosaccharides</td>
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<tr>
<td>Xilo-oligosaccharides</td>
<td>Xilo-oligosaccharides</td>
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</tbody>
</table>
Probiotics

Probiotics, derived from the Greek and meaning *for life*, are defined as live organisms that, when ingested in adequate amounts, exert a health benefit on the host.\(^{113}\) The most widely available probiotics are lactic acid bacteria and nonpathogenic yeasts (Table 4). Although probiotics have been proposed for use in inflammatory, infectious, neoplastic, and allergic disorders, the ideal probiotic strain for any one of these indications has yet to be defined. Although probiotic cocktails also have been advocated to maximize effect, it needs to be noted that some probiotic combinations have been shown to prove antagonistic in certain situations.\(^ {114,115}\) Guidelines for the routine clinical use of probiotics are confounded by insufficient data to guide optimum strain selection, dose, mode of delivery, and methods for monitoring efficacy.\(^ {115}\)

Experimental studies have shown several potential mechanisms of action for probiotics. Thus, competition with pathogens, production of bacteriocins, inhibition of bacterial translocation, enhancement of mucosal barrier function, and signaling between luminal bacteria, the intestinal epithelium, and the immune system all have been reported as possible modes of action for a number of probiotic strains.\(^ {113–122}\) The potent anti-inflammatory effects of some probiotics have emphasized clearly how the therapeutic potential of these agents may extend beyond their ability to displace other organisms and has led to their evaluation in inflammatory bowel disease. In the interleukin-10 knockout model of colitis, for example, McCarthy et al.\(^ {120}\) found that both a *Lactobacillus* and a *Bifidobacterium* produced a marked and parallel reduction in inflammation in the colon and cecum and in the proinflammatory cytokines interferon-\(\gamma\), tumor necrosis factor-\(\alpha\), and interleukin-12, whereas levels of the anti-inflammatory cytokine transforming growth factor-\(\beta\) were maintained at control values. Similar effects have been shown for the probiotic cocktail VSL\#3 in experimental models of colitis; in 2 recent studies, these anti-inflammatory effects could be transmitted by bacterial DNA alone.\(^ {121,122}\) Other studies have shown the ability of probiotics not only to interfere with pathogen adhesion and invasion, but also to neutralize bacterial toxins\(^ {116,117}\) and enhance mucosal barrier function.\(^ {118}\)

Any one or all of the earlier-described probiotic effects could be of benefit to the patient with SIBO and/or intestinal failure. More direct evidence of benefit comes from studies of probiotics in experimental models of translocation. In an acute liver injury model, Adawi et al.\(^ {123}\) showed that *Lactobacillus plantarum*, administered either alone or in conjunction with arginine, reduced the total number of bacteria translocated to mesenteric lymph nodes, portal blood, and the liver through a mechanism that was independent of nitric oxide. Although others have failed to replicate this particular finding,\(^ {124}\) others have reported similar results in other animal models.\(^ {125}\) In experimental models of the short-bowel syndrome, *Bifidobacterium lactis* reduced the rate of translocation\(^ {126,127}\) and *Saccharomyces boulardii* had no effect on either bacterial overgrowth or translocation.\(^ {128}\) Data from human studies are scanty. Based on their study in children with bacterial overgrowth associated with short-bowel syndrome, Young and Vanderhoof\(^ {129}\) suggested that *Lactobacillus plantarum* 299v may either prevent or delay symptom recurrence after antibiotic therapy. In 1 randomized double-blind trial among 12 patients with bacterial overgrowth–related chronic diarrhea, both *L. casei* and *L. acidophilus* strains proved effective\(^ {130}\), in others *L. fermentum*\(^ {131}\) and *S. boulardii*\(^ {29}\) proved ineffective.

Probiotics also may be beneficial for those with complications related to SIBO in intestinal failure: the combination of a probiotic and kanamycin proved effective in a case of recurrent encephalopathy caused by D-lactic acidosis\(^ {32}\) and experimental models have suggested a role for probiotics in nonalcoholic fatty liver disease.\(^ {67}\)

Could probiotics have a role in the prevention of sepsis related to surgery or even intestinal transplantation in the patient with intestinal failure? Direct studies are lacking on this issue; although experimental animal studies indicate a potential for the administration of a variety of probiotics to reduce translocation and even sepsis associated with a vari-

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**Table 4. Microorganisms Used as Probiotic Agents**

<table>
<thead>
<tr>
<th>Lactobacillus species</th>
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<tbody>
<tr>
<td><em>L. acidophilus</em></td>
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<tr>
<td><em>L. bulgaricus</em></td>
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<tr>
<td><em>L. casei</em> (rhamnosus)</td>
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<tr>
<td><em>L. johnsonn</em></td>
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<tr>
<td><em>L. lactis</em></td>
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<td><em>L. plantarum</em></td>
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<td><em>L. reuteri</em></td>
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<tr>
<td><strong>Bifidobacterium species</strong></td>
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<tr>
<td><em>B. adolescentis</em></td>
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<tr>
<td><em>B. bifidum</em></td>
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<td><em>B. breve</em></td>
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<tr>
<td><em>B. infantis</em></td>
</tr>
<tr>
<td><em>B. lactis</em></td>
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<tr>
<td><em>B. longum</em></td>
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<tr>
<td><strong>Other species</strong></td>
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<tr>
<td><em>B. cereus</em></td>
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<tr>
<td><em>B. longum</em></td>
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<tr>
<td><em>Enterococcus faecalis</em></td>
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<td><em>E. coli</em> Nissle 1917</td>
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<td><em>S. boulardii</em></td>
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<td><em>S. cerevisiae</em></td>
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<td><em>S. thermophilus</em></td>
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entity of surgical procedures. Limited studies in human beings have produced conflicting findings.

For the most part probiotics are well tolerated, with infection rates as low as 0.5%–4% being reported in relation to the administration of *Lactobacillus* and *Bifidobacterium* species as probiotics. Instances of significant adverse events such as endocarditis, fungemia, bacteremia, and diarrhea, although reported, are extremely rare. If viability is not essential for probiotic efficacy, as has been reported by some recent studies, irradiated nonviable bacteria or even bacterial products may prove attractive alternates for the immunocompromised patient if indeed there does prove to be a risk from the administration of viable bacteria to such groups.

Probiotics appear, therefore, to possess a number of properties that could be of benefit in bacterial overgrowth and intestinal failure; their introduction into the therapeutic armamentarium, however, must await the results of well-conducted clinical trials as are performed for poorly absorbed antibiotics.

References


