

# INTEGRATED HEALTHCARE PRACTITIONERS

Integrated Healthcare Practitioners' Dietary and Nutritional  
Supplement, and Herbal Remedies Management Program

Author: George Tardik, ND

SUCCESSFUL COMPLETION OF THE QUESTIONS AT THE END OF THIS PAPER HAS BEEN APPROVED FOR CONTINUING  
EDUCATION BY THE BDDT-N; 1 CREDIT PHARMACOLOGY, 1 CREDIT NUTRITIONAL MEDICINE

## STRAIN-SPECIFIC PROBIOTICS DIFFERENTIATING APPROPRIATE PROBIOTIC PRESCRIPTION BASED ON CLINICAL PRESENTATION

Gastrointestinal infections and their consequences are a common clinical problem encountered by all doctors. Presently, there is a very real concern that scientists will no longer be able to develop effective antibiotics at a sufficient rate to match the development of resistance to old antibiotics. Drug-resistant tuberculosis and invasive methicillin-resistant *Staphylococcus aureus* (MRSA) infections are two recent examples that may pose serious threats to global health. These factors have renewed interest in the possibility of deliberately feeding beneficial microorganisms to humans as an alternative to antibiotic therapy in gastrointestinal disorders.

This article focuses on human clinical evidence in the treatment and prevention of gastrointestinal disorders with probiotics. More specifically, it focuses on the specific probiotic strain(s) that are clinically applicable, depending on the gastrointestinal presentation. Not all probiotics deliver equivocal clinical outcomes, and the importance of species-specific applications has been well developed in scientific literature. The following review attempts to provide you with the most current evidence in terms of choosing probiotic strains based on clinical presentation.

### LACTOSE MALABSORPTION (ADULT AND PEDIATRIC)

Lactose malabsorption is a concern for a large proportion of the world's population for whom lactose acts as an osmotic, non-digestible carbohydrate due to a low amount of intestinal B-glucosidase (lactase). The prevalence ranges from 7-20% in Caucasians, 50-85% in African-Asians and anywhere from 90-100% in Asians (Scrimshaw 1988).

The hydrogen breath test is the gold standard for diagnosing lactose intolerance. A lactose dose of 25-50 g is given after an overnight fast. A rise of 20 parts per million (ppm) of hydrogen over baseline suggests hypolactasia. The test has a specificity of 90% (Curigliano 2006).

In a 2005 systematic review, Levri et al concluded that overall probiotics were not successful in alleviating the signs and symptoms of lactose intolerance (Levri 2005). However, a closer examination of the specific studies in the review demonstrated some interesting findings. Of the studies that were successful in treating lactose intolerance in adults, all were using the following strains: *L. Bulgaricus* 449, *S. Thermophilus* and *L. Acidophilus* (Lin 1991, Lin 1998).

The positive results in some studies and no response in others might have to do with the specificity of the strains of bacteria utilized. For lactose intolerance, the implementation of a lactase-positive strain of bacteria appears to be most efficacious. Lactase-positive strains of bacteria have lactase producing properties and reveal positive outcomes for lactose intolerance in humans. They are the same non-pathogenic strains used in fermentation when culturing dairy foods (Sanders 1993). *Streptococcus thermophilus* may be the most important as it preferentially metabolized lactose over glucose in vivo.

*L. acidophilus* and *bulgaricus* metabolize both glucose and lactose. These strains, in addition to the removal of lactose from the diet, can aid in the management of lactose malabsorption in both adult and infants (Saltzman 1999, Shermak 1995).

### POUCHITIS

Pouchitis is inflammation of an internal pouch created in patients who have part of their colon removed to treat ulcerative colitis or familial adenomatous polyposis (FAP) (Ruseler 1994). Patients who have had the colon and rectum removed have a "pouch" that is surgically

made from a loop of the small intestine and serves in place of the rectum for the storage of stool. Sometimes, the lining of this internal pouch becomes inflamed and leads to the complication known as pouchitis (Ruseler 1994). The symptoms are similar to ulcerative colitis, which include diarrhea, abdominal pain (cramping), increased frequency of stool, bleeding, fever, dehydration and joint pain. The condition is normally managed with a short course of Metronidazole antibiotic therapy (Ruseler 1994). A higher incidence of pouchitis is reported in patients with immunologic skin disease, severe inflammatory joint disease, active smokers or those with a history of primary sclerosing (Gionchetti 2000).

Two randomized placebo-controlled trials were conducted to see if a combination of lyophilized bacteria – four strains of *Lactobacillus*, three strains of *Bifidobacterium*, and one strain of *Streptococcus* – known as VSL-3, would help with pouchitis symptoms. One trial found that after nine months, 85% of patients who took VSL-3 did not experience a relapse of pouchitis, while 100% of those in the placebo group experienced a relapse (Gionchetti 2000). In a second trial, 85% of those patients taking VSL-3 did not experience a relapse after one year of therapy. For those taking placebo, 94% experienced a relapse (Mimura 2004). The results of the two trials are remarkably similar, and provide significant support that probiotics may be helpful for individuals with pouchitis or recurrent pouchitis. Once again, the specific strains of bacteria are vitally important to patient outcome.

Other studies in patients with pouchitis utilized *Lactobacillus rhamnosus* GG, *L. acidophilus* and *B. lactis*, with no benefit over placebo (Kuisma 2003). Therefore, based on the available literature, VSL-3 has the highest clinical efficacy in treatment of pouchitis. Dosage of VSL-3 in the trials listed were at 6 g/day - 300 billion viable lyophilized bacteria per gram.

#### IRRITABLE BOWEL SYNDROME

Irritable bowel syndrome (IBS) is the most frequent GI concern in North America (11-14% of North Americans).

IBS is characterized by abdominal pain, flatulence and irregular bowel movements. The etiology is unclear but may include genetic susceptibility, along with behavioural and stress factors (Zuccotti 2008). The increased gas production is suggested to be associated with lower levels of lactobacilli and bifidobacteria colonies and increased anaerobic *Clostridium* species (Zuccotti 2008).

The use of probiotics in the treatment of IBS was controversial until Nobaek et al reported a definite statistical decrease in pain and other symptoms in patients that were treated with *Lactobacillus plantarum* 299V (Nobaek 2000). This was one of three placebo-controlled studies that has been performed with *L. Plantarum* 299V (Niedzielin 2001, Nobaek 2000, Sen 2002).

In the Nobaek trial, the most significant finding was the reduction in abdominal pain and flatulence, but no difference in bloating was observed with *L. Plantarum*. No concurrent medications were taken during the study and after a one year follow-up, the overall reported G.I. pain was significantly better in the probiotic group compared with the placebo group.

A significant decrease in abdominal pain and better overall GI function was also found by Niedzielin et al, in 40 patients using *L. Plantarum* (Niedzielin 2001). Conversely, a small study also using *L. Plantarum* with 12 untreated IBS patients could not find a significant effect (Sen 2002). Results with *Lactobacillus* GG have not demonstrated clinical efficacy over placebo in bloating-positive IBS patients (O'Sullivan 2000).

The multispecies probiotic VSL-3 was studied in 25 diarrhea-predominant patients in a controlled trial. The results displayed no difference in intestinal transit time or bowel function, but a significant reduction in abdominal bloating (Kim 2003). A second study by the same author used VSL-3 and included 48 bloating-predominant IBS patients. Findings included a significant decrease in flatulence and transit time, but no difference in abdominal pain and bloating (Kim 2005).

Larger studies by Saggiaro et al, treated 70 patients with *L. plantarum* plus *Bifidobacterium breve* (n = 24), *L. plantarum* plus *Lactobacillus acidophilus*

(n = 26) or placebo (n = 20) for four weeks, and found significant decreases in pain and the symptom scores in both probiotic-treated groups (Saggiaro 2004). In 2005, the eight-week consumption of *Lactobacillus salivarius* was compared with *Bifidobacterium infantis* and placebo in 77 IBS patients defined by the Rome II criteria. IBS, as defined by the Rome II criteria, is a syndrome lasting for more than three months, and may present either constipation or diarrhea associated with abdominal pain (O'Mahony 2005).

Although *L. salivarius* resulted in significantly improved bowel motility in comparison with placebo, the *B. infantis* group had significantly better scores for abdominal pain, bloating, bowel movement and overall GI function compared with both the *L. salivarius* and the placebo group (O'Mahony 2005).

It is difficult to speculate why *L. Plantarum* 299V may be so effective in the treatment of patients with IBS. Interestingly, *L. plantarum* 299V is known to synthesize nitric oxide by at least three pathways, and nitric oxide is an important mediator of gut motility (Zuccotti 2008). Other strains have also been efficacious in treating IBS. These include *Bifidobacterium infantis* 35624 and *Enterococcus faecium* PR88 (Hunter 1996, Zuccotti 2008).

#### INFLAMMATORY BOWEL DISEASE

Crohn's disease (CD) and ulcerative colitis (UC), collectively referred to as IBD, are chronic aggressive disorders with a prevalence of 0.1-0.5% in North America. The two disorders have distinct features. UC is characterized by inflammation with superficial ulcerations limited to the mucosa of the colon. Inflammation normally starts in the rectum and spreads continuously throughout the large intestine. CD, however, is characterized by a discontinuous pattern, potentially affecting the entire gastrointestinal tract. In contrast to UC, inflammation in CD patients is transmural with large ulcerations, and granulomas are occasionally observed. An exaggerated T-cell response causing mucosal hyper-responsiveness is thought to be an important factor driving inflammation in IBD. T-cells from the

lamina propria of CD patients respond with a Th1 polarized response; in UC patients, a preferential expression of Th2 cytokines IL-4 and IL-5 has been described (Zuccotti 2008).

A number of microbial agents are implicated as initiating factors in the pathogenesis of IBD. These include *Mycobacterium paratuberculosis*, measles virus, *Listeria monocytogenes*, paramyxoviruses and adherent *E. coli*. However, results implicating any single microorganism in the etiology of IBD are controversial (Zuccotti 2008). Although the results are not always consistent, more aerobes (especially *E. coli*) and anaerobes (*Bacteroides* spp.) and lower bifidobacteria and lactobacilli counts have been found in faecal samples of IBD patients in comparison with healthy volunteers (Borodo 2003).

Whether the changes in the intestinal bacterial composition of IBD patients are a cause or a consequence of the inflammation is not yet clear. However, possible manipulation of the indigenous intestinal microbiota as well as the immune system by probiotics provides the rationale for studying the effect of probiotics in IBD.

### ULCERATIVE COLITIS

Many clinical trials have administered *E. coli* strain Nissle 1917 to patients with UC. In a randomized, double-blind clinical trial with 120 UC patients by Kruis et al, oral administration of *E. coli* strain Nissle 1917 (0.2 g) as a maintenance treatment of remission showed no difference in relapse rates compared with patients on Mesalazine (Kruis 1997). Mesalazine, or 5-aminosalicylic acid (5-ASA), is an anti-inflammatory drug used to treat inflammation of the digestive tract (Crohn's disease) and mild to moderate ulcerative colitis.

*E. coli* Nissle 1917 has also been studied in active UC. Rembacken et al evaluated the clinical efficacy of *E. coli* Nissle 1917 and Mesalazine (Rembacken 1999). A total of 116 patients with active UC were recruited for this study, with 75% of the mesalazine group and 68% of the *E. coli* group achieving remission, respectively. The time to relapse was not significantly different between the groups (Rembacken 1999). Another trial,

this time a multicentered randomized, double-blind study of 327 patients assessing remission maintenance, evaluated *E. coli* Nissle 1917 against mesalazine. *E. coli* Nissle 1917 was shown to be as effective as mesalazine in maintaining remission rates. The authors state that, "*E. coli* Nissle 1917 offers an alternative to mesalazine in maintenance of remission in UC patients." (Kruis 2001).

Finally, a compelling study by Tsuda et al, administered four weeks of probiotics and achieved clinical and endoscopic improvements in 55% of patients with active UC refractory or intolerant to conventional therapy (Tsuda 2007). During the active phases of UC, there is limited data to support probiotics as monotherapy. However, the Tsuda trial is one of few that demonstrated clinical and endoscopic improvement accompanying changes of the intestinal microflora pattern in active UC. The strains administered were 2 mg *Streptococcus faecalis*, 10 mg *Clostridium butyricum* and 10 mg *Bacillus mesentericus* (Tsuda 2007).

### CROHN'S DISEASE (CD)

Crohn's disease (CD) is undoubtedly one of the most difficult inflammatory bowel diseases to treat for any clinician when in late stages. Although the data regarding CD in the literature is limited, some preliminary data suggests that probiotics have a role in treatment of CD in mild to moderate disease. However, this is one of the few areas where the possibility of doing harm with probiotics is a reality and should be approached with caution.

### CD - PROBIOTICS AND COADMINISTRATION WITH MEDICATION

Malchow et al, studied active CD patients and found a decreased relapse rate with *E. coli* Nissle 1917 (33%) vs. placebo (64%) when combined with anti-inflammatory medication. The trial focused on adjunctive use of a probiotic with standard prescription medications, and did not evaluate probiotics as a monotherapy (Malchow 1997).

In another trial of adjunctive probiotic use, Guslandi et al studied 32 inactive CD patients and found a decreased

relapse rate (33% vs. 64%) using *S. boulardii* plus mesalazine (2 g/day) vs. mesalazine alone (3 g/day) (Guslandi 2000).

### CD - INDUCTION OF REMISSION WITH PROBIOTICS

For the management of acutely active Crohn's disease, only a single randomized controlled trial exists. This study by Schultz and colleagues examined the effects of *L. rhamnosus* GG (LrGG) (Gionchetti 2000). Only 11 patients started the trial with six not completing the study. The results were understandably insignificant. Two open-label studies, one conducted in pediatric patients and assessing LrGG (Gupta 2000), the other using the probiotic *L. salivarius* UCC118, demonstrated clinical improvements in patients on medication therapy (Schultz 2004). Although these studies are promising, the relapsing/remitting nature of Crohn's disease makes specific inferences from this data difficult.

### CD - MAINTENANCE OF MEDICALLY INDUCED REMISSION

Data regarding maintenance of medically-induced remission are limited to three modest randomized, placebo-controlled trials. The first two trials, using *Escherichia coli* Nissle 1917 (EcN) and *L. rhamnosus* GG, were unable to demonstrate statistically significant results (Malchow 1997, Schultz 2004). However, the data was not entirely without promise. The study involving EcN had a strong positive – albeit nonsignificant – trend. The third of these trials examined the use of *Saccharomyces boulardii* (SB; 1 g per day – 20 billion cells), and showed higher remission rates in patients treated with this probiotic and mesalazine than with mesalazine alone (Guslandi 2000).

### POSSIBLE NEGATIVE OUTCOME IN CROHN'S WITH PROBIOTIC USE

In a study by Preantera et al, 45 patients operated on for CD were randomly allocated to receive 12 billion *Lactobacillus* GG or identical placebo for one year. Clinical recurrence was ascertained in 16.6% on *Lactobacillus* and in 10.5% on placebo. In a second trial, 60% of patients in clinical remission on *Lactobacillus* had

endoscopic recurrence in comparison with 35.3% on placebo (Prantera 2002). There were no significant differences in the severity of lesions between the two groups.

Setting aside the question of probiotic effectiveness, is their use absolutely safe? In CD, antigenic stimuli contribute to maintaining gut inflammation and any bacteria may become a stimulus. In two studies with LGG, recurrence rates were lower in the placebo groups than in the groups treated with probiotics (Bousvaros 2005, Riquelme 2003). The course of CD follows different phases and perhaps probiotics might be more effective in the early stages. Additionally, some case reports of infections caused by probiotics have been published (De Groote 2005, Riquelme 2003). Probiotic strains adhering to the intestinal mucosa could translocate, inducing bacteraemia and sepsis. This risk can increase for patients with severe disease or who are deeply immunocompromised.

In CD, enhanced mucosa permeability may play a pivotal role in causing and perpetuating intestinal inflammation (Hollander 1986). Therefore, it is possible

that administration of probiotics in the very early phases of CD may limit pathological damage and aggravation of symptoms by stabilizing the intestinal barrier. However, in late stages with severe damage to the mucosal barrier, certain strains of probiotics or "beneficial" yeasts may cause harm. Thus far, this is one of the only areas of concern with probiotic application for management of gastrointestinal disease.

#### SUMMARY

Probiotics represent a safe, effective, evidence-based strategy for management of several gastrointestinal ailments. In an effort to decrease reliance on antimicrobials, focus must shift to increase the exploration of the therapeutic applications of probiotics. Probiotics may be used to counteract local immunological dysfunction, to stabilize intestinal mucosal barrier function, to prevent infectious succession of pathogenic microorganisms and to influence intestinal metabolism.

In short, the dosages of key probiotics discussed in this article (*L. Plantarum*, *L. rhamnosus* GG, VSL-3, *S. Boulardii*,

*L. Reuteri*) were all delivered in controlled human trials at over 20 billion CFU. The dosage of VSL-3 in the above-listed studies were 450 billion to 1.3 trillion CFU. Large dosages, as described, appear to be needed for positive clinical outcome.

There are many advantages of probiotics over conventional therapy alone; relatively low cost, failure to contribute to antibiotic resistance, multiple mechanisms by which probiotics presumably inhibit pathogens, and absence of adverse effects (with the noted possible exception of advanced Crohn's disease). As either first-line therapy or adjunctive with standard prescription medications, probiotics have established themselves as a mainstay of several gastrointestinal presentations.

At times, a single strain can offer clinical advantage over multiple strains. With a growing amount of human data, it has become possible to apply specificity to selection of the probiotic chosen for intervention (See Table 1). Knowing which strain(s) most efficaciously treat which disease is vital to proper patient care. ■

### Summary of Strain-Specific Outcomes in Probiotic Therapy of IBD

Indication	Probiotic(s) Administered
Lactose malabsorption	<i>L. Bulgaricus</i> 449, <i>S. Thermophilous</i> and <i>L. Acidiphilous</i>
Pouchitis	*VSL-3
Irritable bowel syndrome	<b>First line</b> <i>L. Plantarum</i> 299V <i>Bifidobacterium infantis</i> <b>Second line</b> VSL-3 <i>Enterococcus faecium</i> PR88
Ulcerative Colitis	<i>E. coli</i> strain Nissle 1917 <i>Streptococcus faecalis</i> , <i>Clostridium butyricum</i> and <i>Bacillus mesentericus</i>
Crohn's	<i>Lactobacillus casei</i> GG <i>Saccharomyces boulardii</i> (only evaluated with anti-inflammatory medication)

**\*VSL-3 - VSL#3 (Seaford Pharmaceuticals) probiotic mixture contains:**

- Four species of *Lactobacilli*: 3.1% of *L. plantarum*, 7.3% of *L. acidophilus*, 16% of *L. casei*, and 8.4% of *L. delbrueckii* subsp. *Bulgaricus*.
- Three species of *Bifidobacteria*: *B. infantis*, *B. breve*, and *B. longum*, representing 17.7% of the mixture.
- *Streptococcus salivarius* subsp. *Thermophilus* representing 47.5% of the mixture

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## QUESTIONS

- A systematic review of probiotics in 2005 by Levri et al revealed that probiotics were effective in the overall treatment of Lactose Malabsorption.
  - True
  - False
- Based on human clinical trials of patients with Irritable Bowel Syndrome (IBS), Lactobacillus GG has the strongest clinical efficacy in treatment of IBS symptoms by a single strain probiotic.
  - True
  - False
- The clinical efficacy of E. coli Nissle 1917 in the treatment of active Ulcerative Colitis displayed a lower rate of remission when compared with anti-inflammatory medication.
  - True
  - False
- A patient presents active Crohn's disease. Approximately 15 ml of bright red blood is observed daily by the patient after bowel movements. The patient is currently taking 20 mg of prednisone TID. The patient has a history of small bowel perforations, fistulas and abscesses. Based on the history of the patient and current disease state, select one of the following.
  - Non-pathogenic probiotic organisms are safe and effective treatment to be prescribed as co-management for this patient.
  - A lower dosage of Saccharomyces boulardii would be the most appropriate probiotic as treatment.
  - Given the current state of the patient, probiotics would not serve as effective therapy and may do harm based on the published case reports.
  - Restoration of mucosal integrity is vital to proper patient care. Based on limited case reports and negative data, administration of probiotics has no potential to cause harm.
- Based on the available human data of medically induced remission of Crohn's disease, which probiotic is best administered with mesalamine for improved remission rates?
  - Saccharomyces boulardii
  - L. Rhamnosus GG
  - Escherichia coli Nissle 1917
  - VSL-3
- A patient presents with diarrhea, abdominal pain and hematochezia two months after surgery. The patient has a history of Ulcerative Colitis and flexible sigmoidoscopy revealed inflammation in the mucosa of the ileoanal "pouch" created after surgery for UC.
  - VSL-3 is the most appropriate probiotic to prescribe at a minimum dosage of 2 Billion CFU for four weeks.
  - VSL-3 is the most appropriate probiotic to prescribe at a minimum dosage of 400 billion CFU for several months.
  - High dose fibre with a single strain of L. Acidophilous is the most appropriate intervention.
  - Probiotics are not safe for treatment of Pouchitis.
- The gold standard for diagnosing Lactose Malabsorption is?
  - Urea Breath Test
  - Hydrogen Breath Test
  - 25 g ingestion of lactose and 24 hr stool culture
  - 50 g ingestion of Galactose and 24 hr stool culture
- Of the following strains of probiotics, which are known to metabolize glucose and lactose and are efficacious for the treatment of lactose malabsorption?
  - L. Bulgaricus 449, S. Thermophilous and L. Acidiphilous
  - L. Bulgaricus 449, S. Thermophilous and L. GG
  - L. Bulgaricus 449, S. Thermophilous and L. Casei strain Shirota (LcS)
  - L. GG, Enterococcus faecium PR88, Bifidobacterium infantis 35624
- Based on patient visits, which of the following GI concerns in North America has the highest frequency?
  - IBD
  - IBS
  - Celiac Sprue
  - Candida
- Probiotic use among individuals with ulcerative colitis has been associated with which of the following clinical endpoints?
  - Maintenance of medication-induced disease remission.
  - Achieving disease remission among patients presenting with active disease.
  - Achieving a meaningful clinical response among treatment refractory individuals (active disease present despite treatment with standard medications).
  - Probiotics have demonstrated all of the above clinical end points among patients with Ulcerative Colitis.

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**416.203.7900**  
**philip@ihpmagazine.com**

