

# Probiotics in Health Maintenance and Disease Prevention

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## Abstract

Probiotic microflora display numerous health benefits beyond providing basic nutritional value. They cooperatively maintain a delicate balance between the gastrointestinal tract and immune system. When this balance is disrupted, disease and inflammation result. Inflammation and over stimulation of the immune system by pathogenic bacteria are competitively inhibited by mucosal adherence of normal beneficial microflora. A healthy gastrointestinal tract with adequate mucus production and appropriate bacterial colonization prevents the overgrowth of pathogenic bacteria, modulates disease processes, and prevents widespread inflammatory disorders. The understanding of the function of probiotics in the maintenance of health and their importance in preventing disease serves to enhance the overall health of patients. With increasing understanding that beneficial microbes are required for health maintenance and disease prevention, probiotics may be commonly used as a therapeutic tool by health care practitioners in the not-too-distant future. This article presents a review of probiotics in health maintenance and disease prevention.

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## Introduction

In the late nineteenth century, microbiologists identified microflora in the gastrointestinal tracts of healthy individuals that differed from those found in diseased individuals. The beneficial microflora found in the gastrointestinal tract

were termed probiotics. Probiotics, literally meaning “for life,” are microorganisms proven to exert health-promoting influences in humans and animals.<sup>1</sup> For example, Metchnikoff discovered and promoted *Lactobacillus bulgaricus* as an aid in souring milk products to extend their shelf life. Tissier demonstrated that Bifidobacteria were helpful in treating infant diarrhea.<sup>2</sup>

Interest continues today as recent technological advances have enabled microorganisms to be isolated and colonized to determine their specific therapeutic properties.<sup>3,4</sup> Studies show these microflora are capable of providing numerous health benefits beyond basic nutritional value.<sup>5-15</sup>

In 1994, the World Health Organization deemed probiotics to be the next-most important immune defense system when commonly prescribed antibiotics are rendered useless by antibiotic resistance.<sup>5</sup> The use of probiotics in antibiotic resistance is termed microbial interference therapy. With increasing understanding that beneficial microbes are required for health, probiotics may become a common therapeutic tool used by health care practitioners in the not-too-distant future.

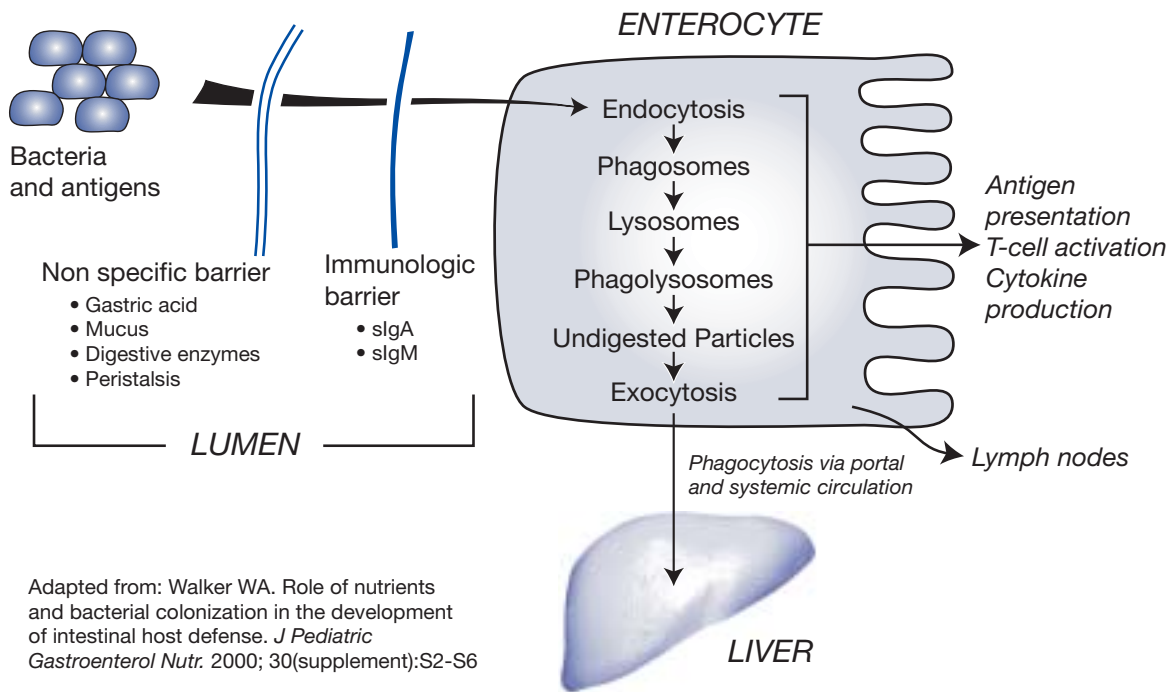
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*Figure 1. Barriers to Antigenic Absorption in the Intestine*



### Colonization

The protective and immune barrier of the human gastrointestinal (GI) tract is diverse. It includes the epithelial layer, the mucous layer, the mechanics of peristalsis and desquamation, and actions of secretory IgA, all of which impact bacterial attachment (Figure 1).<sup>2</sup> After attachment, colonic bacteria are prevented from mixing with the host's eukaryotic cells by the epithelial layer, which acts as a vital barrier to invasion.<sup>16</sup> The barrier's healthy structure and proper functioning are essential for the health of the human host. In this complex system, the delicate balance between the gastrointestinal tract and the microflora is cooperatively maintained.

The GI tract is sterile until an infant ingests vaginal and fecal microflora at delivery.<sup>17</sup> The population of microflora in the infant GI tract is further enhanced by feeding. The breast-fed infant contains a colon population of 90-percent

Bifidobacteria with some Enterobacteriaceae and Enterococci present, but virtually no Bacteroides, Staphylococci, Lactobacilli, or Clostridia. In contrast, Bifidobacteria do not predominate in the bottle-fed infant. Breast-fed infants switched to cow's milk or solid foods colonize Bifidobacteria, Clostridia, Lactobacilli, Bacteroides, Streptococci, and enterics.<sup>13</sup>

The type and number of indigenous microflora increase distally along the length of the gastrointestinal tract.<sup>2,18</sup> The upper GI tract has relatively fewer bacteria secondary to saliva production and increased intestinal motility, which effectively move bacteria along the intestine and prevent large numbers from adhering to mucosal surfaces. In addition, gastric acid suppresses growth in the stomach. The relatively sparse flora of the upper intestine generally numbers less than 10<sup>5</sup> colony forming units (cfu) per milliliter (mL) of contents, until the mid ileum where the population increases to 10<sup>7</sup> cfu/mL of contents,

indicating a shift toward the flora that heavily populates the colon.<sup>2,18</sup>

Favorable characteristics found in probiotics colonizing the human gut are exhibited by *Lactobacillus plantarum*, *L. rhamnosus*, *L. reuteri*, and *L. agilis*.<sup>5</sup> However, these Lactobacilli species are scarce in people living in industrialized nations. *L. plantarum* is carried by 25 percent of the general population in the United States; whereas, nearly 100 percent of the population in Africa and Asia are colonized with favorable Lactobacilli species. The most significant reason is that a Western diet contains drastically decreased amounts of Lactobacilli.<sup>5</sup>

To qualify as a beneficial microflora, the following criteria must be met: (1) it must be acid and bile resistant; (2) it must be metabolically active in the GI tract; (3) it must be able to adhere to the GI tract; (4) it must possess antimicrobial activity toward pathogenic bacteria; and (5) it must reduce colon pH.<sup>2,5,19</sup> There are several species of Lactobacilli and Bifidobacteria within this milieu possessing complex enzymes and functions that have the potential to either benefit or harm the health of the host.<sup>20</sup> When there are alterations in the gastrointestinal barrier or in the composition of the microflora of the gut, there is opportunity for resultant malfunction and disease. For instance, overgrowth of one bacterial species can upset the ecosystem of the gut and result in derangement of beneficial characteristics.

Overgrowth of one bacterial species or imbalances in microflora resulting from a disturbed mucosal layer can alter digestive function, intestinal products, and/or immunological function.<sup>16</sup> In addition, a defective epithelial layer can allow bacteria to gain entry into the human host. This breach can arouse an inflammatory response in the host that has the potential to further alter normal function.

## Function of the Gut

Colonization of the gut with appropriate microflora contributes to its ability to function normally. Commensal microflora byproducts contribute to the health of the intestinal tract and include short-chain fatty acids (SCFAs), polyamines,

vitamins, antioxidants, and amino acids.<sup>1,5,20</sup> For example, the SCFA butyric acid, derived from carbohydrate fermentation, provides the main fuel for colonocytes in the large intestine. In addition, Lactobacillus species can prevent food decay, preserve antioxidants and vitamins, remove toxic food components, and prevent pathogenesis of Enterobacteriaceae, *S. aureus*, and Enterococci found in fermented foods.

Probiotics modulate not only the endogenous flora of the GI tract, but also the immune system.<sup>10,15,16,21</sup> Lactobacilli augment both cellular and humoral immunity.<sup>22</sup> Lactic acid-producing bacteria stimulate various aspects of the immune system, including phagocytic function of macrophages, natural killer cells, monocytes, and neutrophils.

Following a rotavirus vaccination, Lactobacillus GG induce IgM-secreting cells and improve IgA seroconversion, which enhances immunoglobulin response to vaccines.<sup>16</sup> In addition, IgA response to rotavirus is enhanced by administration of Lactobacillus GG.<sup>17</sup> These reports confirm the positive effects of probiotics on innate and acquired immune enhancement, most likely resulting from an ability to bind to gut epithelium. After binding, antibody production is stimulated and the complement and reticuloendothelial system is activated. The interaction between probiotics and epithelial cells has been termed bacterial-epithelial cross-talk.<sup>16</sup> In another study, Lactobacillus GG enhanced the antibody response in adults receiving a typhoid vaccination.<sup>22</sup>

Another example of a probiotic enhancing the immune response can be seen in the activation of the reticuloendothelial system and complement cascade by *Saccharomyces boulardii*.<sup>17</sup> Clearly, interaction of commensal gastrointestinal flora with the gut-associated immune system is an important key in maintaining normal immune function.

Table 1a. Activity of Specific Probiotics

Microflora	Associated Actions	Reference
Bacteroides species	Chronic colitis, gastritis, arthritis (increased bacterial urease activity in chronic juvenile arthritis)	(22)
<i>Bifidobacterium animalis</i>	Decreases <i>Candida albicans</i> systemic dissemination in euthymic or athymic beige mice	(2)
Bifidobacteria species	Reduced incidence of neonatal necrotizing enterocolitis	(8)
<i>Enterococcus faecium</i> SF 68 or <i>Escherichia faecium</i> SF 68	a. Decreased duration of acute diarrhea from gastroenteritis b. No benefit in diarrhea due to <i>Vibrio cholerae</i> and <i>Escherichia coli</i>	a. (24,54) b. (2,55)
<i>Escherichia coli</i> nonpathogenic strain (serotype O6:D5:H1)	As effective as mesalamine in maintaining remission of ulcerative colitis	(6)
Lactobacillus strains	a. Administration of multiple organisms, predominantly Lactobacillus strains shown to be effective in ameliorating pouchitis b. Lactose digestion improved, decreased diarrhea and symptoms of intolerance in lactose intolerant individuals, children with diarrhea, and in individuals with short-bowel syndrome c. Microbial interference therapy – the use of non-pathogenic bacteria to eliminate pathogens and as an adjunct to antibiotics d. Improved mucosal immune function, mucin secretion, and prevention of disease	a. (22,40) b. (24) c. (5) d. (14,40,56)
<i>Lactobacillus acidophilus</i>	a. Significant decrease of diarrhea in patients receiving pelvic irradiation b. Decreased <i>Candida albicans</i> systemic dissemination in euthymic or athymic beige mice c. Decreased polyps, adenomas, and colon cancer in experimental animals d. Prevented urogenital infection with subsequent exposure to three uropathogens <i>E. coli</i> , <i>K. pneumoniae</i> , <i>P. aeruginosa</i> e. Lowered serum cholesterol levels	a. (24) b. (32) c. (18) d. (33) e. (20)
Lactobacillus GG	a. Reduced duration and/or risk of rotavirus diarrhea b. Decreased polyps, adenomas, and colon cancer in experimental animals c. Reduced duration of acute diarrhea most often caused by gastroenteritis d. Reduced diarrheal illness in formula-fed toddlers e. Reduced occurrence of <i>Clostridium difficile</i> diarrhea f. When co-administered with antibiotics in children, non- <i>Clostridium difficile</i> antibiotic-associated diarrhea is reduced g. Reduced risk of traveler's diarrhea h. Reduced severity of pneumonia in children with cystic fibrosis i. Decreased <i>Candida albicans</i> systemic dissemination in euthymic or athymic beige mice j. Increased IgA-specific antibody secreting cells to rotavirus and reduced the duration of diarrhea k. Increased IgA secretion in Crohn's disease l. Prevented recurrent, chronic vaginitis m. Lactobacillus vaginal suppositories effective in reducing the incidence of recurrent urinary tract infections n. Reduced food allergies and atopic dermatitis o. Increased interleukin-10 production in atopic children	a. (22,24,41,57) b. (18) c. (24) d. (22) e. (39) f. (10,22) g. (10,24) h. (22) i. (2) j. (2) k. (2) l. (17) m. (17) n. (15) o. (30)

Table 1b. Activity of Specific Probiotics (continued)

Microflora	Associated Actions	Reference
<i>Lactobacillus fermentum</i> strain KLD	Traveler's diarrhea—no effect	(24)
<i>Lactobacillus plantarum</i>	Produced and preserves key nutrients, vitamins, and antioxidants; eliminated toxic components from food; protected food from decay; eradicated pathogens such as Enterobacteriaceae, <i>S. aureus</i> , and Enterococci	(5)
<i>Lactobacillus plantarum</i> (299v and DSM 9843)	a. Reduced incidence of diarrhea in daycare centers when administered to only half of the children b. Especially effective in reducing inflammation in inflammatory bowel; e.g., enterocolitis in rats, small bowel bacterial overgrowth in children, pouchitis c. Reduced pain and constipation of irritable bowel syndrome d. Reduced bloating, flatulence, and pain in irritable bowel syndrome in controlled trial e. Positive effect on immunity in HIV+ children	a. (22) b. (22; 40) c. (17) d. (51) e. (31)
<i>Lactobacillus reuteri</i>	a. Shortened the duration of acute gastroenteritis b. Decreased <i>Candida albicans</i> systemic dissemination in euthymic or athymic beige mice c. Prevented development of methotrexate-induced and acetic acid-induced colitis in rats d. Shortened acute diarrhea	a. (24) b. (2) c. (2) d. (37)
<i>Lactobacillus rhamnosus</i> (HN001)	Enhanced cellular immunity in healthy adults in controlled trial	(58)
<i>Lactobacillus salivarius</i>	Suppressed and eradicated <i>Helicobacter pylori</i> in tissue cultures and animal models by lactic acid secretion	(25)
<i>Saccharomyces boulardii</i> (yeast)	a. Reduced recurrence of <i>Clostridium difficile</i> diarrhea b. Effects on <i>C. difficile</i> and <i>Klebsiella oxytoca</i> resulted in decreased risk and/or shortened duration of antibiotic-associated diarrhea c. Shortened the duration of acute gastroenteritis d. Decreased only functional diarrhea, but not any other symptoms of irritable bowel syndrome e. Decreased duration of diarrhea induced by tube feedings f. Ineffective for small intestinal bacterial overgrowth g. May reduce HIV-related chronic diarrhea h. Childhood diarrhea i. Extends remission time of Crohn's disease j. Increased IgA anti-toxin A responses in pretreated mice	a. (39; 46) b. (24) c. (24) d. (24) e. (24) f. (24) g. (24) h. (38) i. (11) j. (59)
<i>Saccharomyces cerevisiae</i> (a yeast containing sucrase)	Enhanced digestion of sucrose load was shown in infants with sucrase deficiency	(24)



## The Effect of Probiotics on Pathogenic Bacteria

Probiotics reduce plasma levels of bacterial endotoxin concentrations, at least in part, by inhibiting translocation of bacteria across the GI lumen into the bloodstream.<sup>22</sup> Lactobacillus colonization in germ-free rats has been shown to decrease gut permeability to mannitol.<sup>17</sup> In addition, administration of Lactobacillus to interleukin-10 knockout mice decreased translocation of bacteria to extraintestinal sites and reduced myeloperoxidase concentrations, often associated with inflammation in the bowel.<sup>23</sup>

Decreases in translocation of bacteria may occur as a result of the ability of probiotics to tighten the mucosal barrier.<sup>16</sup> Although very little is known about specific molecular mechanisms by which indigenous flora tighten the mucosal barrier, this may be accomplished by bacterial-epithelial cross-talk and up-regulation of growth factors and receptor sites. Whatever the method of barrier to bacterial entry, the net effect is to modulate systemic intestinal allergy and inflammation. Allergy-induced intestinal inflammation mediated by fecal tumor necrosis factor-alpha is decreased by Lactobacillus GG. Lactobacillus GG also increases mucosal regeneration and reduces fecal urease production, a correlate of inflammation associated with chronic arthritis.<sup>17</sup>

There are several ways probiotic microflora can prevent pathogenic bacteria from adhering and colonizing gut mucosa. Probiotics disallow colonization by disease-provoking bacteria through competition for nutrients, immune system up-regulation, production of antitoxins,<sup>24</sup> and up-regulation of intestinal mucin genes.<sup>14</sup> Increased mucous production prevents adherence and colonization by competing microflora, thereby preventing imbalances.

Probiotics lower colon luminal pH and foster growth of non-pathogenic commensal bacteria by SCFA production.<sup>2</sup> One SCFA, acetic acid, has antimicrobial activity against molds, yeasts, and bacteria.<sup>20</sup> In addition, probiotics exert protective effects through production of hydrogen peroxide and benzoic acid, which inhibit many pathogenic, acid-sensitive bacteria.<sup>5,13,20,25</sup>

Probiotics can also reduce the growth of *Clostridium difficile* and alter toxin receptors for *C. difficile* toxin-A through enzymatic actions on the receptor.<sup>17</sup>

The inhibition of pathogenic bacteria by probiotics is an orchestrated combination of structure and function. Interestingly, bacteriocins – antibacterial compounds produced by *L. acidophilus* – are antagonistic within a specific spectrum by inhibiting other strains of Lactobacilli. Therefore, the practice of combining probiotics needs to include beneficial bacteria that do not inhibit other included strains.<sup>20</sup>

Adherence of normal, beneficial flora competitively inhibits colonization of the mucosa by pathogenic bacteria and reduces over-stimulation of the immune system. A healthy colon with adequate mucus production and appropriate bacterial colonization prevents the adherence of pathogenic bacteria, modulates disease processes, and prevents widespread inflammatory disorders.

## Probiotics in Specific Disorders

Recent advances have been made in the understanding of when to use probiotics and how they impact specific pathological states. Increasing numbers of animal and human studies point to appropriate uses of probiotics as therapeutic agents in myriad conditions. Tables 1a and 1b summarize specific probiotics and their uses.

### Inflammation/Arthritis

Probiotic supplementation has both direct and indirect effects. Probiotics exhibit direct effects locally in the GI tract, including modulation of resident bacterial colonies and vitamin production. There are also indirect effects exerted at sites outside the GI tract, including the joints, lungs, and skin. Indirect effects most likely result from an impact on immunity, via changes in inflammatory mediators such as cytokines. Modulation of inflammatory responses may be related to regulating or modulating the immune system both locally in the GI tract and systemically.

It is speculated that inflammation associated with rheumatoid arthritis may be modulated by the use of probiotics.<sup>22,26</sup> Thirty patients with

chronic juvenile arthritis were randomly allocated to receive *Lactobacillus* GG or bovine colostrum for a two-week period.<sup>26</sup> Immunological and non-immunological gut defenses were investigated in blood and feces. The authors concluded that gut defense mechanisms are disturbed in chronic juvenile arthritis, and suggested orally administered *Lactobacillus* GG has potential to reinforce mucosal barrier mechanisms in this disorder. When inflamed, the gastrointestinal tract becomes permeable and serves as a link between inflammatory diseases of the GI tract and extra-inflammatory disorders such as arthritis. Modulation or down-regulation of the immune system and subsequent reduction in GI permeability can result from consuming probiotics.<sup>16,17</sup>

### Allergies/Eczema

Probiotic bacteria are important in down-regulating inflammation associated with hypersensitivity reactions in patients with atopic eczema and food allergy.<sup>15,27</sup> Perinatal administration of *Lactobacillus rhamnosus* GG decreased subsequent occurrence of eczema in at-risk infants by one-half.<sup>27</sup> In newborn infants, the initial bacteria to colonize the sterile GI tract may establish a permanent niche and have lasting impact on immune regulation and subsequent development of atopic disorders. In infants with already established eczema, significant improvements in dermatitis were noted after a one-month trial with *Lactobacillus* GG-fortified hydrolyzed whey formula. The authors suggest probiotics may enhance endogenous barrier mechanisms of the gut and alleviate intestinal inflammation, providing a useful tool for treating food allergy.<sup>15</sup>

Associated studies have confirmed the positive effect probiotics have on the immune system, both in animal and human trials.<sup>28-30</sup> In mildly hypersensitive patients, probiotics down-regulated a milk-induced inflammatory response.<sup>28</sup> This was found to be secondary to prevention of increased receptor expression in monocytes and neutrophils. Interestingly, individuals in the same study without milk sensitivity were not found to have receptor down-regulation when taking probiotics.

Probiotics have also been found to up-regulate anti-inflammatory cytokines, such as interleukin-10, in atopic children.<sup>30</sup> This is seen both as an immunostimulatory effect in healthy subjects and as a down-regulation effect of immunoinflammatory responses in hypersensitive patients.

Similarly, in animal models, it has been demonstrated that probiotics reinforce mucosal degradation of antigens by enhancing breakdown of macromolecules.<sup>29</sup>

### HIV/Compromised Immunity

Further evidence of a positive effect of probiotics on the immune system can be seen in a study examining *Lactobacillus plantarum* 299v supplementation in children congenitally exposed to HIV.<sup>31</sup> Children with HIV infections have episodes of diarrhea and frequently experience malabsorption associated with possible bacterial overgrowth. Seventeen HIV-infected children were randomized to receive either *Lactobacillus plantarum* 299v or placebo. In the treatment group, colonization with *Lactobacillus plantarum* 299v occurred within two weeks but did not persist after cessation. No adverse events were reported. Improvements were noted in height and weight in follow-up visits. The authors noted a marked augmentation in immune response demonstrated by a change from complete anergy to normal immune response in one patient. These data suggest *L. plantarum* 299v can be given safely to immunocompromised hosts, may indeed have a positive effect on immune response, and has the potential to improve growth and development.

Further confirmation of enhanced immunity and increased resistance to infection has been demonstrated in both animals and humans. In the immunodeficient euthymic mouse model, *Lactobacillus* sp. and Bifidobacteria decreased disseminated systemic *Candida albicans*.<sup>32</sup> In addition, in a placebo-controlled trial, children with cystic fibrosis were found to have reduced severity of pneumonia when *Lactobacillus* GG was administered. It is possible that protection from respiratory disease is related to up-regulation of mucin cells along with the enhanced antibody response. Expanding the use of probiotics in immune-compromised patients appears promising.

### Hyperlipidemia

Another unexpected benefit of probiotics is serum lipid reduction. Several authors have reported that *Lactobacillus acidophilus* NCFM and *L. sporogenes* were found to take up cholesterol in the presence of bile and in the absence of oxygen, both conditions present in the intestinal tract.<sup>20,33,34</sup> The effect on cholesterol assimilation was thought to be strain-dependent. Studies ranged from *in vitro* to animal to human studies, with mixed results. Certain strains of *Lactobacillus* have ability *in vitro* to assimilate cholesterol, demonstrated by identification of cholesterol in cells during growth and decreases in the concentration of cholesterol in the growth medium. Uptake of cholesterol occurred only when the culture was grown anaerobically in the presence of bile, such as would be expected to occur in the human gastrointestinal tract. This may have important implications in preventing reabsorption of cholesterol back into systemic circulation.

### Hepatic Disease

An interesting case report was published documenting the effect of a high potency, multicultured probiotic preparation in liver cirrhosis.<sup>35</sup> The probiotic preparation was identified as VSL #3, containing *Streptococcus thermophilus*, Bifidobacteria, *Lactobacillus acidophilus*, *L. plantarum*, *L. casei*, *L. debrueckii bulgaricus*, and *Streptococcus faecum* at a concentration of  $10^{11}$  microflora per gram. The authors hypothesized that oral bacteriotherapy could improve microbial balance and lower portal pressure with a reduction in the risk of bleeding. A 76-year-old male patient with cirrhosis and esophageal varices was given the probiotic preparation for one month followed by a one-month washout period and a second one-month cycle of treatment. Blood velocity and flow were measured in portal, splenic, and superior mesenteric veins at baseline and during treatment. The mean blood velocity and flow were greatly increased in the portal vein after one month of treatment, but at the end of the washout period both parameters returned toward baseline levels. After a second cycle of treatment, blood velocity and flow in the portal vein were again strongly

increased in comparison to baseline. Patients with liver cirrhosis have altered microflora, over-populated with urea-splitting bacteria. On this basis, oral antibiotics are commonly administered to reduce the production of mediators involved in the pathogenesis of hepatic encephalopathy, portal hypertension, and variceal bleeding. The authors suggest that, instead of antibiotics, probiotics should be administered and demonstrate this could be a safe way to regulate portal pressure. They conclude that not all bacteria should be regarded as pathogenic in liver cirrhosis and portal hypertension.<sup>35</sup>

### Maldigestion

Lactose maldigestion occurs frequently in the general population.<sup>24</sup> Persons with lactose intolerance experience better digestion and tolerance of lactose in yogurt than that contained in milk. Viable cultures of lactic acid bacteria are speculated to be essential since pasteurization reduces the observed digestibility. Digestion of lactose in the gut lumen by lactase contained in yogurt bacteria is coupled with slower intestinal delivery or transit time of yogurt compared with milk. The replacement of milk with yogurt or fermented dairy products may allow for better digestion and decreased diarrhea and other symptoms associated with lactose intolerance.

A similar benefit was identified in infants with a sucrase deficiency, which causes diarrhea from sucrose ingestion. Enhanced digestion of sucrose was demonstrated when *Saccharomyces cerevisiae*, a yeast containing the enzyme sucrase, was administered therapeutically.<sup>24</sup>

### Diarrhea

One of the most well recognized uses of probiotics is for diarrheal diseases. The prevention and management of acute viral and bacterial diarrhea as well as the control of antibiotic-associated diarrhea are areas of significant potential benefit. A number of specific strains, including *Lactobacillus* GG, *L. reuteri*, *Saccharomyces boulardii*, Bifidobacteria species, and others, have been shown to have significant benefit for diarrhea.<sup>2,14,22,24,36-41</sup> In the pediatric population,



probiotics appear to benefit viral diarrhea, possibly by increasing secretory IgA and decreasing viral shedding, suggesting an immunological mechanism. Although numerous strains of probiotics, doses, and different populations in these studies make generalizations difficult, it is clear probiotic agents are becoming an important tool in the treatment of gastrointestinal problems in infants and children.

Although gastroenteritis as the cause of acute diarrhea may heal spontaneously within a few days, it can be associated with morbidity and increased direct and indirect medical costs.<sup>24</sup> Acute diarrheal episodes can be related to viral, bacterial, or parasitic pathogens. Several studies have demonstrated improvement when acute diarrheal disorders, including rotavirus infection, traveler's diarrhea, and more serious bacterial infections such as *Clostridium difficile*, are treated with probiotics.<sup>2,22,24,36-41</sup> Importantly, studies using *Lactobacillus* species or *Saccharomyces boulardii* suggest a beneficial role during *C. difficile*-related infections.<sup>22,39,40,42-46</sup> In populations with small bowel bacterial overgrowth, and in particular those with short bowel syndrome, *Lactobacillus* species were shown to be efficacious in ameliorating the symptom complex.<sup>22,47</sup> However, in 10 patients during a seven-day, double-blind, randomized trial comparing antibiotic therapy to *Saccharomyces boulardii*, *S. boulardii* was ineffective in eliminating overgrowth of small bowel intestinal bacteria once it was established.<sup>24</sup>

*In vitro* studies demonstrate probiotic agents inhibit adherence of dysbiotic organisms to intestinal epithelial cells. This inhibition is hypothesized to be mediated through the ability to increase expression of MUC2 and MUC3 intestinal mucins.<sup>14</sup> Bacterial-to-epithelial cell binding is a multi-stage process, the first stage of which is characterized by an initial interaction of bacteria with the enterocyte layer. Probiotics increase intestinal mucin production, which prevents the attachment of enteropathogens. The attachment could be prevented by steric hindrance (a slight structural difference in the bacterial ligand interfering with proper attachment to the receptor) or through competitive inhibition for attachment sites

on mucins mimicking epithelial cell bacterial attachment sites. Enhancement of innate defense mechanisms in the gastrointestinal tract, such as mucin production, might be preventive or therapeutic, but this remains to be elucidated.

### **Helicobacter pylori Infections**

Evidence for the use of probiotics in the treatment of *Helicobacter pylori* infection has been conflicting. *H. pylori* may not always be eradicated with antibiotics and acquisition of resistance is often a serious problem. Aiba et al showed *Lactobacillus salivarius* capable of producing high amounts of lactic acid, which can inhibit the growth of *H. pylori in vitro*.<sup>25</sup> This was subsequently confirmed *in vivo* in a murine model. The authors concluded probiotics could be effective against *H. pylori*. It was found that the higher the level of lactic acid production by *Lactobacillus*, the more potent was the effect on reducing *H. pylori*'s urease activity. In addition, the number of *H. pylori* colonies decreased to an undetectable level with regression of inflammation in some of the treated mice.

When comparing *Lactobacillus acidophilus*, *L. casei*, and *L. salivarius*, *L. acidophilus* specifically was unable to suppress *H. pylori in vivo*, possibly due to a low level of lactic acid production resulting from poor colonization and growth in the stomach. *Lactobacillus salivarius* was found to be most effective. This is consistent with a human clinical trial that reported oral administration of *L. acidophilus* was unable to suppress *H. pylori* or reduce inflammation in patients with *H. pylori*-positive gastritis.<sup>48</sup> Identification of appropriate strains with increased adherence and lactic acid production is paramount in future studies.

### **Conditions of the Genitourinary Tract**

There is a developing role for the use of probiotics in the genitourinary (GU) system, especially for vaginitis, whether from bacterial or fungal etiology. A report on the use of *L. sporogenes* in non-specific vaginitis revealed symptomatic relief in the majority of women who

used the probiotic vaginally.<sup>34</sup> In another study, 29 women were randomized to receive either *L. rhamnosus* GR-1 and *L. fermentum* RC-14 or commercially available *L. rhamnosus* GG. *L. rhamnosus* GR-1 and *L. fermentum* RC-14 were chosen because of a reported specific benefit in the genitourinary tract and the ability to express anti-infective proteins against GU pathogens. Improved colonization was demonstrated with the combination product when compared to *L. rhamnosus* GG alone. The combination product containing *L. rhamnosus* GR-1 and *L. fermentum* RC-14 consistently inhibited growth of *Candida albicans* when compared to *Lactobacillus rhamnosus* GG alone. The investigators concluded that not all probiotic strains, even those of the same species, necessarily act similarly at the same site.<sup>49</sup> Other reports demonstrate efficacy of *Lactobacillus acidophilus* in treating vaginal *Candida* after oral use. The study points to vaginal contamination with fecal flora as the possible rationale for the effectiveness of this therapy.<sup>17</sup>

Both oral probiotics and vaginal suppositories of probiotics have been shown to reduce the incidence of recurrent urinary tract infection.<sup>17,33</sup>

### Neonatal Enterocolitis

A report by Caplan and Jilling found probiotic supplementation may be effective in preventing neonatal necrotizing enterocolitis (NEC).<sup>8</sup> The investigators developed a murine model that showed clinical and pathological characteristics of NEC by 96 hours of life. *Bifidobacterium infantis* organisms were found effective in reducing the risk of developing NEC. The authors state the mechanism was most likely through modulation of the inflammatory cascade, although the pathophysiology has not been fully elucidated.

### Colon Cancer

Further effects of probiotics in the GI tract have been observed in experimental models of colon cancer.<sup>18,22</sup> Bacterial metabolism of various dietary constituents results in production of many compounds, some of which may be carcinogenic and some which may be anticarcinogenic. The

composition of intestinal flora may significantly effect production of such compounds.<sup>50</sup> Indeed, in animal studies, the rates of formation of colon tumors were reduced in those receiving *Lactobacillus* strains.<sup>18,22</sup> Several species of lactic acid-producing bacteria appear to prevent carcinogenic compounds from inducing the first crucial step of tumorigenesis that may ultimately act as a proto-oncogene or inactivate tumor suppressor genes. Administration of *Lactobacillus* GG has been shown to suppress bacterial enzyme activity such as  $\beta$ -glucuronidase, urease, fecal glycocholic hydrolase, nitroreductase, and tryptic activity.<sup>10</sup> Of particular interest are reductions in glucuronidase, nitroreductase, and azoreductase, all of which might play a role in activation of procarcinogens in the large intestine. Human trials will be needed to confirm these findings.

### Irritable Bowel Syndrome

Probiotics exhibit a direct effect in the gut in the treatment of inflammatory and functional bowel disorders. In one of the most common functional bowel disorders, irritable bowel syndrome, *Lactobacillus plantarum* 299v and DSM 9843 strains were shown in clinical trials to reduce abdominal pain, bloating, flatulence, and constipation.<sup>17,51</sup> It was also observed that *Saccharomyces boulardii* decreased diarrhea in irritable bowel syndrome, but was not effective in alleviating other symptoms of the syndrome.<sup>24</sup> Further investigation of the use of probiotics in patients with irritable bowel syndrome is currently underway at the University of Kansas Medical Center.

### Inflammatory Bowel Disease

It has been reported that probiotic combination therapies may benefit patients with inflammatory bowel disease.<sup>7</sup> Twenty-six patients received VSL #3 at 6 grams per day for 12 months and were assessed clinically throughout the trial. The authors report 75 percent of the patients remained in remission during treatment.

*Saccharomyces boulardii* in patients with Crohn's disease was found to extend remission time and reduce relapse rates.<sup>11</sup> Thirty-two patients

with established Crohn's disease but in remission were randomized to receive either 3 g daily mesalamine or 2 g daily mesalamine plus *Saccharomyces boulardii*. Six of 16 patients enrolled in the pharmaceutical-only arm relapsed while only one of 16 in the probiotic arm relapsed. Both *Saccharomyces boulardii* and Lactobacillus GG have been reported to increase secretory IgA levels in the gut. Ongoing investigation into the use of probiotics in inflammatory bowel disease has generated considerable interest.<sup>52,53</sup>

## Conclusion

Current evidence supports the concept that oral administration of probiotic therapies may be beneficial in a multitude of disorders both inside and outside the gastrointestinal tract. The direct effects of probiotics in the GI tract are well documented and include up-regulation of immunoglobulins such as IgA, down-regulation of inflammatory cytokines, and enhancement of gut barrier function. Exciting new evidence supports indirect, systemic effects of probiotics for a widely divergent set of disorders, including atopic disease, immune compromise, and vaginal infections.

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