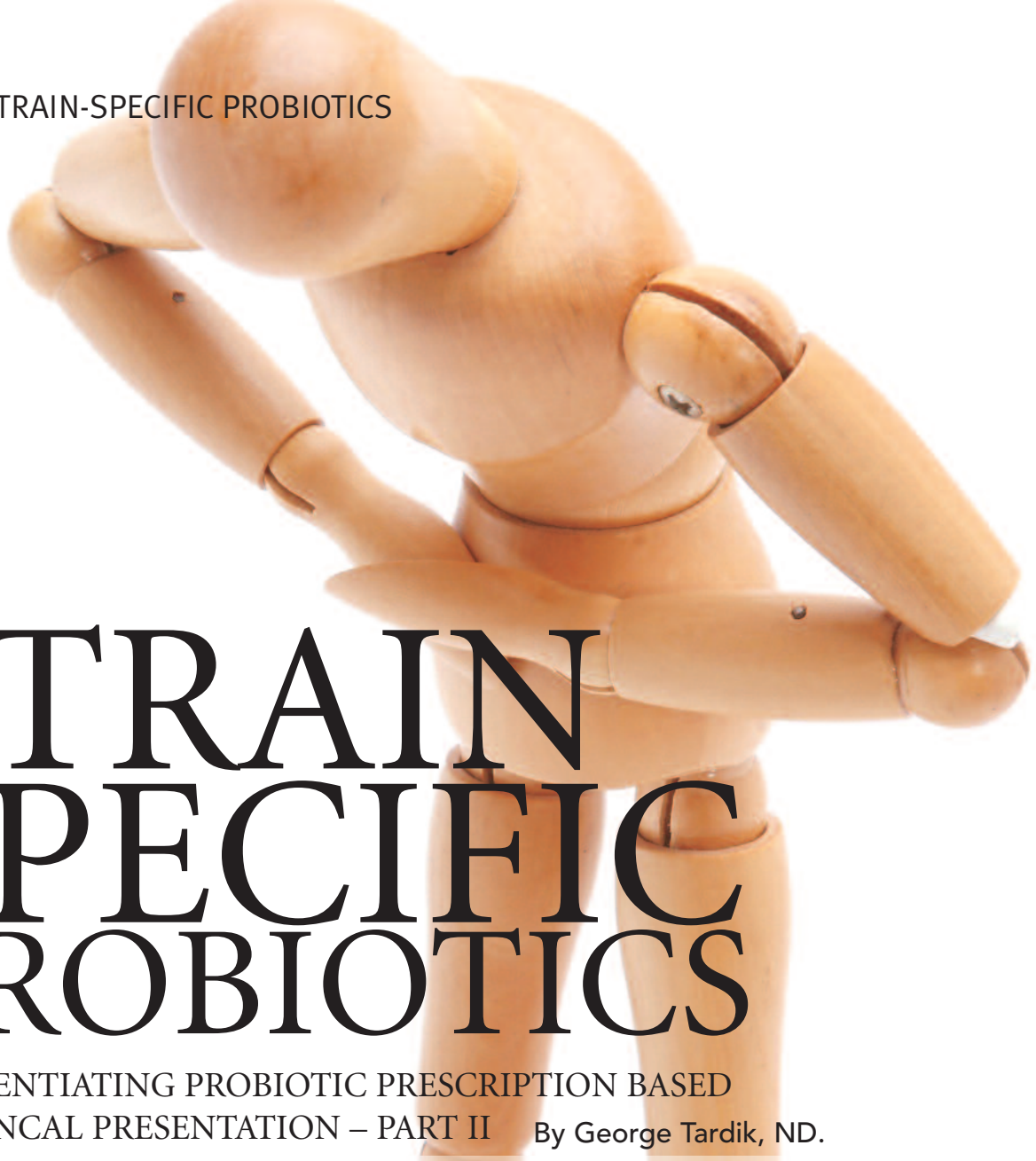

STRAIN SPECIFIC PROBIOTICS

DIFFERENTIATING PROBIOTIC PRESCRIPTION BASED ON CLINCAL PRESENTATION – PART II

By George Tardik, ND.

Mild acute diarrhea can be caused by a number of conditions, including a change in dietary habits, food allergies and taking antibiotics. Serious, acute diarrhea can be caused by a variety of viruses, bacteria and parasites, including rotavirus, E.Coli (0157:H7), Salmonella and Giardia lamblia.

Rotavirus is the most common cause of severe diarrhea for infants and young children in North America. Illness from rotavirus usually starts with fever, upset stomach and vomiting, followed by diarrhea. The diarrhea can be mild to severe and generally lasts three to nine days. High concentrations of virus remain in the stool for 10 to 12 days after the symptoms begin in otherwise healthy children. Severe diarrhea and dehydration occur primarily among children three to 35 months of age. Children can spread rotavirus both before and after they show signs of being sick. The virus is extremely contagious, often transmitted from one infected child to another by contaminated hands or objects (CDC 1992).

PROBIOTICS AND TREATMENT OF ACUTE DIARRHEA IN CHILDREN

Probiotics have been extensively studied in the treatment and prevention of infectious gastroenteritis. The most convincing evidence of decreasing symptom duration is in the pediatric population, specifically in the treatment of mild to moderate rotavirus diarrhea that has been treated with oral rehydration therapy (ORT) in association with Lactobacillus GG (*Lactobacillus Casei strain sp. Rhamnosus – LGG*). (Guandalini 2000, Isolauri 1991 Kaila 1992, Szajewska 2001, Szymański 2006)

LGG has the ability to significantly decrease the duration of diarrhea in children either as a nutraceutical (supplement) or as a functional food (in fermented milk), early in the course of the condition (Guandalini 2000, Isolauri 1991).

Lactobacillus reuteri has demonstrated similar results in children by reducing the duration of illness (Rosenfeldt 2002). Two controlled trials with *Sacromyces boulardii* ameliorated purge

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during acute diarrheal illness (Billoo 2006, Kurugol 2005, Villarruel 2007). For infant acute diarrhea that is non-rotavirus in origin, Lactobacillus Paracasei (*Lactobacillus F19*) ST11 has shown significant inhibition of watery diarrhea in hospitalized infants. This same strain is not effective for rotavirus associated diarrhea (Sarker 2005).

PREVENTION OF DIARRHEAL DISEASE IN CHILDREN

Clinicians often suggest probiotics to children as "ongoing prevention." The specific population of children where this is most applicable are non-breastfed infants.

Regular consumption of S. Thermophilous over several weeks and months has been shown to decrease diarrheal disease in chronically hospitalized children (Mastretta 2002). This has also been shown using Lactobacillus Casei GG in underprivileged periurban areas. However, children in the trial that were breastfed had little or no preventative influence from prophylactic probiotics in diarrheal disease rates (Mastretta 2002).

PROBIOTICS AND ANTIBIOTIC-ASSOCIATED DIARRHEA DISEASE IN CHILDREN (AADD)

AADD is defined as an otherwise unexplained diarrhea occurring in association with antibiotic administration. AADD occurs in 5-30% of the general population during antibiotic treatment (Szajewsk 2006). Almost all antibiotics, particularly those against anaerobes, can cause diarrhea. However, the risk seems higher in those using aminopenicillins, cephalosporins and clindamycin.

Some strains of probiotics are associated with a decrease risk of AADD. Sacromyces boulardii has been shown to be highly successful in treating AADD in a recent Meta analysis (Szajewsk 2006). S. boulardii has been shown to live at optimal temperatures of 37C, resists digestion, and reaches the colon in a viable state. S. boulardii has also been shown to be inhibit recurrence rates of C. Difficile infection.

The notion that probiotics should not be consumed simultaneously with antibiotics is false. Antibiotics can severely disrupt gut microbial ecology. Ingestion of a probiotic with a prescribed antibiotic can reduce the effect of such microbial alteration and any resulting changes in stool consistency and frequency.

Several controlled studies have evaluated the efficacy of several agents in the management of non–C. difficile, antibiotic associated diarrhea. Agents used included: Enterococcus faecium SF68, Lactobacillus GG, Lactobacillus acidophilus, L. bulgaricus and S. boulardii and L. Sporogenes. In general, these agents reduced negative changes in bowel habits, decreasing changes in stool consistency and the duration of loose stools associated with antibiotic use (Szajewsk 2006).

PROBIOTICS AND PREVENTION OF ANTIBIOTIC RESISTANCE

Probiotics may also be of direct use in preventing antibiotic resistance. The use of beta-lactam antibiotics can induce an increase in beta-lactamase production in the fecal flora, thereby increasing bacterial resistance to other beta-lactam drugs (Zoppi 2001).

Zoppi et al evaluated 51 children (25 female, 26 male; mean age, 5.1 years) admitted to the hospital for febrile respiratory tract infections. Ceftriaxone (cephalosporin AB) 50 mg/kg per day was administered parenterally alone (Tx 1) or with one of the following probiotic/prebiotic preparations: *Saccharomyces boulardii* (Tx 2); *Enterococcus* species (Tx 3); lactulose (Tx 4); *Lactobacillus casei* GG (Tx 5); *Lactobacillus rhamnosus, Lactobacillus bifidus*, and *Lactobacillus acidophilus* (Tx 6); *Bifidobacterium bifidum* and *L acidophilus* (Tx 7); or a mixture of various lactobacilli and bifidobacteria at high concentrations (Tx 8) (Zoppi 2001). A lower incidence of beta-lactamase positive samples (30–40%) was observed with *B. bifidum* and *L. acidophilus*, or a mixture of various lactobacilli and bifidobacteria at high concentrations groups only (TX 7,8).

This data indicates very high concentrations of probiotic (20 billion to 360 billion per day) are necessary to restore the balance of the intestinal ecosystem during antibiotic therapy. In addition to the reduction of beta-lactamase (30-40%) in the high dose group (Tx 8 – 360 billion mixed lactobacilli and bifidobacteria) there was trend towards increased Beta-glucuronidase activity in the lower probiotic groups, but not in the higher dosage groups (Tx 7, 8). *Beta-glucuronidase* is an inducible enzyme elaborated by anaerobic E. coli, Bacteroides, and Clostridia. Increased activity of this enzyme has been implicated in increased enterohepatic recirculation of toxins, steroid hormones, drugs, and carcinogens. Ordinarily, toxins, hormones and drugs are excreted from the body after being conjugated to a glucuronide molecule. By uncoupling glucuronides in the intestine, beta-glucuronidase can deconjugate potential toxins, increasing the formation of carcinogens in the bowel and promoting the enterohepatic recirculation of toxins, hormones and various drugs in the body (Macfarlane 1999).

HIGH DOSAGE AND AADD

High dosage of other probiotics has been reported to be vital in proper colonization of the G.I. tract with various other strains of probiotics. Most research in humans has utilized one billion to 40 billion CFUs (Colony forming units) per day. It has been suggested that doses at the lower end of this range might not colonize the intestine.

Zoppi et al hypothesized that low dosages in a variety of trials may be responsible for the clinical, and thus statistical, heterogeneity of probiotic research related to antibiotics and diarrhea. Studies utilizing 5- 40 Billion single strain probiotics (LGG, L. Sporogenes and Sacchromyces) display strong evidence for a preventative effect of antibiotic associated diarrhea. Five billion CFUs daily has been suggested to be the lowest dosage required to prevent AADD.
For clinicians contemplating the use of probiotics in their pediatric practice, the use of Lactobacillus GG, L. sporogens, S. boulardii or

mixed Lactobacilli at a dose of 5–40 billion CFUs per day appears to hold promise in co-administration with antibiotics. Research of one billion CFUs gives less predictable outcomes.

ANTIBIOTICS AND CLOSTRIDIUM DIFFICILE DIARRHEA (ADULTS)

The use of certain antibiotics, specifically Clindamycin, Cephalosporins, and Penicillins, can cause Clostridium difficile-induced diarrhea. Not uncommon in the healthy intestinal tract, C.difficile can be abnormally high after antibiotic use, which may cause disruption of the indigenous microbiota. This abnormal elevation of C. difficile and subsequent symptoms are related to toxin production (protein exotoxins, toxin A and toxin B). C. difficile can have serious consequences, particularly in the elderly and debilitated; these include pseudomembranous colitis, toxic megacolon, intestinal perforation and death. Standard treatment of C. difficile–associated intestinal disease involves either Vancomycin or Metronidazole. 25% of patients relapse with disease once treatment is discontinued (Levett 1991).

TREATMENT OF CLOSTRIDIUM DIFFICLE WITH PROBIOTICS AND ANTIBIOTIC THERAPY

Multiple relapses of C. difficile can occur and the relapses can be more severe than the original disease. The mechanism of relapse is unknown, but is probably due to the survival of C.difficile spores in the intestinal tract until the antibiotic is discontinued (Levett 1991).

In a placebo-controlled study, McFarland et al examined antibiotic therapy (metronidazole or vancomycin) with co-administration of S. boulardii or placebo in 124 adult patients. 64 patients had an initial episode of C. difficile disease and 60 patients had a history of at least one prior episode of C. difficile disease (McFarland 1994).

The researchers found that in patients with an initial episode of C. difficile, no significant difference in recurrence rates of C. difficile disease were observed in the placebo versus the S. boulardii groups. However, in patients with a prior C. difficile infection, S. boulardii significantly inhibited further disease recurrence. The researchers concluded that in combination with standard antibiotics, S. boulardii is an effective and safe therapy for patients with recurrent C. difficile (Mcfarland 1994).

TRAVELLER'S DIARRHEA (TD)

The treatment of TD yields conflicting data. Variance of location, infectious organisms, and heterogeneity of the populations studied are likely contributors to the conflicting nature of available evidence.

Acute diarrhea occurs in approximately half of the travellers visiting high-risk areas. Most cases are mild and self-limiting but there is a considerable morbidity. Antibiotics are effective prophylaxis, but are not recommended for widespread use and thus probiotics serve as a viable treatment alternative. Several studies have been performed with the use of probiotics in TD. Various trials have evaluated S. boulardii with only one trial showing significant benefit (Oksanen 1990, Hilton 1997). It is interesting that S. boulardii seems to have stronger effects on bacterial diarrhea, whereas Lactobacillus GG (LGG) has been shown to be more effective against viral and idiopathic diarrhea (Katelaris 1995, Szajewska 2006). More research is needed in this area.

PROBIOTICS AND URINARY TRACT INFECTIONS (UTI)

Specific lactobacilli strains have the ability to interfere with the adherence, growth and colonization of the urogenital human epithelium. This interaction is important in the maintenance of a normal urogenital flora and in the prevention of infections. Genitourinary infections in women are often characterized by an alteration in the local flora from predominance of lactobacilli to coliform uropathogens as a result of hormone deficiency, sexual activity, contraceptive measures and other factors (Colodner 2003).

Lactobacillus species have been studied for their probiotic potential, based on their metabolic production of lactic acid from sugars. However, not all species of Lactobacilli colonize the vaginal tract and a variance of adhesion to vaginal epithelial cells of different lactobacilli are responsible for the variable results in humans. For example, the very well studied *L. rhamnosus* GG has very poor adhesion to vaginal epithelial cells, exemplified in a trial in 2003 by Colodner et al. 42 post-menopausal healthy women were given one to two doses of yogurt containing *L. rhamnosus* GG daily for one month (10 billion cells). The cultures of vaginal fluid specimens showed only 9.5% (4 of 42) of the studied women were colonized with *L. rhamnosus* GG (Colodner 2003). The authors suggested that *L. rhamnosus* GG based on its poor colonization in the vaginal tract may not be an effective probiotic agent in preventing UTIs. In a review of other trials using L. rhamnosus GG in suppositories with active UTI failed to reduce symptoms, and there was no difference in periurethral colonization counts of lactobacilli in either treated or control groups (Falagas 2006).

Positive outcome trials evaluating vaginal colonization in humans have focused on oral or intravaginal therapy with combination *L. rhamnosus* GR-1 and *L. reuteri RC-14* (previously called L. fermentum RC-14). The use of oral formulations of these strains has been associated with normalization of vaginal lactobacilli within 28-60 days of treatment (Cadieux 2002). The best illustration of the long-term preventative effects of these strains was by Reid et al, 1995. The researchers evaluated women with a history of UTI. Once-weekly, 25 subjects administered a vaginal suppository containing 101 *L. rhamnosus* GR-1 and *L.Reuteri* RC-14 for 1 year. Rate of UTI infection was decreased from a pretreatment mean of six infections per year to a mean rate of 1.6 infections per year (Reid 1995).

L. rhamnosus GR-1 and *L. reuteri* RC-14 are the most effective among the studied lactobacilli for the prevention and treatment of recurrent UTI. L. casei shirota and L. crispatus CTV-05 have also shown efficacy in some studies (Cadieux 2002).

PROBIOTICS AND BACTERIAL VAGINOSIS (BV)

Some women with BV remain asymptomatic, however as many as 50-60% of patients with BV report the occurrence of malodorous

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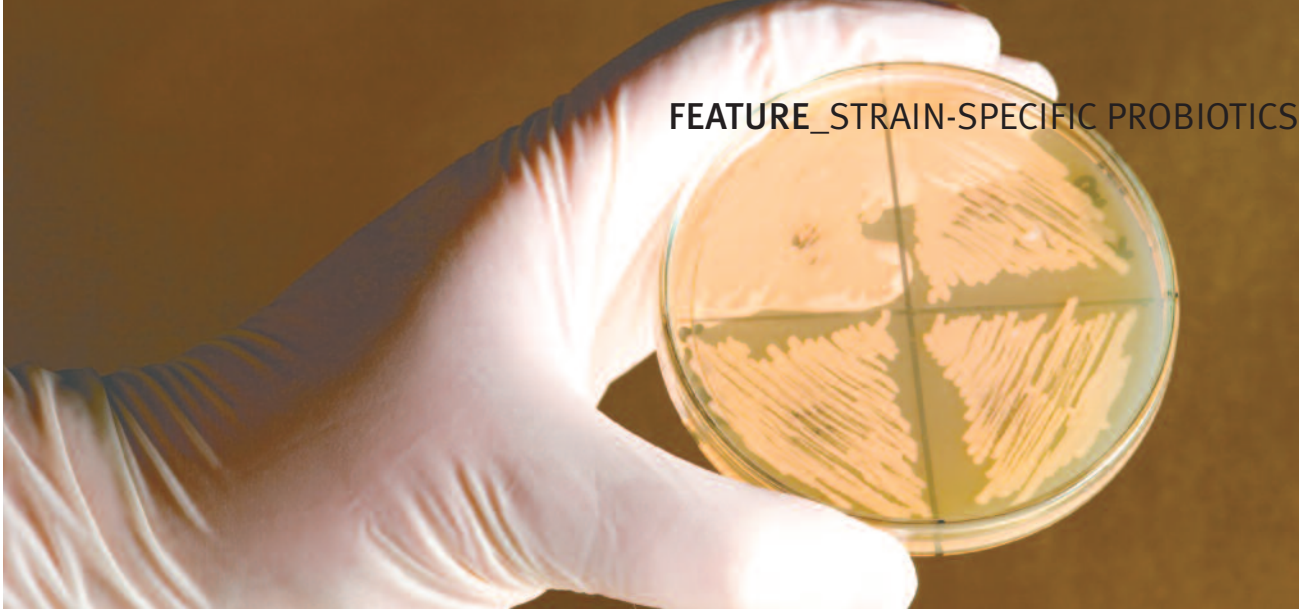

"fishy" vaginal discharge. A positive diagnosis is based on the presence of at least three of the following: presence of a thin greyish homogenous discharge; vaginal pH greater than 4.5; presence of clue cells on Gram stain; positive whiff test (detection/enhancement of fishy odour on addition of potassium hydroxide to the vaginal specimen).

In terms of preventing or treating BV similar clinical outcome is observed with the same strains used to treat UTI's (*L. rhamnosus* GR-1 and *L. Reuteri* RC-14). Several studies utilizing these strains have shown that daily ingestion of capsules containing *L. rhamnosus* GR-1 and *L. Reuteri* RC-14 in women with a BV microbiota resulted in a normal microbiota (Reid 1994, Reid 2001, Reid 2001a, Reid 2003)

HELICOBACTER PYLORI AND PROBIOTICS

Helicobacter pylori (H. pylori) infection is a major cause of chronic gastritis and peptic ulcer disease, and it is also designated as a class-I carcinogen for stomach cancer. The role of probiotics in the treatment of gastrointestinal infections is increasingly documented as a complement to antibiotics, with the potential to increase the effectiveness of antibiotic therapy and decrease their adverse effects.

Several strains of probiotics have been studied to access their ability to eradicate H. pylori or be co-administered with antibiotic therapy. The Lactobacillus species have been the focus of many clinical trials as they have the ability to

TABLE 1: STRAIN- SPECIFIC CLINICAL APPLICATIONS OF PROBIOTICS

INDICATION	PROBIOTIC STRAINS
Acute diarrhea in children	*First Line - Rotavirus* Lactabacillus GG (Lactobacillus Casei strain sp. Rhamnosus – LGG) Lactobacillus reuteri *First line – Non Rotavirus* Lactobacillus Paracasei (Lactobacillus F19)
Prevention of diarrhea in Non-breast fed children	*First line* Lactabacillus GG
Antibiotic-associated diarrhea disease in children (AADD)	*First line* S. boulardii *Second line* Enterococcus faecium SF68, Lactobacillus GG, L. acidophilus, L. bulgaricus and L. Sporogenes.
Prevention of antibiotic resistance (children using greater than 3 courses of AB/year)	*First line* (high dose of a mixture 5-40 Billion CFU during and one month after AB) Lactobacillus acidophilus Lactobacillus bifidus Bifidobacterium bifidum Lactobacillus casei GG *The addition of L. sporogens or S. boulardii could be added to the above mixture.*
Recurrent C. difficile in Adults	*First line* S. boulardii
Travellers diarrhea (TD)	**Conflicting research (based on available)** S.boulardi
Urinary tract infections positive data)	*First line* L. rhamnosus GR-1 and L. reuteri RC-14 ***Second line*** L. casei shirota and L. crispatus CTV-05
H.Pylori	*First line* **Adults** L. johnsonii La1 L. brevis (CD2) Lactobacillus gasseri OLL2716 (LG21) L. Reuteri **Children** L casei DN-114 001

tolerate low pH and transiently reside in the stomach. Several animal trials have displayed a variety of mechanisms by which Lactobacilli inhibit H.Pylori. Induction of cell autolysis, lactic acid mediated suppression and inhibition of H.pylori binding to the glycolipid receptors in gastric mucosa.

Michetti et al, compared *L. johnsonii La1* plus omeprazole, or *L. johnsonii La1* with placebo. A marked decrease in urea breath test values was found in both groups. A six- week follow-up displayed low levels of H.Pylori after the treatment in the probiotic group, although biopsies showed persistent infection (Michetti 1999). Lactobacillus johnsonii La1 has been evaluated in other studies in children and adults, suggesting a decrease in bacterial load even in asymptomatic patients with H.pylori. Lactobacillus johnsonii La1 has also been studied in combination with clarithromycin with findings suggesting decreased *H pylori* density in the gastric antrum and corpus when compared with placebo, although it did not improve the eradication rate (Cruchet 2003, Gotteland 2003).

In a multi-centre prospective randomized double-blind controlled study of 86 symptomatic H. pylori-positive children, the addition of L casei DN-114 001 to standard treatment with omeprazole, amoxicillin, and clarithromycin led to improvement in H pylo*ri* eradication (84.6% versus 57.5% without probiotics) (Sykora 2005). Furthermore, *L. casei* was studied as a second-line therapy in patients resistant to an initial course of treatment for H pylori. An improvement in eradication rate over that seen with a 10-day course of quadruple therapy alone was observed (Kim 2003).

Lactobacillus gasseri OLL2716 (LG21) was evaluated for the treatment of helicobacter pylori infection in 31 subjects infected with the bacterium. The subjects ingested yogurt containing LG21 daily for an eight-week period. The [(13)C]urea breath test and assays of serum pepsinogens revealed a significant improvement following LG21 treatment. LG21 was thus determined to be effective in both suppressing H. pylori and reducing gastric mucosal inflammation (Sakamoto 2001).

In children, the addition of L casei DN-114 001 to standard treatment with omeprazole, amoxicillin, and clarithromycin led to improvement in H pylo*ri* eradication (84.6% versus 57.5% without probiotics) (Sykora 2005). Furthermore, *L casei* was studied as a second-line therapy in patients resistant to an initial course of treatment for H pylori. An improvement in eradication rate over that seen with a 10-day course of quadruple therapy alone was observed (Kim 2003)

A pilot study of *L. Reuteri* led to significant improvements of H.pylori symptoms in 40 H.Pylori positive subjects. *L. Reuteri* administration was followed by a significant decrease in the Gastrointestinal Symptom Rating Scale as compared to pretreatment value that was not present in those receiving placebo. L. *Reuteri* is capable of reducing frequency and intensity of antibiotic associated side effects during eradication therapy for H. pylori (Mukai 2002)

In summary, several lactobacillus species have shown efficacy at decreasing the bacterial load of *H pylori* in controlled trials, although their effect on eradication remains unclear. Probiotics may have an adjunctive role in reducing the side effects that are associated with traditional eradication therapy. ■

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