# Role of Probiotic Therapy in IBD

*Kim Isaacs, MD,* and Hans Herfarth, MD**

**Abstract:** There is mounting evidence that probiotic therapy may alter disease expression in both animal models of IBD and in patients with IBD. The effects appear to be modest at best and may reflect the choice of probiotic organism, the variability in concentrations of organisms administered, and the variability of the diseases being treated. This review examines the data of all fully published articles currently available for the role of probiotics in the treatment of IBD.

(*Inflamm Bowel Dis 2008;14:1597–1605)*

**Key Words:** Crohns' disease, ulcerative colitis, pouchitis, probiotics

Over the past decade there is increasing evidence that, at least in part, intestinal inflammation seen in inflammatory bowel disease (IBD) results from an altered mucosal immune response to luminal bacterial antigens.[1,2] The discovery of *NOD2/CARD15* gene polymorphisms in Crohn's disease (CD), which function in bacterial peptidoglycan recognition, further supports the link between enteric bacterial interaction with the host immune response.[3,4] In mice that are deficient in NOD2 there is an increased susceptibility to bacterial infection through the luminal route.[3] Likewise in patients with IBD, through a variety of mechanisms including abnormalities of the NOD2 protein, there may be decreased tolerance to enteric bacteria with a secondary inflammatory response in the gut. Alteration of the bacterial flora both in terms of specific content and concentration may be beneficial in patients with IBD. To this end, antibiotics have been used with varying success in IBD, with the most significant beneficial impact in the treatment of pouchitis.[5] Probiotics also provide a mechanism for altering the enteric flora. Probiotics are defined as "living organisms, which upon ingestion in a certain number exert health benefits beyond inherent basic nutrition."[6] There is mounting evidence that probiotic therapy may alter disease expression in both animal models of IBD and in patients with IBD. The effects appear to be modest at best and may reflect the choice of probiotic organism, the variability in concentrations of organisms administered, and the variability of the diseases being treated. This review examines the data of all fully published articles currently available for the role of probiotics in the treatment of IBD.

Received for publication February 22, 2008; Accepted February 26, 2008.

From the *University of North Carolina at Chapel Hill, Division of Gastroenterology and Hepatology.

H. Herfarth is supported by a Senior Research Award of the CCFA.

Reprints: Kim Isaacs, MD, University of North Carolina at Chapel Hill, Division of Gastroenterology and Hepatology, CB# 7032, Room 7200 MBRB, Chapel Hill, NC 27599-7032 (e-mail: klisaacs@med.unc.edu).

Copyright © 2008 Crohn's & Colitis Foundation of America, Inc.

DOI 10.1002/ibd.20465

Published online 17 April 2008 in Wiley InterScience (www.interscience.wiley.com).

## CROHN'S DISEASE (TABLE 1)

In CD the use of probiotics is somewhat disappointing, with trials showing mixed results. The available trials are small and very few are double-blind, randomized, and controlled clinical trials. Fujimori et al[7] treated 10 active patients with CD not responding to 5-ASA and prednisone therapy with a symbiotic therapy, comprising *Bifidobacterium* and *Lactobacillus* and the prebiotic psyllium, a species in the Plantago family, for longer than 12 months. Six patients went into remission, 1 had a partial response with improvement of the number of bowel movements, and 3 patients were nonresponders. No significant differences between C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) values were observed before and after therapy. Malchow[8] reported no significant differences in 28 patients with active Crohn's colitis treated with prednisone and *E. coli* Nissle or placebo in the time needed to induce remission (median 21 days in the *E. coli* group versus 23 days in the placebo group) and the induction of remission (75% *E. coli* Nissle, 92% placebo) In the pediatric literature an open-label pilot trial, including 4 children (aged 10–18) who were treated with $10^{10}$ colony-forming units (CFU) *Lactobacillus* GG reported a significant improvement in the clinical activity after 1 week. However, a placebo-controlled randomized trial by Bousvaros et al[10] did not demonstrate a significant benefit of this probiotic in the maintenance of remission in a pediatric population (see below).

### Maintenance of Remission

Schultz et al[9] used *Lactobacillus* GG in a placebo-controlled trial in 11 patients. The patients had mild to moderate CD and were given both antibiotics and a tapering steroid regimen at presentation. After 1 week of ciprofloxacin (500 mg bid) and metronidazole (250 mg tid) the patients were randomized to receive either *Lactobacillus* GG ($2 \times 10^9$ CFU/day) or placebo. Patients received a total of 2 weeks of antibiotics, steroid taper over 12 weeks, and probiotic/placebo for 6

**TABLE 1.** Clinical Studies Published as Full Papers Investigating the Effects of Probiotics and Prebiotics in the Induction and Maintenance of Remission in Crohn's Disease

| Author | Probiotic Microorganism | *n* | Study Design | Comparator | Study Duration | Outcome Measures | Outcome |
|---|---|---|---|---|---|---|---|
| Induction of remission | | | | | | | |
| Malchow 1997[8] | Steroid taper + E. coli Nissle 1917 $5\times10^{10}$/day | 28 | Randomized, placebo controlled, single center | Steroid taper + placebo | 12 weeks | CDAI | No difference |
| Fujimori 2007[7] | Synbiotic mixture‡ | 10 | Open label, single center | — | Mean 13 months | CDAI, IOIBD score | Significant improvement |
| Maintenance of remission | | | | | | | |
| Malchow 1997[7] | E. coli Nissle 1917 $5\times10^{10}$/day | 28 | Randomized, placebo controlled, single center | Placebo | 12 months | CDAI | Trend towards better outcome in probiotic group, but not significant. |
| Guslandi 2000[11] | Saccharomyces boulardii (1g/day)† | 32 | Randomized, single center | Mesalazine 3g/day | 6 months | CDAI | Probiotic superior to mesalazine ($P <$ 0.04) |
| Schultz 2004[9] | Lactobacillus GG $2\times10^{9}$ CFU/day | 11 | Randomized, double blind, placebo controlled, single center | Placebo | 6 months | CDAI, relapse and time to relapse | No difference between both groups, small number of patients |
| Bousvaros 2005[10] | Lactobacillus GG $2\times10^{10}$ bacteria +295mg inulin/day | 75 | Randomized, double blind, placebo controlled, multi center | Placebo (395 mg inulin) | 24 months | *PCDAI, relapse and time to relapse | No difference between both groups. |

*Pediatric CDAI.
†+ 2G mesalazine daily.
‡Bifidobacterium breve and Lactobacillus casei each $3\times10^{10}$ CFU daily, Bifidobacterium longum $1.5\times10^{10}$ CFU daily, 3.3g psyllium (plantago ovata) daily.

months. The primary endpoint was sustained remission at 6 months. There was no difference in numbers of patients who relapsed during the study period (LGG 2/4, placebo 3/5) and mean time to relapse (LGG 16 ± 4 weeks; placebo 12 ± 4.3 weeks). The conclusion was that LGG therapy did not improve remission rates in patients; however, the very small number of patients in each arm of the study makes it unlikely that a difference would be seen in this population.

Bousvaros et al[10] looked at *Lactobacillus* GG as additive therapy to see if the addition of LGG to standard therapy could prolong remission in children with CD. In all, 75 children were randomized to receive either LGG ($10^{10}$ bacteria daily) or placebo and followed for up to 2 years. The endpoint of the trial was clinical relapse; 31% of patients in the LGG group relapsed compared to 17% in the placebo group (NS) and the median time to relapse was 9.8 months in the LGG group and 11 months in the placebo group (NS). The authors concluded that LGG did not prolong time to relapse in children given the LGG as an adjunct to standard therapy. This trial had a larger number of patients; however, the initial sample size calculations suggested that double the number of patients were required to detect a difference between the 2 groups. In addition, the patient's were on different medications to maintain remission. They were not pretreated with antibiotics prior to receiving the probiotics. It is not clear whether this is necessary to make the probiotics more effective in changing the intestinal flora.

Alternatives to the *Lactobacillus* GG include *E. coli* Nissle and *Saccharomyces boulardii. E. coli* Nissle 1917 is a nonpathogenic *E. coli* that colonizes the intestine and inhibits the growth of enteropathogenic and other enteric bacteria. It is proposed that this organism, by suppressing enteropathogenic bacteria, may have a long-term effect to suppress remission. Malchow[8] performed a pilot study in 28 patients with active colonic CD. Patients were treated with a tapering course of prednisolone and either placebo or *E. coli* Nissle 1917 (Mutaflor). The *E. coli* Nissle was given in an increasing dosage over 24 days to the final dose of $5 \times 10^{10}$ bacteria per day for a year. The endpoints were remission, prednisolone dosage, and relapse. Similar percentages of patients entered remission. There was a higher relapse rate in the placebo group (63.6%) as compared to the *E. coli* group (33.3%). This did not reach statistical significance due to the small numbers treated but are interesting observations regarding this therapy. Interestingly, this is 1 of the few trials in CD that looked at disease restricted to the colon. The bulk of the enteric bacteria reside in the colon, making that a reasonable target for the use of probiotics.

Guslandi et al[11] studied the yeast *Saccharomyces boulardii* in 32 patients with CD in remission: 32 patients with CD in remission were treated over a 6-month period with either mesalamine 3 g per day or mesalamine 2 g per day plus 1 g per day of *S. boulardii.* Remission was defined as a Crohn's Disease Activity Index (CDAI) $<150$ and relapse

**TABLE 2.** Clinical Studies Published as Full Papers Investigating the Effects of Probiotics and Prebiotics in the Maintenance of Surgically Induced Remission in Crohn's Disease

| Author | Probiotic Microorganism | *n* | Study Design | Comparator | Study Duration | Outcome Measures | Outcome |
|---|---|---|---|---|---|---|---|
| Prantera 2002[12] | Lactobacillus GG $12\times10^9$ cfu daily | 45 | Randomized, double blind, placebo controlled, single center | Placebo | 12 months | Endoscopic recurrence (Rutgeerts score), Clinical recurrence (CDAI) | No difference. |
| Marteau 2006[14] | Lactobacillus johnsonii LA1 $4\times10^9$cfu daily | 98 | Randomized, double blind, placebo controlled, multi center | Placebo | 6 months | Endoscopic recurrence (Rutgeerts score), Clinical recurrence (CDAI) | No difference. |
| Chermesh 2007[16] | Synbiotic 2000* | 30 | Randomized, double blind, placebo controlled, multi center | Placebo | 24 months | Endoscopic recurrence (Rutgeerts score), Clinical score | No difference |
| Van Gossum 2007[15] | Lactobacillus johnsonii LA1 $1\times10^{10}$cfu daily | 70 | Randomized, double blind, placebo controlled, multi center | Placebo | 3 months | Endoscopic recurrence (Rutgeerts score), Clinical recurrence (CDAI) | No difference. |

*Synbiotic 2000 contains 4 probiotic starins and 4 prebiotic fibers: $10^{10}$ Pediacoccus pentoseceus, $10^{10}$ L. raffinolactis, $10^{10}$ L. paracasei subsp. paracasei 19, $10^{10}$ L. plantarum 2362; 2.5 g $\beta$ -glucans, 2.5 g inulin, 2.5 g pectin, 2.5 g resistant starch.

was defined as a 100-point increase in CDAI from baseline and CDAI >150 at 2 visits. 37.5% of patients relapsed in the mesalamine-only group compared to a 6.25% relapse rate in the patients receiving mesalamine and *S. boulardii* ($P = 0.04$). *Saccharomyces* has also been shown to be beneficial in patients with antibiotic-induced and *Clostridium difficile*-associated diarrhea. It is also trophic to the intestinal mucosa and induces release of intestinal IgA.

## Postoperative Prophylaxis (Table 2)

Recurrence of CD after surgical resection of all active disease remains an important clinical problem. Several groups have used probiotics to attempt to decrease the incidence of recurrent ulcerations and clinical recurrence after surgery. All of the published trials of probiotics in this setting have used the strategy of looking at early endoscopic recurrence as a marker for those patients who will develop problems with disease recurrence. The first look at this issue was by Prantera et al[12] in a 1-year treatment trial of *Lactobacillus* GG ($2 \times 10^{10}$ bacteria daily) or placebo in 45 patients who had undergone a "curative" ileocecal resection in CD. Ileocolonoscopy at 1 year or at the time of symptom recurrence was performed with endoscopic recurrence defined as a Rutgeerts score of greater than 2.[13] There was clinical recurrence in 3 (16.6%) patients who received *Lactobacillus* GG and in 2 (10.5%) who received placebo. Eight of the 48 patients were excluded from the analysis due to noncompliance and protocol violations. Nine of 15 (*Lactobacillus* GG) and 6/17 (placebo) patients in clinical remission had endoscopic recurrence at the end of the treatment trial ($P = 0.297$). There was significant clinical and endoscopic relapse in both groups, with no benefit to adding *Lactobacillus* GG in the postoperative setting.

Marteau et al[14] enrolled 98 patients in a double-blind placebo-controlled trial of *Lactobacillus johnsonii* LA1 in postoperative prophylaxis of recurrent CD. The study population included patients who had undergone resection of less than 1 m of small bowel within 21 days prior to study enrollment. All active disease was resected. The patients were randomized to 2 packets per day of *L. johnsonii* ($2 \times 10^9$ CFU) or placebo for 6 months. The primary endpoint was endoscopic recurrence defined as >1 in the Rutgeert's classification scheme at the 6-month timepoint.[13] Endoscopic recurrence was seen in 64% (30/47) patients in the placebo group and 49% (21/43) in the *L. johnsonii* group. ($P = 0.15$). In terms of clinical recurrences, there were 4 in the *L. johnsonii* group and 3 in the placebo group. The patients received no other treatments, including antibiotic therapy prior to the probiotic.

Van Gossum et al[15] verified this result in a 3-month trial of *L. johnsonii* or placebo that was started immediately after ileocecal resection for CD. Inclusion parameters were similar. A larger dose ($10^{10}$ CFUs) of *L. johnsonii* was used in this study. There was no difference in endoscopic score, severe endoscopic recurrence, and clinical relapse between the 2 groups. Four patients in the *L. johnsonii* group and 2 patients in the placebo group relapsed at 3 months.

It is possible that in these 3 trials that limiting the probiotic administered to a single microorganism may have

led to the "wrong" probiotic agent used to prevent the outcome of endoscopic recurrence. Chermesh et al[16] attempted to address this issue by looking at Synbiotic 2000, which combines 4 different probiotic species with 4 prebiotics. Prebiotics are compounds that stimulate the growth of intestinal "probiotic" bacteria such as the bifidobacteria. Synbiotic 2000 contains $10^{10}$ *Pediacoccus pentoseceus,* $10^{10}$ *Lactobacillus raffinolactis,* $10^{10}$ *Lactobacillus paracasei* subsp *paracasei* 19, and $10^{10}$ *Lactobacillus plantarum* 2362 and the prebiotics (fermentable fibers) 2.5 g $\beta$-glucans, 2.5 g Inulin, 2.5 g pectin, and 2.5 g resistant starch. Thirty patients were enrolled and randomized to receive Synbiotic 2000 or placebo in a 2:1 randomization.[16] The endpoints were clinical and endoscopic relapse. Treatment was administered up to 24 months after trial entry. Endoscopy was performed at 3 months and at the end of the trial. There was no difference between the 2 groups in terms of clinical or endoscopic relapse. Only 9 patients completed 24 months of the trial. Two of 10 placebo patients and 5/20 Synbiotics patients had an exacerbation of disease activity during the trial.

## ULCERATIVE COLITIS (TABLE 3)

There is more of a precedence for the use of probiotics in ulcerative colitis (UC) than in CD. In 1918, Alfred Nissle[17] developed an *E. coli* strain that was to be nonpathogenic and had beneficial effects in patients with gastrointestinal illness. This strain of bacteria is now referred to as *E. coli* Nissle.

### Induction of Remission

There is very little randomized trial experience in the treatment of active UC with probiotics. One of the few double-blind studies that examines patients with active UC is a trial that combines a probiotic, *Bifidobacterium longum,* with a prebiotic composed of an inulin-oligofructose growth substrate (Synergy 1).[18] It was a small trial with a total of only 18 patients randomized. Nine patients were assigned to the treatment group and 9 to the placebo group. All patients had had symptoms of active colitis for 1 month. Patients were assessed with a clinical activity index, sigmoidoscopic appearance, and a histologic score. Measurements of gut inflammatory markers were performed on biopsy sample. The patients were treated with the symbiotic (probiotics + prebiotic) or a placebo twice daily for 4 weeks. At the end of the month the patients were reassessed. The patients receiving the synbiotic mixture exhibited reduced mucosal inflammatory markers in colonic biopsies. There was an improvement microscopically. There was no significant difference in the sigmoidoscopy scores or the clinical indices between the synbiotic and placebo groups. The small study size and the dropout of 2 patients from the placebo group make this study underpowered to detect a difference. There was significant reduction in TNF-$\alpha$ and IL-$\alpha$ levels in mucosal biopsies in patients treated with the active therapy as compared to placebo. These findings are provocative and larger trials using this approach should be considered in patients with active UC.

Tursi et al[19] examined the role of combining VSL#3, a probiotic containing 8 strains of bacteria (*Bifidobacterium breve, B. longum, B. infantis, Lactobacillus acidophilus, L. plantarum, L. casei, L. bulgaricus, Streptococcus thermophilus*) (300 billion viable bacteria per gram) with balsalazide in the treatment of patients with mild to moderate active colitis. Ninety patients were randomized and assessed by Colitis Activity Index (CAI), endoscopic, and histologic evaluations. Patients received either a balsalazide/VSL#3 combination, balsalazide alone, or mesalazine alone. The primary endpoint was the proportion of patients in symptomatic remission 2, 4, and 8 weeks after starting treatment. Balsalazide plus VSL#3 was superior to balsalazide alone or mesalazine alone in the time needed to induce remission (4 versus 7.5 versus 13 days, respectively; $P < 0.01$) and in the overall induction of remission (per-protocol; 85.71% versus 80.77% versus 72.73% respectively; $P < 0.02$). In addition, there was a greater improvement in well being, bowel frequency, and endoscopic and histologic scores in patients who received the combination therapy.

In an open-label experience, 34 patients with active UC not responding to conventional therapy had a 77% induction of remission/response rate at the end of a 6 week therapeutic trial of VSL#3 3,600 billion bacteria daily.[20] *Saccharomyces boulardii* 750 mg/day administered to 24 patients with a mild to moderate flare of UC was associated with a 68% response rate.[21] The prebiotic preparation Bifidogenic growth stimulator (BGS), which is produced by *Propionibacterium freudenreichii* isolated from Swiss cheese, induced a significant decrease in the clinical and endoscopic activity in 12 patients with mild to moderate UC.[22] The fecal concentrations of several short-chain fatty acids (SCFA), especially butyrate, were increased in nearly all patients, suggesting that the clinical and endoscopically visible improvement might be mediated by the inhibition of proinflammatory cytokines by the SCFA in the inflamed colonic mucosa.

### Maintenance of Remission

Zocco et al[23] evaluated the efficacy of lactobacillus GG in patients with quiescent colitis. The treatment groups were *Lactobacillus* GG alone, *Lactobacillus* GG plus 2400 mg/day mesalazine, and 2400 mg per day of mesalazine alone. This was a 12-month treatment trial with a primary endpoint of relapse of disease activity. A total of 187 patients were randomized into the trial with primary endpoint evaluations at 6 and 12 months. The relapse rates for 6 and 12 months were similar among all groups studied with an 8%/15% relapse rate for *Lactobacillus* GG, 13%/20% for the combination, and 6%/16% for the mesalazine alone. The results of this trial suggest that *Lactobacillus* GG has the same efficacy as me-

**TABLE 3.** Clinical Studies Published as Full Papers Investigating the Effects of Probiotics and Prebiotics in the Induction and Maintenance of Remission in Ulcerative Colitis

| Author | Probiotic Microorganism | *n* | Study Design | Comparator | Study Duration | Outcome Measures | Outcome |
|---|---|---|---|---|---|---|---|
| Induction of remission | | | | | | | |
| Rembacken 1999[27] | E. coli Nissle 1917 $1\times10^{11}$/day (+prednisone gentamicin) | 120 | Randomized, double dummy, single center | Mesalazine 2.4g/day (+prednisone gentamicin) | 3 months | Predefined clinical index, endoscopic Baron index | No difference between both groups after induction of remission in combination with steroid+antibiotics |
| Guslandi 2003[21] | S. boulardii 750mg/day | 25 | Open label, single center | — | 1 month | Rachmilewitz activity index | Remission 68% |
| Furrie 2005[18] | $2\times10^{11}$ Bifidobacterium longum + 6 g fructo-oligosaccharide/ inulin mix | 18 | Randomized, double blind, placebo controlled, single center | Placebo | 1 month | CAI, Baron index | Improvement with symbiotic therapy |
| Tursi 2004[19] | VSL#3[#] $9\times10^{11}$ bacteria/day + 2.25 g balsalazide/day | 90 | Randomized, multi center trial | 4.5g balsalazide or 2.4g meslazazine /day | 8 weeks | CAI, histology | Probiotic significant superior in inducing remission compared to mesalazine |
| Kato 2004[43] | Yakult[†], 100ml daily | 20 | Randomized, placebo controlled, single center | Placebo | 3 months | CAI, endoscopic evaluation | Probiotic significant superior. |
| Biblioni 2005[20] | VSL#3[§] $3.6\times10^{12}$ bacteria/day | 34 | Open label, multi center | — | 6 weeks | UCDAI[‡] | Remission/response rate 77% |
| Suzuki 2006[22] | Bifidogenic growth stimulator 4.5 g/ daily | 12 | Open label, single center | — | 1 months | CAI and EI | Significant decrease in CAI and EI |
| Maintenance of remission | | | | | | | |
| Kruis et al. 1997[25] | E. coli Nissle 1917 $5\times10^{10}$/day | 120 | Randomized, double blind, double dummy, multi center | Mesalazine 1.5g/day | 3 months | CAI* | No difference between both groups, equivalence to mesalazine postulated |
| Rembacken 1999[27] | E. coli Nissle 1917 $5\times10^{9}$/day | 120 | Randomized, double dummy, single center | Mesalazine 1.2g/day | 12 months | Predefined clinical index, endoscopic Baron index | No difference between both groups, equivalence to mesalazine postulated |
| Ishikawa 2003[24] | Yakult[†], 100ml daily | 21 | Randomized open label, single center | Standard UC therapy | 12 months | Predefined clinical index | Significant better outcome in Yakult group |
| Kruis et al. 2004[26] | E. coli Nissle 1917 100 mg daily (2.5–25 $10^{9}$/ bacteria/ day) | 327 | Randomized, double blind, double dummy, multi center | Mesalazine 1.5g/day | 12 months | Rachmilewitz activity index | No difference between both groups, statistically proven equivalence to 1.5 g mesalazine |
| Zocco 2006[23] | Lactobacillus GG $18\times10^{9}$ bacteria/day | 187 | Open label, randomized, single center | Mesalazine 2.4g/day | 12 months | CAI | No difference |

*CAI; clinical activity index.
[†]Bifidobacterium breve, Bifidobacterium bifidum, Lactobacillus acidophilus $1\times10^{9}$/ 100 mL.
[‡]UCDAI; ulcerative colitis disease activity index.
[§]VSL#3 comprises four strains of lactobacilli (acidophilus, delbrueckii subsp. bulgaricus, casei, plantarum), three strains of bifidobacteria (breve, longum, infantis), and one strain of Streptococcus salivarius subsp thermophilus.

salazine in maintaining remission in UC. One small trial demonstrated that the additional daily supplementation of 100 mL of *Bifidobacteria* fermented milk, which contains *Bifidobacterium breve, Bifidobacterium bifidum, Lactobacillus acidophilus*, to the basic therapy (mesalazine or sulfasalazine) of 10 patients resulted in a significant reduction of disease exacerbations over a 12-month period compared to a control group (10 patients; $P < 0.02$).[24]

There are 3 trials that examined the efficacy of *E. coli* Nissle 1917 in maintenance of remission in UC. Kruis et al[25] performed 2 of the trials. The first was a blinded 12-week treatment trial comparing mesalazine 1500 mg daily to an oral preparation of viable *E. coli* strain Nissle 1917 (Mutaflor, 100 mg = $25 \times 10^{9}$ viable bacteria). The primary endpoint was relapse based on an increase in the CAI to >4. A total of 120 patients were randomized with 103 patients included in the intention to treat analysis. The relapse rate was 16% in the *E. coli* group and 11.3% in the mesalazine group, which was

not statistically different. In addition, there were no differences in the secondary endpoint of histologic activity between the 2 treatment groups. The same group looked at a larger group of patients ($n = 327$) in a 12-month blinded treatment trial of *E. coli* Nissle 1917 200 mg per day or mesalazine 500 mg TID (1500 mg/day).[26] The patients were assessed by clinical and endoscopic activity indices and histology. In all, 36.4% of patients in the *E. coli* group relapsed as compared to 33.9% of patients in the mesalazine group. The conclusion of this study was that the drugs were equivalent in preventing relapses. Both of these studies evaluated patients in clinical remission at the start of the trial. Rembacken et al[27] also looked at *E. coli* as compared to mesalamine in the maintenance of remission in patients with UC; however, at entry into the trial the patients were required to have active UC. They received what was considered standard therapy to induce remission as well as a dose of gentamicin and randomization to either *E. coli* Nissle 1917 (4 capsules per day, $2.5 \times 10^{10}$ viable bacteria per capsule) or 2400 mg per day of mesalamine. After 12 weeks only those patients in remission were enrolled in the follow-up study, where they received 1200 mg/day of mesalamine or 2 capsules per day of the *E. coli.* In all, 83 patients went into remission with the standard therapies, 44 (75%) in the mesalamine group and 39 (68%) in the *E. coli* group, and continued into the maintenance phase. At the end of the study only 11 (25%) of patients in the mesalamine group and 10 (26%) in the *E. coli* group remained in remission. There is equivalence between the 2 therapies but the relapse rate is very high in the population and by allowing standard therapies to induce remission the initial study population is quite heterogeneous.

Despite the study limitations the controlled trials support the concept of probiotics as efficacious in maintenance of remission in UC.

## POUCHITIS (TABLE 4)

Pouchitis is an idiopathic inflammatory disease of the ileal pouch that occurs in 15%–53% of patients who undergo total abdominal colectomy with ileal pouch-anal anastomosis (IPAA) for UC.[28,29] Fecal stasis with immunologic reactivity appears to be important in the pathogenesis of this disease.[30] As a result, this area of study has garnered the most support for the use of and efficacy of probiotics in the IBD.

### Induction of Remission

Kuisma et al[31] treated 20 patients with active pouchitis with either *Lactobacillus* GG ($2–4 \times 10^{10}$CFU/day) or placebo for 3 months. Only 40% of the patients were colonized with this probiotic strain and overall no improvement was noted with regard to the PDAI or histologic assessment of inflammation.

Using the dietary fiber Inulin (24 g/day), Welters et al[32] demonstrated after a short treatment period of 3 weeks a significant but moderate decrease of pouchitis as measured by an endoscopic and histologic score. The effects correlated with a significant alteration of fecal pH, fecal butyrate, and secondary bile acid concentration. With regard to the fecal flora only a moderate but significant decrease of *Bacteroides fragilis* was observed. No decrease in the clinical symptoms was noted, which could be attributed to the selected patients, who had only endoscopic and histological signs of inflammation but were clinically stable at the time of inclusion.

### Maintenance of Remission

Two clinical trials investigated the maintenance of remission in patients with chronic relapsing pouchitis.[33,34] In the study by Gionchetti et al,[34] 40 patients, who went into clinical and endoscopic remission after 1 month of combined antibiotic therapy with rifaximin 2 g/day and ciprofloxacin 1 g/day, were randomized to either VSL#3 (6 g, $1.8 \times 10^{12}$ bacteria/day) or placebo for 9 months. All patients in the placebo relapsed as defined as an increase in clinical symptoms and endoscopic inflammatory activity, whereas 17/20 patients (85%) in the VSL#3 group were still in remission after 9 months. A collaborative study of the same group with the St. Mark's Hospital in London essentially confirmed the results.[33] In that study patients with recurrent pouchitis (at least 2 episodes of pouchitis during the previous year or requiring continuous antibiotic therapy) were first treated with metronidazole (800 mg/day) and ciprofloxacin (1 g/day) for 1 month and then maintained on VSL#3 (6 g, $1.8 \times 10^{12}$ bacteria/day) for 12 months. Remission was maintained at 1 year in 17 patients (85%) on VSL#3 and in 1 patient (6%) on placebo ($P < 0.0001$).

In a prospective open-label trial, Shen et al[35] analyzed the effectiveness of VSL#3 (6 g, $1.8 \times 10^{12}$ bacteria/day) in 31 patients with antibiotic-dependent pouchitis, defined as 4 or more episodes of pouchitis/year, responding each time to antibiotics or patients requiring long-term low-dose or frequent pulse antibiotic therapy. All patients were initially treated with 1 g ciprofloxacin/day for 2 weeks before VSL#3 was started. After 8 months only 6 patients (19%) were still on VSL#3, whereas the other 25 patients had discontinued the therapy either because of recurrent symptoms (23 patients, 84%) or the development of side effects (2 patients, 16%).

Laake et al[36] investigated the effects of a fermented milk product in an open-label trial, which included UC patients after IPAA (UC-IPAA), familial adenomatous polyposis (FAP-IPAA), as well as UC patients with an ileorectal anastomosis only (UC-IRA); 20% in the UC-IPAA group had active pouchitis at the time of inclusion. Clinical symptoms as well as the endoscopically visible inflammation in the pouch in UC-IPAA patients improved with the probiotic therapy, whereas this therapy was only partially or not effective in the FAP-IPAA and in the UC-IRA groups.

**TABLE 4.** Clinical Studies Published as Full Papers Investigating the Effects of Probiotics and Prebiotics in the Prevention of Pouchitis and Induction and Maintenance of Remission in Pouchitis Patients

| Author | Probiotic Microorganism | *n* | Study Design | Comparator | Study Duration | Outcome Measures | Outcome |
|---|---|---|---|---|---|---|---|
| Prevention of pouchitis | | | | | | | |
| Gionchetti 2003[37] | VSL#3† $9\times10^{11}$ bacteria/day | 40 | Randomized, double blind, placebo controlled, single center | Placebo | 12 months | *PDAI | VSL#3 significant superior to placebo in preventing pouchitis |
| Gosselink 2004[38] | Lactobacillus rhamnosus GG $4\times10^{10}$ bacteria/day | 42 | Open label, single center | Historic control (n=78) | 12 months | Clinical, endoscopic and histological judgement | Fewer pouchitis episodes in patients treated with probiotic |
| Induction of remission | | | | | | | |
| Welters 2002[32] | Inulin (24g/day) | 20 | Randomized, double blind, placebo controlled, crossover design, single center | Placebo | 3 weeks | PDAI and histology | Significant decrease of endoscopic and histologic score |
| Kuisma 2003[31] | Lactobacillus GG $2–4\times10^{10}$ bacteria/day | 20 | Randomized, double blind, placebo controlled, single center | Placebo | 3 months | *PDAI and histology | No effect on pouchitis |
| Maintenance of remission | | | | | | | |
| Gionchetti 2000[34] | VSL#3† $1.8\times10^{12}$ bacteria/day | 40 | Randomized, double blind, placebo controlled, single center | Placebo | 9 months | *PDAI | VSL#3 significant superior to placebo in maintaining remission in patients with recurrent pouchitis |
| Mimura 2004[33] | VSL#3† $1.8\times10^{12}$ bacteria/day | 36 | Randomized, double blind, placebo controlled, two centers | Placebo | 12 months | *PDAI | VSL#3 significant superior to placebo in maintaining remission in patients with recurrent pouchitis |
| Laake 2005[36] | 500 ml Cultura‡/day | 61§ | Open label, single center | — | 1 month | *PDAI | Decrease of PDAI during study period |
| Shen 2005[35] | VSL#3† $1.8\times10^{12}$ bacteria/day | 31 | Open label, single center | — | 14±7 months | *PDAI | VSL#3 effective in 19% of included patients |

*PDAI; Pouchitis disease activity index.
†VSL#3 comprises four strains of lactobacilli (acidophilus, delbrueckii subsp. bulgaricus, casei, plantarum), three strains of bifidobacteria (breve, longum, infantis), and one strain of Streptococcus salivarius subsp thermophilus.
‡Cultura (fermented milk product) comprises lactobacilli and bifidobacteria at a concentration of $10^8$/mL.
§51 UC and 10 FAP patients with ileal pouch anal anastomosis (IPAA).

## Prophylactic Therapy to Prevent Pouchitis

In a randomized, double-blind, placebo-controlled study 40 patients were randomized within a week after surgery to receive either VSL#3 (3 g, $9 \times 10^{11}$ bacteria/day) or placebo for 12 months.[37] Two of 20 (10%) of the patients treated with VSL#3 developed an episode of acute pouchitis compared to 8/20 patients (40%) in the placebo group ($P < 0.01$). Patients treated with VSL#3 and no signs of pouchitis had a median stool frequency of 5 (range, 3–9) at the end of the trial compared to 8 (range, 6 –12) in the placebo group (with no signs of pouchitis; $P < 0.001$).

In an open label study performed by the Erasmus Medical Center in Rotterdam the incidence of pouchitis was significantly lower in 39 patients receiving *Lactobacillus rhamnosus* GG ($4 \times 10^{10}$ bacteria/day) compared to a historic control group ($n = 78$) (7% versus 29% at 3 years, $P < 0.01$).[38] Also, fewer cases of recurrent or chronic pouchitis were observed in the probiotic therapy group.

## WHAT ARE THE POTENTIAL DOWNSIDES TO PROBIOTIC THERAPY?

Probiotic use, although generally considered a safe intervention, may have some potential negative effects. Bacteremia and endocarditis have been described with lactic acid bacteria.[39]

In a review of 200 cases of *Lactobacillus* infections reported in the literature between 1950 and 2003, 114 cases of

bacteremia were noted, with a mortality rate of 32%.[39] All patients had significant comorbidity including malignancy. In this same series there were 61 cases of endocarditis with a 22.9% mortality rate. Bacteremia associated with sepsis has also been reported, with *S. boulardii* as 1 of the more common organisms seen.[40,41] Other theoretic risks include antibiotic resistance transfer from the probiotics bacteria to other bacteria in the gastrointestinal tract and immunologic effects.[42] These issues need to be considered when contemplating the use of probiotics in the severely ill UC patient who is likely at a greater risk of bacterial translocation across the diseased colonic mucosa.

## CONCLUSIONS

A convincing role for the routine use of probiotics in patients with inflammatory disease is lacking. The combined data from the use of probiotics in UC is provocative and suggests that there may be a benefit of probiotics use in select patients. Pouchitis is a unique entity in which antibiotic therapy followed by probiotics therapy may sustain remission in patients with chronic pouchitis. Caution must be taken with the use of these agents in patients who are severely ill, where there is an increased likelihood of bacterial translocation and subsequent sepsis.

## REFERENCES

1. Sartor RB. Therapeutic manipulation of the enteric microflora in inflammatory bowel diseases: antibiotics, probiotics, and prebiotics. *Gastroenterology*. 2004;126:1620–1633.
2. Seksik P, Sokol H, Lepage P, et al. Review article: the role of bacteria in onset and perpetuation of inflammatory bowel disease. *Aliment Pharmacol Ther*. 2006;24:11–18.
3. Kobayashi K, Chamaillard M, Ogura Y, et al. Nod2-dependent regulation of innate and adaptive immunity in the intestinal tract. *Science*. 2005;307:731–734.
4. Inohara N, Ogura Y, Fontalba A, et al. Host recognition of bacterial muramyl dipeptide mediated through NOD2. Implications for Crohn's disease. *J Biol Chem.* 2003;278:5509–5512.
5. Pardi DS, Sandborn WJ. Systematic review: the management of pouchitis. *Aliment Pharmacol Ther*. 2006;23:1087–1096.
6. Reid G. Safe and efficacious probiotics: what are they? *Trends Microbiol*. 2006;14:348–352.
7. Fujimori S, Tatsuguchi A, Gudis K, et al. High dose probiotic and prebiotic cotherapy for remission induction of active Crohn's disease. *J Gastroenterol Hepatol*. 2007;22:1199–1204.
8. Malchow HA. Crohn's disease and Escherichia coli. A new approach in therapy to maintain remission of colonic Crohn's disease? *J Clin Gastroenterol*. 1997;25:653–658.
9. Schultz M, Timmer A, Herfarth H, et al. Lactobacillus GG in inducing and maintaining remission of Crohn's disease. *BMC Gastroenterol*. 2004;4:5.
10. Bousvaros A, Guandalini S, Baldassano R, et al. A randomized, double-blind trial of Lactobacillus GG versus placebo in addition to standard maintenance therapy for children with Crohn's disease. *Inflamm Bowel Dis*. 2005;11:833–839.
11. Guslandi M, Mezzi G, Sorghi M, et al. Saccharomyces boulardii in maintenance treatment of Crohn's disease. *Dig Dis Sci*. 2000;45:1462–1464.
12. Prantera C, Scribano ML, Falasco G, et al. Ineffectiveness of probiotics in preventing recurrence after curative resection for Crohn's disease: a randomised controlled trial with Lactobacillus GG. *Gut*. 2002;51:405–409.
13. Rutgeerts P, Geboes K, Vantrappen G, et al. Predictability of the postoperative course of Crohn's disease. *Gastroenterology*. 1990;99:956–963.
14. Marteau P, Lemann M, Seksik P, et al. Ineffectiveness of Lactobacillus johnsonii LA1 for prophylaxis of postoperative recurrence in Crohn's disease: a randomised, double blind, placebo controlled GETAID trial. *Gut*. 2006;55:842–847.
15. Van Gossum A, Dewit O, Louis E, et al. Multicenter randomized-controlled clinical trial of probiotics (Lactobacillus johnsonii, LA1) on early endoscopic recurrence of Crohn's disease after ileo-caecal resection. *Inflamm Bowel Dis*. 2007;13:135–142.
16. Chermesh I, Tamir A, Reshef R, et al. Failure of synbiotic 2000 to prevent postoperative recurrence of Crohn's disease. *Dig Dis Sci*. 2007;2:85–389.
17. Nissle A. The antagonistic treatment of chronic gut disorders with E. coli bacteria. *Med Klinik*. 1918;1918:29–30.
18. Furrie E, Macfarlane S, Kennedy A, et al. Synbiotic therapy (Bifidobacterium longum/Synergy 1) initiates resolution of inflammation in patients with active ulcerative colitis: a randomised controlled pilot trial. *Gut*. 2005;54:242–249.
19. Tursi A, Brandimarte G, Giorgetti G, et al. Low-dose balsalazide plus a high-potency probiotic preparation is more effective than balsalazide alone or mesalazine in the treatment of acute mild-to-moderate ulcerative colitis. *Med Sci Monit*. 2004;10:PI126–131.
20. Bibiloni R, Fedorak R, Tannock G, et al. VSL#3 probiotic-mixture induces remission in patients with active ulcerative colitis. *Am J Gastroenterol*. 2005;100:1539–1546.
21. Guslandi M, Giollo P, Testoni P. A pilot trial of Saccharomyces boulardii in ulcerative colitis. *Eur J Gastroenterol Hepatol*. 2003;15:697–698.
22. Suzuki A, Mitsuyama K, Koga H, et al. Bifidogenic growth stimulator for the treatment of active ulcerative colitis: a pilot study. *Nutrition*. 2006;22:76–81.
23. Zocco M, dal Verme L, Cremonini F, et al. Efficacy of Lactobacillus GG in maintaining remission of ulcerative colitis. *Aliment Pharmacol Ther*. 2006;23:1567–1574.
24. Ishikawa H, Akedo I, Umesaki Y, et al. Randomized controlled trial of the effect of bifidobacteria-fermented milk on ulcerative colitis. *J Am Coll Nutr*. 2003;22:56–63.
25. Kruis W, Schütz E, Fric P, et al. Double-blind comparison of an oral Escherichia coli preparation and mesalazine in maintaining remission of ulcerative colitis *Aliment Pharmacol Ther*. 1997;11:853–858.
26. Kruis W, Fric P, Pokrotnieks J, et al. Maintaining remission of ulcerative colitis with the probiotic Escherichia coli Nissle 1917 is as effective as with standard mesalazine. *Gut*. 2004;53:1617–1623.
27. Rembacken B, Smelling A, Hawkey P, et al. Non-pathogenic Escherichia coli versus mesalazine for the treatment of ulcerative colitis: a randomised trial. *Lancet*. 1999;354:635–639.
28. Simchuk E, Thirlby R. Risk factors and true incidence of pouchitis in paitnets after ileal pouch-anal anastomosis. *World J Surg*. 2000;24:851–856.
29. Mahadevan U, Sandborn W. Diagnosis and management of pouchitis. *Gastroenterology*. 2003;124:1636–1650.
30. de Silva H, Millard P, Soper N, et al. Effects of the faecal stream and stasis on the ileal pouch mucosa. *Gut* 1991;32:1166–1169.
31. Kuisma J, Mentula S, Jarvinen H, et al. Effect of Lactobacillus rhamnosus GG on ileal pouch inflammation and microbial flora. *Aliment Pharmacol Ther*. 2003;17:509–515.
32. Welters CF, Heineman E, Thunnissen FB, et al. Effect of dietary inulin supplementation on inflammation of pouch mucosa in patients with an ileal pouch-anal anastomosis. *Dis Colon Rectum*. 2002;45:621–627.
33. Mimura T, Rizzello F, Helwig U, et al. Once daily high dose probiotic therapy (VSL#3) for maintaining remission in recurrent or refractory pouchitis. *Gut*. 2004;53:108–114.
34. Gionchetti P, Rizzello F, Venturi A, et al. Oral bacteriotherapy as maintenance treatment in patients with chronic pouchitis: a double-blind, placebo-controlled trial. *Gastroenterology*. 2000;119:305–309.
35. Shen B, Brzezinski A, Fazio VW, et al. Maintenance therapy with a probiotic in antibiotic-dependent pouchitis: experience in clinical practice. *Aliment Pharmacol Ther*. 2005;22:721–728.
36. Laake KO, Bjorneklett A, Aamodt G, et al. Outcome of four weeks'

intervention with probiotics on symptoms and endoscopic appearance after surgical reconstruction with a J-configurated ileal-pouch-anal-anastomosis in ulcerative colitis. *Scand J Gastroenterol*. 2005;40:43–51.

37. Gionchetti P, Rizzello F, Helwig U, et al. Prophylaxis of pouchitis onset with probiotic therapy: a double-blind, placebo-controlled trial. *Gastroenterology*. 2003;124:1202–1209.
38. Gosselink MP, Schouten WR, van Lieshout LM, et al. Delay of the first onset of pouchitis by oral intake of the probiotic strain Lactobacillus rhamnosus GG. *Dis Colon Rectum*. 2004;47:876–884.
39. Cannon J, Lee T, Bolanos J, et al. Pathogenic relevance of Lactobacillus: a retrospective review of over 200 cases. *Eur J Clin Microbiol Infect Dis*. 2005;24:31–40.
40. Lherm T, Monet C, Nougière B, et al. Seven cases of fungemia with Saccharomyces boulardii in critically ill patients. *Intensive Care Med*. 2002;28:797–801.
41. Cassone M, Serra P, Mondello F, et al. Outbreak of Saccharomyces cerevisiae subtype boulardii fungemia in patients neighboring those treated with a probiotic preparation of the organism. *J Clin Microbiol*. 2003;41:5340–5343.
42. Snydman D. The safety of probiotics. *Clin Infect Dis*. 2008;46(Suppl 2):S104–S111.
43. Kato K, Mizuno S, Umesaki Y, et al. Randomized placebo-controlled trial assessing the effect of bifidobacteria-fermented milk on active ulcerative colitis. *Aliment Pharmacol Ther*. 2004;20:1133–1141.