CHAPTER 14

Probiotics and Prebiotics as Nutraceuticals

Seema Y. Pathak, Cathy Leet, Alan Simon, and Yashwant Pathak

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GENESIS OF HUMAN MICROBIOTA

It is estimated that 500–1,000 species of bacteria live in the human body [Sears 2005]. Bacterial cells are much smaller than human cells, and there are at least 10 times as many bacteria as human cells in the body (approximately $10^{14}$ versus $10^{13}$ [$10^{13} = 1$ trillion]) [Savage 1977; Berg 1996]. Although normal flora are found on all surfaces exposed to the environment (on the skin and eyes, in the mouth, nose, small intestine, and colon), the vast majority of bacteria live in the large intestine. The terms intestinal “microflora” or “microbiota” refer to the microbial ecosystem colonizing the GI tract. Ninety-nine percent of the bacteria isolated from human fecal specimens will not grow in the presence of atmospheric oxygen [Savage 1977]. Bacteria make up most of the flora in the colon [University of Glasgow 2005] and 60% of the dry mass of feces [Guarner and Malagelada 2003]. This fact makes feces an ideal source to test for gut flora.

The stomach and proximal small intestine contain relatively low numbers of microbes ($10^3$–$10^5$ bacteria/g or ml content) because of a low pH and rapid flow in this region. Acid-tolerant lactobacilli and streptococci predominate in the upper small intestine. The distal small intestine (ileum) maintains a more diverse microbiota and higher bacterial numbers ($10^6$ or ml content) than the upper bowel and is considered a transition zone preceding the large intestine. The large intestine (colon) is the primary site of microbial colonization because of slow turnover and is characterized by large numbers of bacteria ($10^{10}$–$10^{11}$/g or ml content), low redox potential, and relatively high short-chain fatty acid (SCFA) concentrations. In addition to an increasing gradient of indigenous microbes from the stomach to the colon, there are also characteristic spatial distributions of organisms within each gut compartment. At least four microhabitats have been described: the intestinal lumen, the unstirred mucus layer or gel that covers the epithelium of the entire tract, the deep mucus layer found in intestinal crypts, and the surface of mucosal epithelial cells [Lee 1984; Berg 1996]. The processes involved in the establishment of microbial populations are complex, involving microbial succession as well as microbial and host interactions and eventually resulting in dense, stable populations inhabiting specific regions of the gut.

Babies are born with no bacterial presence and are practically sterile. Microbes that originate from the surroundings and from the mother establish themselves with the course of time. *Escherichia coli* from the mother’s feces start contaminating the infant in vaginal delivery. The length of delivery process is an important contributing factor [Bettelheim et al. 1974; Brook et al. 1979]. Bacteria from the mother’s cervix also colonize the alimentary canal of the baby. The naso-pharynx of the baby receives bacteria from the mother’s vagina [MacGregor and Tunnesseen 1973]. In cesarean delivery, the baby’s first exposure to microbes comes from air; nursing staff and other surgical equipment act as a vector in this situation [Bettelheim et al. 1974; Lennox-King et al. 1976a,b]. The transmission of microbes from generation to generation is ensured by human expressions of neonatal care, such as kissing, touching, and sucking [Tannock 1994].

There is an obvious difference in exposure and acquisition of bacteria in babies born in developing countries. Enterobacteria and streptococci can be the first group...
established in most cases. *E. coli* is established within 48 h after contamination [Mata and Urrutia 1971]. The infants in developing countries get exposed to environmental bacteria, regardless of the mode of delivery, compared with developed countries. This explains the absence of certain groups of intestinal bacteria in the babies born in western countries. After the exposure to the breast milk, the gut now is in a continuous process of acquiring new microbes [Moughan et al. 1992].

The staphylococci, streptococci, corynebacteria, lactobacilli, micrococci, propionibacteria, and bifidobacteria all originate from the mothers nipple, surrounding skin, and milk ducts [Asquith and Harrod 1979; West, Hewitt, and Murphy 1979]. In formula-fed infants, the exposure to bacteria comes from dried powder, water, and equipment used in the manufacturing process.

Cooperstock and Zedd [1983] divide the development of intestinal bacteria in infants into four different stages. The phase one is the initial acquisition phase lasting over the first two weeks. Breast feeding period is phase two. Weaning and introduction of supplements is phase three. Phase four starts after the weaning is complete. The initial colonization of *E. coli* in large numbers is later responsible for the establishment of anaerobic genera, *Bacteriodes*, *Bifidobacterium*, and *Clostridium*. This happens during the time period of four to seven days. *Bifidobacteria* have dominance in breast-fed infants. This changes once the dietary supplementation begins in the breast-fed infants and *Bifidobacteria* are no longer the prominent genera.

By the second year of life, with the introduction of solid food almost complete, the fecal microbiota of the baby resembles the adult fecal microbiota [Stark and Lee 1982; Copperstock and Zedd 1983].

In phases three and four, other bacterial groups, including eubacteria, veionella, staphylococci, propionibacteria, bacilli, fusobacteria, and yeast, establish themselves along with the *Bacteriodes* and anaerobic gram-positive cocci [Conway 1997].

Antimicrobial and antibiotic agents have a significant influence in the microflora of infants [Bennet et al. 1982, 1986; Bennet and Nord 1989]. A specific component of the microbiota becomes more vulnerable than others because of this exposure. Mutations in the microbiota can be seen after finishing the drug treatment. The effects of the drug regimen can be persistent [Finegold, Mathisen, and George 1983].

Diet is the most powerful tool to influence intestinal microbiota. Targeted ingredients in the formula, such as oligosaccharides, affect colon fermentation [Knol et al. 2005]. Breast milk itself contains antimicrobial activity, which helps to stimulate development and maturation of intestinal mucosa. This phenomenon now further promotes stability and decreased intestinal disturbances [Palmer et al. 2007].

**PROBIOTICS**

The word probiotic comes from pro, meaning “for,” and bios, meaning “life.” So probiotic literally means “for life.” The term probiotic is used to describe nutritional supplements and other products that contain live bacteria. There are literally hundreds of probiotic supplements available to buy. Although they all promise to help restore and replenish our gut microflora, many are so deficient in living or viable...
bacteria that the package they come in has more value than what is inside [Dekker et al. 2007].

In 1905, Dr. Elie Metchnikoff, a Russian scientist working at the famous Institut Pasteur in Paris, was the first to write about the health benefits of probiotics. Dr. Metchnikoff, who later won a Nobel Prize for his research on the immune system, wrote that Bulgarian peasants who consumed large amounts of yogurt lived long, healthy lives. Examination of the yogurt by Dr. Metchnikoff led to his discovery of a unique lactic-acid-producing bacteria that helped digestion and improved the immune system [Dekker et al. 2007]. The historical association of probiotics with fermented dairy products led to extensive research validating Dr. Metchnikoff’s early observations. Investigations during the past several decades have demonstrated numerous health-supportive properties of probiotics on human health [Isolauri 2001; Goossens et al. 2003; Porth 2004; The United States Probiotics Organization 2007].

Structurally, the GI or digestive tract is a hollow tube that runs from the mouth to the anus. Mastication (the chewing of food), peristalsis (the movement of food), enzymes, and stomach fluids break down the food into small, absorbable molecules. In the lining of the small intestines, specialized cells act as a barrier, separating needed nutrients from the molecules. By the time food leaves the small intestine and enters the colon, all of the nutrients in food will have entered the bloodstream [Berg 1996]. In addition to digestion, the GI tract also provides several important immune response activities. Large numbers of white blood cells (lymphocytes) reside under the tonsils and in the appendix. Clumps of lymphocytes and lymphatic tissues make up Payer’s patches, immune system structures located within the small intestine. Within the walls of the large intestine, huge numbers of immune system modulators and regulators reside [Goossens et al. 2003; Guyton and Hall 2005]. Evidence has demonstrated that the health status of the tonsils, appendix, and the small and large intestine have an impact on the health of the immune system. Numerous strains of gut microflora reside in significant numbers in the small intestine (10^6—10^8/g of small intestinal contents) and even greater numbers in the colon (10^11—10^12/g of colon contents) or large intestine. Microflora of the large intestine perform several activities beneficial to human health, including supporting healthy digestion through fermentation, promoting healthy bacterial and yeast balance, and stimulating certain immune system components [Goossens et al. 2003].

Probiotics, as defined by the United States Probiotics Organization, are “live microorganisms administered in adequate amounts which confer a beneficial health effect on the host” [Guyton and Hall 2005]. Probiotics bacteria are frequently, but not always, chosen from bacteria that normally inhabit the GI system of humans. The genera Lactobacillus acidophilus (LA) and Bifidobacterium longum (normal inhabitants of the healthy intestine) are the most clinically validated of all probiotics strains [Kailasapathy and Chin 2000; Goossens et al. 2003; Porth 2004; The United States Probiotics Organization 2007]. Scientific study has shown repeatedly that two-strain probiotics supplements containing L. acidophilus and B. longum are highly effective in the following:

- Supporting overall human health [Bai and Ouyang 2006; Quigley and Flourié 2007]
- Responding to small daily challenges [Gopal et al. 2001; Reid et al. 2001; Marelli, Papaleo, and Ferrari 2004]
When humans are under increased physical, emotional, or intellectual stress, changes often occur within the GI environment [Kailasapathy and Chin 2000]. Examples of these changes include slowed secretory responses, increased formation of reactive oxygen species, increased transit times of fecal material, disruption of mucosal cells, and altered epithelium tissues. These changes often result in occasional gas, bloating, and constipation and may interfere with probiotics functionality [Dong and Kaunitz 2006; Miyake, Tanaka, and McNeil 2006; Davidson, Kritas, and Butler 2007].

The effectiveness of all probiotics is dependent on the ability of the organisms to reach the large intestine in a viable state and adhere to the intestinal wall. Only then can colonization of the microflora succeed. Researchers have discovered recently that certain broad-spectrum probiotic combinations are able to function well within altered GI environments [Miyake, Tanaka, and McNeil 2006]. To date, the probiotic combination of \textit{L. acidophilus}, \textit{L. rhamnosus}, \textit{B. bifidum}, \textit{B. breve}, \textit{B. longum}, and \textit{B. lactis} shows great promise in the following:

- Supporting long-term colon care
- Providing deep intestinal support
- Helping the body respond during times of increased physical, emotional, or mental stress [Karimi and Pena 2003; Collado, Meriluoto, and Salminen 2007a]

The probiotic supplement should be proven to function \textit{in vivo}, tolerate harsh intestinal environments, and successfully adhere to the intestinal wall. Table 14.1 gives the list of the strains useful in probiotics formulations, and Table 14.2 describes their applications in various disease conditions.

**PREBIOTICS**

Gibson and Roberfroid [1995] define prebiotics as “non-digestible food ingredients that beneficially affect the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon, and thus improve host health.” Prebiotics are simply the “food” for beneficial bacteria.

Prebiotics modify the balance of the intestinal microbiota by stimulating the activity of beneficial bacteria, such as \textit{Lactobacilli} and \textit{Bifidobacteria} [Gibson and Roberfroid 1995; Collins and Gibson 1999]. There is now considerable evidence that manipulation of the gut microbiota by prebiotics can beneficially influence the health of the host [Ginson and Roberfroid 1995; Roberfroid 1999; Delzenne and Kok 2001; Sartor 2004; Rastall et al. 2006; Parracho, McCartney, and Gibson 2007]. In particular, many attempts have been made to control serum triacylglycerol concentrations through modification of dietary habits with regard to consumption of prebiotics and probiotics [Delzenne and Kok 2001; Parracho, McCartney, and Gibson 2007]. Furthermore, unlike probiotics, prebiotics are not subject to biological viability problems and thus can be incorporated into a wide range of alimentary products (such as milk, yogurt, and infant formula), and they target organisms that are natural residents of the gut microbiota [Gibson and Roberfroid 1995]. For example, oligosaccharides
Table 14.1  Commonly Used Strains in Probiotic Products

<table>
<thead>
<tr>
<th>Probiotic</th>
<th>Structure/Function Claim</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactobacillus acidophilus</td>
<td>Helps alleviate occasional gas, constipation, and lactose intolerance symptoms in children</td>
<td>Salazar-Lindo et al. 2007</td>
</tr>
<tr>
<td></td>
<td>Supports healthy bowel movements while traveling</td>
<td>McFarland 2007</td>
</tr>
<tr>
<td></td>
<td>Works with the body's own ability to modulate occasional intestinal discomfort</td>
<td>Rousseaux et al. 2007</td>
</tr>
<tr>
<td>Lactobacillus plantarum</td>
<td>Used postoperative immune stimulation</td>
<td>Sanders 2007</td>
</tr>
<tr>
<td>Lactobacillus reuteri</td>
<td>Immune stimulation against diarrhea</td>
<td>Sanders 2007</td>
</tr>
<tr>
<td>Lactobacillus rhamnosus</td>
<td>Immune stimulation, alleviates atopic eczema</td>
<td>Sanders 2007</td>
</tr>
<tr>
<td>Lactobacillus salivarius</td>
<td>Positive effects with intestinal ulcers and inflammation</td>
<td>Sanders 2007</td>
</tr>
<tr>
<td>Lactobacillus rhamnosus</td>
<td>Supports healthy balance of enterococci</td>
<td>Manley et al. 2007</td>
</tr>
<tr>
<td></td>
<td>May support healthy skin integrity</td>
<td>Sawada et al. 2007</td>
</tr>
<tr>
<td></td>
<td>Relieves occasional abdominal discomfort in school children</td>
<td>Gawroniska et al. 2007</td>
</tr>
<tr>
<td>Lactobacillus casei</td>
<td>Reduces symptoms of lactose intolerance, prevents bacterial overgrowth in small intestine</td>
<td>Sanders 2007</td>
</tr>
<tr>
<td>Lactobacillus johnsonii</td>
<td>Immune stimulation and active against Helicobacter pylori</td>
<td>Sanders 2007</td>
</tr>
<tr>
<td>Bifidobacterium bifidum</td>
<td>Supports healthy immune system responses</td>
<td>DeSimone et al. 1992</td>
</tr>
<tr>
<td></td>
<td>Prevents occasional loose stools</td>
<td>Saavedra et al. 1994</td>
</tr>
<tr>
<td>Bifidobacterium lactis</td>
<td>Supports healthy intestinal colonization</td>
<td>Sanders 2006</td>
</tr>
<tr>
<td></td>
<td>Restores healthy immune responses in the elderly</td>
<td>Gill et al. 2001</td>
</tr>
<tr>
<td>Bifidobacterium breve</td>
<td>Maintains healthy gut microflora colonies</td>
<td>Wang et al. 2007; Li et al. 2004</td>
</tr>
<tr>
<td>Bifidobacterium longum</td>
<td>Supports healthy liver enzyme activity</td>
<td>Malaguarnera 2007</td>
</tr>
<tr>
<td></td>
<td>Supports healthy bowel movements in adults</td>
<td>Amenta et al. 2006</td>
</tr>
<tr>
<td></td>
<td>Supports the body's natural anti-inflammatory response</td>
<td>Xiao et al. 2007</td>
</tr>
<tr>
<td></td>
<td>In laboratory research, <em>Bifidobacterium longum</em> removed lead and cadmium from water</td>
<td>Halttunen et al. 2007</td>
</tr>
<tr>
<td>Bifidobacterium animalis</td>
<td>Supports healthy development of cells</td>
<td>Xu et al. 2007</td>
</tr>
<tr>
<td>Bifidobacterium lactis</td>
<td>Stabilizes intestinal passage, immune stimulation, improves phagocytic activity, alleviates atopic eczema, prevents diarrhea in children and traveler’s diarrhea</td>
<td>Sanders 2007</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>Immune stimulation</td>
<td></td>
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</tbody>
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### Table 14.2 Common Applications of Probiotics Products in Different Disease Conditions

<table>
<thead>
<tr>
<th>Disease</th>
<th>Probiotics</th>
<th>Research Results</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon cancer</td>
<td><em>Lactobacillus rhamnosus</em> and <em>Bifidobacterium longum</em></td>
<td>In a small but well-designed Irish study, 80 people who had either colon cancer or benign polyps were randomly assigned to receive either a probiotic or a placebo to determine the effects on their tumors, growths, and intestines. The probiotic contained two types of bacteria, <em>Lactobacillus rhamnosus</em> and <em>Bifidobacterium longum</em>; the placebo was an inactive pill. After 12 weeks, the patients who received the probiotics showed decreased DNA damage in the lining of the colon and decreased growth and reproduction of colon cells.</td>
<td>Rafter et al. 2007</td>
</tr>
<tr>
<td>Antibiotic-induced diarrhea</td>
<td><em>Lactobacillus acidophilus</em></td>
<td>To see whether probiotics could prevent or reduce the diarrhea that often occurs during treatment with antibiotics, researchers randomized 135 hospitalized patients to receive either a probiotic drink (57 patients) containing <em>Lactobacillus</em> or a placebo (56 patients) twice a day while being treated with antibiotics and for one week after the course finished. Only seven patients (12%) in the probiotic group developed diarrhea compared with 19 patients (34%) in the placebo group.</td>
<td>Hickson et al. 2007</td>
</tr>
<tr>
<td>Chemotherapy-induced diarrhea</td>
<td><em>Lactobacillus rhamnosus</em></td>
<td>For most, diarrhea is an uncomfortable and embarrassing problem that almost always resolves after two to three days. For people being treated with chemotherapy, however, diarrhea can be deadly. It can lead to dehydration, hospitalization, and, if severe enough, discontinuation of the chemo drugs. In a Swedish study, colon cancer patients were randomly assigned to receive daily supplements of <em>Lactobacillus rhamnosus</em> during chemotherapy or a placebo. Those who received the probiotic <em>Lactobacillus</em> supplements had significantly less severe diarrhea (grades 3 and 4) than those who did not: 22 versus 37%. They also had less abdominal pain, were hospitalized less often, and needed fewer chemo dose reductions attributable to bowel problems.</td>
<td>Osterlund et al. 2007</td>
</tr>
</tbody>
</table>

(Continued)
Traveler's diarrhea is most often caused by a bacterial infection, such as *Escherichia coli*, *Campylobacter*, *Shigella*, or *Salmonella* and is transmitted in undercooked or raw foods, contaminated food, contaminated water, or contaminated ice cubes. In a review of 12 clinical studies, a mixture of *Lactobacillus acidophilus* and *Bifidobacterium bifidum* worked the best to prevent and reduce the severity of traveler’s diarrhea. No serious adverse reactions to the probiotics were reported in the trials.

Ten active Crohn’s outpatients with diarrhea and abdominal pain were enrolled into a probiotic study. All 10 had received prescription drugs to reduce their symptoms, but they remained painful. They took probiotics containing *Bifidobacterium* and *Lactobacillus* for four months. By the end of therapy, seven patients had improved clinical symptoms after combined probiotics and prebiotic therapy. Six patients had a complete response.

To determine how effective *L. acidophilus* alone or in combination with mesalazine, an ulcerative colitis medication, is in achieving remission. A total of 187 ulcerative colitis patients were randomized to receive *L. acidophilus* (65 patients), mesalazine alone (60 patients), or *L. acidophilus* with mesalazine (62 patients). After 12 months, treatment with *L. acidophilus* was more effective than standard treatment with mesalazine in prolonging the relapse-free time.

A total of 104 children who complained of “idiopathic tummy aches,” or stomach pain without any identifiable cause, were enrolled in a double-blind, randomized controlled trial in which they received *L. acidophilus* (n = 52) or placebo (n = 52) for four weeks. The results showed that the children in the probiotics group were more likely to have no pain than those in the placebo group (25 versus 9.6%).

<table>
<thead>
<tr>
<th>Disease</th>
<th>Probiotics</th>
<th>Research Results</th>
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<tr>
<td>Traveler’s diarrhea</td>
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<td>Traveler’s diarrhea is most often caused by a bacterial infection, such as <em>Escherichia coli</em>, <em>Campylobacter</em>, <em>Shigella</em>, or <em>Salmonella</em> and is transmitted in undercooked or raw foods, contaminated food, contaminated water, or contaminated ice cubes. In a review of 12 clinical studies, a mixture of <em>Lactobacillus acidophilus</em> and <em>Bifidobacterium bifidum</em> worked the best to prevent and reduce the severity of traveler’s diarrhea. No serious adverse reactions to the probiotics were reported in the trials.</td>
<td>McFarland 2007</td>
</tr>
<tr>
<td>Crohn’s disease</td>
<td><em>Bifidobacterium</em> and <em>Lactobacillus</em></td>
<td>Ten active Crohn’s outpatients with diarrhea and abdominal pain were enrolled into a probiotic study. All 10 had received prescription drugs to reduce their symptoms, but they remained painful. They took probiotics containing <em>Bifidobacterium</em> and <em>Lactobacillus</em> for four months. By the end of therapy, seven patients had improved clinical symptoms after combined probiotics and prebiotic therapy. Six patients had a complete response.</td>
<td>Fujimori et al. 2007</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td><em>Lactobacillus acidophilus</em></td>
<td>To determine how effective <em>L. acidophilus</em> alone or in combination with mesalazine, an ulcerative colitis medication, is in achieving remission. A total of 187 ulcerative colitis patients were randomized to receive <em>L. acidophilus</em> (65 patients), mesalazine alone (60 patients), or <em>L. acidophilus</em> with mesalazine (62 patients). After 12 months, treatment with <em>L. acidophilus</em> was more effective than standard treatment with mesalazine in prolonging the relapse-free time.</td>
<td>Zocco et al. 2006</td>
</tr>
<tr>
<td>Stomach pain in children</td>
<td><em>Lactobacillus acidophilus</em></td>
<td>A total of 104 children who complained of “idiopathic tummy aches,” or stomach pain without any identifiable cause, were enrolled in a double-blind, randomized controlled trial in which they received <em>L. acidophilus</em> (n = 52) or placebo (n = 52) for four weeks. The results showed that the children in the probiotics group were more likely to have no pain than those in the placebo group (25 versus 9.6%).</td>
<td>Gawrońska et al. 2007</td>
</tr>
</tbody>
</table>
have been suggested to represent the most important prebiotic dietary factor in human milk, promoting the development of a beneficial intestinal microbiota [Bode 2006]. When oligosaccharides are consumed, the undigested portion serves as food for the intestinal microflora. Two common supplemental sources are fructo-oligosaccharides (FOS) and inulin. FOS, which are found in many vegetables, consist of short chains of fructose molecules. Inulin has a much higher degree of polymerization than FOS and is a polysaccharide. FOS and inulin are found naturally in Jerusalem artichoke, burdock, chicory, leeks, onions, and asparagus. FOS products are derived from chicory root that contain significant quantities of inulin. Inulin is considered a soluble fiber. As a soluble dietary fiber, inulin also shortens fecal transit time, slightly increases fecal bulk, reduces constipation, has been shown to reduce both serum and hepatic cholesterol and triglycerides, and may provide improved absorption of minerals such as calcium, magnesium, iron, and phosphate. Furthermore, unlike FOS, inulin’s longer chain length makes it more easily tolerated by the human intestinal system [Tokunaga, Oku, and Hosoya 1986]. Other benefits noted with FOS or inulin supplementation include increased production of beneficial SCFAs.

Regarding SCFAs, about 60 g of carbohydrate is fermented by the bacteria each day to SCFAs, which are rapidly absorbed. The SCFAs produced include acetic acid, propionic acid, and butyric acid. These acids have important actions in the colon and in the body as a whole. Acetic acid is an energy source for the body and is a substrate for fat synthesis in the liver. Propionic acid is also an energy source for the liver, is gluconeogenic (i.e., can be used to make glucose), and may reduce cholesterol synthesis. Butyric acid is the major fuel for colonic cells and has been shown to stimulate differentiation and programmed cell death of cancer cells. SCFA enemas have been used effectively in the treatment of ulcerative colitis [University of Glasgow 2005]. SCFAs produced in the colon increase cell proliferation throughout the whole gut. SCFAs are also very important because they promote water absorption and prevent osmotic diarrhea. SCFAs inhibit the growth of pathogenic bacteria [University of Glasgow 2005].

Another supportive factor in modulation of healthy microbiota is lactoferrin. Research shows that supplemental lactoferrin modulates the release of messenger proteins known as essential nutrients, trypsin, and protease inhibitors that protect it from destruction in the GI tract [Orsi 2004]. It is also rich in antioxidants, and its receptors have been found on most immune cells, including lymphocytes, monocytes, macrophages, and platelets [Orsi 2004]. Its presence in neutrophils suggests that lactoferrin is also involved in phagocytic immune responses [Lonnerdal and Iyer 1995]. Because of its iron-binding properties, lactoferrin has been proposed to play a role in iron uptake by the intestinal mucosa [Legrand et al. 2005].

Because it strongly binds iron, lactoferrin supports healthy modulation of gut microflora and assists the attachment of beneficial bacteria to the intestinal wall [Legrand et al. 2005]. Lactoferrin may support healthy development and differentiation of T lymphocytes. Preliminary research suggests that it supports the healthy production of cytokines and lymphokine, such as TNF-α and IL-6 [Ward, Paz, and Conneely 2005]. More recently, lactoferrin receptors have been found in both a variety of immune system cells, including natural killer cells, and intestinal tissue [Legrand et al. 2005; Ward, Paz, and Conneely 2005]. This discovery demonstrates that supplemental lactoferrin might have a profound impact on immune health.

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To be effective, however, supplemental lactoferrin must be digested in the small intestine. Breast milk has a multitude of biological activities benefiting the newborn infant. To reach the small intestine (in which nutrients are digested and released into the infant’s bloodstream), the nutrients must be able to withstand exposure to stomach fluids. Although the pH of an infant’s stomach fluids rarely dips below 4–5 for the first six months of life, the pH of an adult’s gastric fluids ranges between 1 and 2. This high acidity is lethal to lactoferrin. Therefore, just as probiotics need protection to survive the normal GI fluids of the stomach, so do lactoferrins [Orsi 2004].

**SOURCES OF PROBIOTICS**

There are many sources available from food to dietary supplement liquids and pills. Bacteria must be viable in storage and viable in delivery to the intestines. To date, scientists have shown that, as a result of manufacturing processes, storage environment, and inhibition through the digestive tract, many products are not delivering label claims.

Probiotic supplements need to be protected from the environment. They cannot be exposed to air, sunshine, artificial light, or moisture [The Centers for Disease Control 2008]. In addition, probiotics bacteria need to be protected from the digestive juices and enzymes in the stomach [Collado, Meriluoto, and Salminen 2007b]. Research has shown as much as 90% of a supplemented probiotic is destroyed in stomach gastric secretions and/or 50% loss in exposure to environment in storage.

**ENTERIC COATING OF PROBIOTICS**

Enteric coating of probiotics is intended to allow the passage of a tablet or capsule through the gastric fluids of the stomach to prevent the release of product contents before it reaches the intestines. However, because of the complexities involved with applying an enteric coating on a tablet or capsule, some enteric coatings do not entirely inhibit stomach acid from entering the encapsulation. As a result, stomach acid can interact with the sensitive bacteria, leading to a significant decrease in viability. In addition, the enteric coating manufacturing process frequently uses solvents such as methacrylate copolymers. The tablets and capsules are sprayed with these solvents at high temperatures to create the enteric coating. This type of application further exposes microbes to conditions that can dramatically reduce the product shelf-life. There is a new technology used in protecting viable ingredients that is a patented, encapsulation technique, known as True Delivery™ Technology, which results in a product that is stable at room temperature for up to 18 months. Additionally, the unique coating protects the bacteria from harsh stomach acid so they can be released live and intact in the intestines, in which they need to arrive in live form to perform their beneficial function. Research may show that other methods support viability; for example, combining strains with specific fibers to buffer
the probiotic from stomach acidity has shown some results. However, to date, the patented encapsulation has demonstrated the best effects on stability and protection. The important factors related to probiotics stability are as follows:

- Stable: guaranteed to deliver live, intact probiotics throughout product shelf-life, not just at time of manufacture
- Protected: protects the probiotics from harsh stomach acid
- Effective: contains clinically studied probiotics bacteria and has been shown to colonize in the intestines

OTHER TYPES OF PROBIOTICS

Probiotics are defined as live microorganisms that confer a health benefit on the host. Although most probiotics are bacteria, one strain of yeast, *Saccharomyces boulardii*, has been found to be an effective probiotics in double-blind clinical studies. Studies in areas of antibiotic include diarrhea, traveler’s diarrhea, acute diarrhea in children, recurrent clostridium difficile-associated diseases, and IBDs. *S. boulardii* does not colonize in the intestines but will be eliminated in stool within five to seven days after usage is discontinued. Because of this being a noncolonizing strain that is not naturally present in human gut flora, questions are highlighted regarding its long-term safety of this or any other non human strain of bacteria being introduced to the human gut flora. *S. boulardii* is administrated to patients in a lyophilized form, and the treatment is well tolerated. However, some rare cases of *S. boulardii* fungemias have been reported in patients with an indwelling central venous catheter [Kotowska, Albrecht, and Szajewska 2005; Llanos et al. 2006]. The origin of the fungemia is thought to be either a digestive tract translocation or a contamination of the central venous line by the colonized hands of health workers [Kotowska, Albrecht, and Szajewska 2005]. This raises the question of the risk-benefit ratio of *S. boulardii* in critically ill or immunocompromised patients. Thus, administration of *S. boulardii* should be contraindicated for patients of fragile health, as well as for patients with central venous catheter [Herbrecht and Nivoix 2006].

SOME INTERESTING CLINICAL APPLICATIONS OF PROBIOTICS

Probiotics, Infection, and Immunity

The review by Macfarlane et al. [2002] summarizes the most recent contributions to this rapidly developing area. Probiotic bacteria, mainly *Bifidobacteria* and *Lactobacilli* for historical reasons, can prevent or ameliorate some diseases. Many empirical studies have been done, but work to develop the ideal characteristics of probiotics lags behind. Current literature covers survival of probiotics in the gut, mucosal adherence, antibacterial/pathogen mechanisms, effects on immune function, and clinical studies. Probiotics bacteria are effective in preventing and reducing the severity of acute diarrhea in children. They are also useful in antibiotic-associated
diarrhea, but not for elimination of *Helicobacter pylori*. In IBD, especially ulcerative colitis, probiotics offer a safe alternative to current therapy. Probiotics have been used to prevent urogenital tract infection with benefit and, perhaps more intriguingly, to reduce atopy in children. Probiotics do not invariably work, and study of mechanisms is urgently needed.

**The Potential Role of Probiotics in Pediatric Urology**

The research paper by Reid [2002] studied the potential role that probiotics therapy may have in pediatric urology. Many children around the world die of diseases, such as GI infection and HIV, whereas many have urinary tract infections that subsequently recur frequently in adulthood. Until recently, the role of intestinal and urogenital (vaginal, urethral, and perineal) microflora in health and disease has received scant attention. The data available in the literature on this topic were examined, and a personal viewpoint is presented on how they may relate to urology. There is mounting evidence that certain strains of *Lactobacilli* and *Bifidobacteria* have a major part in the maintenance and restoration of health in children and adults. Implications for pediatric urology include a decreased risk of infection and stone disease as well as possible positive effects on preventing and managing inflammatory and some carcinogenic diseases.

**High-Dose Oral Bacteria Therapy for Chronic Nonspecific Diarrhea of Infancy**

Balli et al. [1992] evaluate the effectiveness of oral bacteriotherapy using a combination of anaerobe fecal *Lactobacilli* for chronic, nonspecific diarrhea of infancy. A double-blind study was performed in a total of 40 children treated with low and high doses of bacteria. The results confirm the importance of fecal flora in this disease and support the hypothesis that oral bacteriotherapy can improve clinical and laboratory presentation, especially when given at high doses.

**Bifidobacteria and Lactobacilli in Human Health**

The gastrointestinal microflora is a complex ecological system, normally characterized by a flexible equilibrium [Orrhage and Nord 2000]. The most important role of the microflora, from the point of view of the host, is probably to act in colonization resistance against exogenous, potentially pathogenic, microorganisms. *Bifidobacteria* and *Lactobacilli* are gram-positive, lactic-acid-producing bacteria constituting a major part of the intestinal microflora in humans and other mammals. Administration of antimicrobial agents may cause disturbances in the ecological balance of the GI microflora, with several unwanted effects such as colonization by potential pathogens. To maintain or reestablish the balance in the flora, supplements of intestinal microorganisms, mainly *Bifidobacteria* and *Lactobacilli*, sometimes called probiotics, have been successfully used. This article reviews the role of *Bifidobacteria* and *Lactobacilli* in human health.
Live Probiotics Protect Intestinal Epithelial Cells from the Effects of Infection with Enteroinvasive Escherichia coli

The colonic epithelium maintains a lifelong, reciprocally beneficial interaction with the colonic microbiota. Disruption is associated with mucosal injury. Resta and Barret [2003] proposed that probiotics may limit epithelial damage induced by enteroinvasive pathogens and promote restitution. Human intestinal epithelial cell lines (HT29/c1.19A and Caco-2) were exposed to enteroinvasive E. coli (EIEC 029:NM) and/or probiotics (Streptococcus thermophilus [ST], ATCC19258; and LA, ATCC4356). Infected cells and controls were assessed for transepithelial resistance, chloride secretory responses, alterations in cytoskeletal and tight junctional proteins, and responses to epidermal growth factor stimulation. Exposure of cell monolayers to live ST/LA, but not to heat inactivated ST/LA, significantly limited adhesion, invasion, and physiological dysfunction induced by EIEC. Antibiotic killed ST/LA reduced adhesion somewhat but were less effective in limiting the consequences of EIEC invasion of cell monolayers. Furthermore, live ST/LA alone increased transepithelial resistance, contrasting markedly with the fall in resistance evoked by EIEC infection, which could also be blocked by live ST/LA. The effect of ST/LA on resistance was accompanied by maintenance (actin, zona occludens-1) or enhancement (actinin, occludin) of cytoskeletal and tight junctional protein phosphorylation. ST/LA had no effect on chloride secretion by themselves but reversed the increase in basal secretion evoked by EIEC. EIEC also reduced the ability of epidermal growth factor to activate its receptor, which was reversed by ST/LA. Live ST/LA interact with intestinal epithelial cells to protect them from the deleterious effect of EIEC via mechanisms that include, but are not limited to, interference with pathogen adhesion and invasion. Probiotics likely also enhance the barrier function of naive epithelial cells not exposed to any pathogen.

Breakdown of Lactose

Lactose is an important sugar that is converted to lactic acid by lactic-acid-producing bacteria, such as Lactobacillus acidophilus and Bifidobacterium longum [Marteau, Vesa, and Rambaud 1997]. Impaired conversion of lactose to lactic acid can result in symptoms such as occasional gas, bloating, and indigestion, attributable to accumulated non-absorbed lactose in the GI tract [DeSimone et al. 1992; Garman, Coolbear, and Smart 1996 et al]. Lactic acid bacteria can help metabolize the non-absorbed lactose in the GI tract and therefore reduce symptoms of lactose intolerance. In a randomized, controlled clinical trial, Bifidobacterium longum was shown to support the breakdown of lactose and reduce flatulence [Lactose 2008].

Immune System Support

Although a normal microflora is associated with good health, changes in intestinal health are associated with altered immune function. A well-functioning GI immune system mediates immune responsiveness at mucosal sites and throughout
the entire body via the control of the quality and quantity of foreign substances
gaining access to the immune system [Schrirrin et al. 1997]. Lactobacillus acidophi-
lus and Bifidobacterium longum have been shown to possess immunoprotective
and immunomodulatory properties. These benefits include modulation of cytokine
and various IL production, autoimmunity, natural killer cell cytotoxicity, lympho-
cyte proliferation, and antibody production. In an open, randomized, controlled trial,
Lactobacillus acidophilus and Bifidobacterium bifidum were supportive of colon
health in older adults. In addition, B cell (important antibody producing immune
cells) levels increased compared with the untreated group. The probiotics were very
well tolerated, with no significant side effects or variations in clinical chemistry or
hematologic parameters [Gibson et al. 1997].

Decrease Occasional Constipation

Constipation is defined as infrequent or difficult defecation that can result from
decreased motility of the intestines. It is a common problem, particularly in older
adults. When the feces remain in the large intestine for prolonged periods, there is
excessive water absorption, making the feces dry and hard [Garman, Coolbear, and
Smart 1996]. Lactobacillus acidophilus and Bifidobacterium longum promote regular
bowel movements by contributing to the reestablishment of healthy intestinal fl-
ora and stimulation of intestinal peristalsis via lactic acid production [Bennet and Eley 1976].

Support of Putrefactive Processes

When unbalanced conditions are present in the intestines (i.e., unbalanced diet,
high acidity, and/or low levels of lactic acid bacteria), organic matter may be putrifi-
(decomposed or rotting) by certain bacteria and produce undesirable compounds
[Gibson et al. 1997]. Probiotics promote homeostasis (balance) in both the intestine
and the vagina [Hilton et al. 1992; Witsell et al. 1995]. These activities are car-
rried out via support of direct production of antibodies, competition with adhesion to
intestinal cells, or indirect modulation of the immune system. Probiotics also support
a healthy yeast balance [On-line Medical Dictionary 2000].

Support Digestion

Normal microflora of the large intestine help support and complete digestion via
fermentation [Wagner et al. 1997]. Oral ingestion of probiotics produces a stabilizing
effect on the gut flora.

Additional Benefits

The benefits of probiotics extend beyond digestion support and immune support.
Lactobacillus acidophilus and Bifidobacterium longum also help support the better
utilization and bioavailability of nutrients, including vitamins, minerals, proteins,
fats, and carbohydrates [Witsell et al. 1995].
REFERENCES


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