Probiotic Bacteria in the Prevention and the Treatment of Inflammatory Bowel Disease

Richard Fedorak, MD, FRCP, FRCP(London), FRS*, Denny Demeria, MD, FRCPC

INTRODUCTION

The traditional classification of IBD into Crohn disease and ulcerative colitis offers health care providers a logical and evidenced-based approach in developing a meaningful therapeutic approach for the prevention and treatment of these diseases. Current therapies may leave many patients and physicians frustrated, because persistent symptomatology and endoscopic or histopathologic evidence of active disease usually persist despite optimum medical and surgical management. As comprehension of these diseases has progressed, advanced pharmacologic biologic therapies have been developed, such as anti–tumor necrosis factor \( \alpha \) (anti–TNF-\( \alpha \)) agents,...

The authors have nothing to disclose.
Division of Gastroenterology, University of Alberta, 2-14A Zeidler Building, 130 University Campus, Edmonton, Alberta T6G 2X8, Canada
* Corresponding author.
E-mail address: Richard.fedorak@ualberta.ca

http://dx.doi.org/10.1016/j.gtc.2012.08.003
gastro.theclinics.com
0889-8553/12/$ – see front matter © 2012 Elsevier Inc. All rights reserved.
which have resulted in improved symptom and disease control in many patients. Currently, however, a definitive curative strategy for these diseases, using medical therapy alone, remains elusive. Furthermore, these medications are not without significant cost nor are they without risk of potential, and often substantial, side effects. For these reasons, there is a prevalent interest in patients with IBD in pursuing nonconventional avenues of therapy for both symptoms and disease control.\(^1\)

Given these considerations, there has been an increasing appreciation of the importance in understanding the complexities of the interactions between the human host immune system and its resident gastrointestinal luminal microbial population. Current models for the pathogenesis of IBD have demonstrated evidence for a disturbance in this equilibrium, resulting from either an aberrant host immune response to usual luminal microbiota,\(^2\) an exaggerated physiologic immune phenomenon to an abnormal population of microbes in the gastrointestinal tract,\(^3\) or a combination of both.

Probiotic organisms, which are defined as “live microorganisms which when administered in adequate amounts confer a health benefit on the host,”\(^4\) have been used in attempts to take advantage of this relationship to treat various gastrointestinal diseases, including acute traveler’s diarrhea,\(^5\) infectious diarrhea,\(^6\) and irritable bowel syndrome;\(^7\) in the prevention of infantile necrotizing enterocolitis in neonates;\(^8\) and to alter gut microflora in patients with minimal hepatic encephalopathy to prevent the growth of ammonia-producing bacteria in patients with hepatic cirrhosis.\(^9\)

Although the spectrum of diseases of the intestines is broad, this article focuses on the actual and potential roles of the probiotic organism in patients with Crohn disease and ulcerative colitis. To begin with, the basic aspects of the enteric microorganism are reviewed, as they pertain to the development of IBD, and they are compared and contrasted with the host-specific responses to probiotic administration, in both the IBD and non-IBD host. Then the available clinical literature is reviewed, focusing on the use of probiotics in Crohn disease and ulcerative colitis, examining the roles of the probiotic organism in induction of remission as maintenance therapy and in the surgical patient with IBD. Finally, future roles of probiotic therapy in the realm of IBD are proposed.

**GASTROINTESTINAL MICROBES AND IBD**

The human gastrointestinal tract provides a suitable environment to a diverse microbial population, with more than 400 to 500 different species of bacteria currently identified.\(^10\) The primary introduction of this array to the host most likely occurs in close relationship to labor and delivery of the neonate, with *Lactobacillus* and *Prevotella* spp predominating within the vaginal canal at the time of delivery.\(^11,12\) Once established, this microbial population maybe susceptible to changes in diet,\(^13\) age of the host,\(^14\) disease states, and lifestyle. Nevertheless, the specific changes that are effected in the microbial population by each of these variables, however, remain to be fully elucidated.

The importance of the microbe in IBD is demonstrated by clinical and histologic improvement in fecal diversion in patients with Crohn disease;\(^15\) recurrence of symptoms and inflammation with re-exposure of the terminal ileum to luminal contents is the rule. Several studies have magnified the importance of enteral microorganisms in the development and maintenance of IBD. Analysis of mucosal-associated and fecal bacteria reveals diminished commensal microbial diversity (decreased numbers of *Faecalibacterium prausnitzii* and *Lactobacillus*),\(^16-21\) an increased number of mucosal-associated microorganisms,\(^22,23\) and an orientation toward phylogenetic groups of proinflammatory microbes, such as *Escherichia coli*, in patients with active inflammation in Crohn disease and ulcerative colitis.\(^24,25\) It remains to be seen whether
this dysbiotic environment is a prerequisite for developing IBD or is a result of it and which bacteria are specifically involved.

To date, the identification of one or more causative organisms in IBD has not been found. Although early association of *Mycobacterium avium* subsp *paratuberculosis* with spontaneous granulomatous enterocolitis provided a potential causative organism for IBD, its specific role in IBD remains to be determined. Similarly, although there is a higher prevalence of *Yersinia* and *Campylobacter* species in patients with Crohn disease compared with controls their roles too remain to be investigated. Particular attention has been paid to the presence of pathogenic adherent-invasive *E coli*, which has been identified in 36.4% of patients with Crohn disease versus 6% of controls. The reasons for this difference most likely represent a combination of host characteristics (ie, Paneth cell dysfunction; genetic mutations in *NOD2*, *ATG16L1*, or *IRGM*; and abnormal ileal expression of carcinoembryonic antigen-related cell adhesion molecule 6) and microbial properties (type 1 pili variants and increased TNF-α and IFN-γ secretion). The specific relationships between the host immune system and microbiota in IBD are beyond the scope of this article and are reviewed elsewhere.

The microbe and IBD recall points

- 400–500 Species of bacteria reside within human gastrointestinal tract.
- The human host is colonized at birth with bacteria from caregivers. The majority of the bacteria are constant whereas a small proportion can change with time and circumstance (age, disease, lifestyle, and so forth).
- IBD involves dysbiosis and/or abnormal immune host response to the dysbiosis.

**PROBIOTICS**

The alteration of the type or number of bacteria within the gastrointestinal tract in states of disease may have various effects on the host. Thus, the potential to manipulate enteric flora for positive therapeutic purposes is an attractive approach for patients with IBD. Probiotic organisms have had a history of both local and systemic beneficial effects. Box 1 summarizes the multiple beneficial effects, relative to IBD, which probiotic bacteria exert on the gastrointestinal tract. Examples of these were investigated in a pilot study, which examined the effects of various *Lactobacillus* species on various mediators of inflammation and found that the intestinal *Lactobacillus* of elderly persons are tightly associated with increased serum white blood cell count (*Lactobacillus reuteri*), reduced blood glucose levels (*L. fermentum*), and oxidized low-density lipoprotein content (various *Lactobacilli*). In another study, one specific probiotic mixture, VSL3, was found to enhance the anti-inflammatory cytokine pathway via induction of mucosal-associated CD425+ and CD4+ LAP cells and reduce the level of proinflammatory cytokines, including TNF-α, interleukin 1β, and interferon γ.

Not all probiotics have similar mechanisms of action and even those with proved efficacy in IBD may exhibit only a few of the beneficial mechanisms outlined in Box 1. Nevertheless, the ability of probiotics to modulate the microbial-intestinal–immune cascade, even on a minor scale, provides a rational basis for their use in patients with IBD.

Probiotics recall points

- Probiotics are microorganisms, which provide a benefit to the host.
- Probiotics have been shown to have both local and systemic effects on the host.
- Therapeutically successful probiotics have a predominantly anti-inflammatory effect.
PROBIOTICS IN THE TREATMENT OF INFLAMMATORY BOWEL DISEASE

Ulcerative Colitis

Induction of remission

Currently, the data to support clear and consistent clinical benefits in inducing remission in patients with active ulcerative colitis are encouraging, although conflicting data exist (Table 1). The data for probiotics in the induction and maintenance of ulcerative colitis are summarized in Table 1.

Recently, Sood and colleagues38 from India conducted a randomized, multicenter, double-blind, controlled trial evaluating twice-daily probiotic mixture, VSL3 (3.6 × 10^9 colony-forming units [CFU]), in inducing remission in 77 patients with mild to moderately severe ulcerative colitis versus 70 patients given placebo. The primary endpoint was a 50% decrease in ulcerative colitis disease activity index (UCDAI) score at 6 weeks, with final evaluation at 12 weeks. The percentage of patients achieving the primary endpoint was higher in the VSL3 group than the placebo group, both at week 6 (32.5% vs 10%, P < .001) and at week 12 (42.9% vs 15.7%, P < .001).

In a follow-up study, of similar design, Tursi and colleagues39 sought to evaluate the utility of VSL3 in the treatment of relapsing-remitting mild to moderate ulcerative colitis in a double-blind, placebo-controlled trial involving 144 patients randomly treated for 8 weeks with VSL3 (3600 billion CFU/d) (71 patients) or with placebo (73 patients). As a secondary endpoint, 31 (47.7%) patients in the VLS3 group and 23 (32.4%) patients in the placebo group had remission induced by the end of 8 weeks, yet this difference did not reach statistical significance.

Given the potential efficacy of VSL3 in patients with ulcerative colitis, the authors examined its effect in 32 patients with active ulcerative colitis in 2005.40 As an open-label trial, twice-daily dosing of 1800 billion bacteria was administered to patients, who were on concomitant medical therapy (steroids, 5-aminosalicylic acid...
Table 1
Induction and maintenance of remission in ulcerative colitis: a summary of evidence investigating the effect of probiotic treatments

<table>
<thead>
<tr>
<th>First Author, Year</th>
<th>Design Duration</th>
<th>Probiotic</th>
<th>Comparator</th>
<th>Concomitant Therapy</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ulcerative colitis: induction of remission</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rembacken et al, 42 1999</td>
<td>DB, R, C 1 y</td>
<td><em>E. coli</em> Nissle 1917 (1 × 10^{11} CFU) n = 57</td>
<td>Mesalamine (2.4 g) n = 59</td>
<td>Prednisolone or hydrocortisone enemas</td>
<td>As effective as mesalamine at attaining remission</td>
</tr>
<tr>
<td>Borody et al, 81 2003</td>
<td>Case reports 2–13 y</td>
<td>Fecal enema n = 6</td>
<td>None</td>
<td>None</td>
<td>100% Remission</td>
</tr>
<tr>
<td>Guslandi et al, 82 2003</td>
<td>O 4 wk</td>
<td><em>S. bouardii</em> (750 mg) n = 25</td>
<td>None</td>
<td>Mesalamine</td>
<td>Reduction in UCDAI scores</td>
</tr>
<tr>
<td>Kato et al, 83 2004</td>
<td>DB, R, C 12 wk</td>
<td><em>Bifidobacterium</em>-fermented milk (100 mL) n = 10</td>
<td>Placebo n = 10</td>
<td>Sulfasalazine and mesalamine</td>
<td>Reduction in UCDAI (P&lt;.05)</td>
</tr>
<tr>
<td>Tursi et al, 84 2004</td>
<td>R, O 8 wk</td>
<td>Balsalazide (2.25 g) and VSL3 (1 × 10^{11} CFU) n = 30</td>
<td>Balsalazide (4.5 g) n = 30</td>
<td>None</td>
<td>Balsalazide and VSL3 outperformed the 2 comparator groups (symptoms assessment, endoscopic appearance, and histologic evaluation)</td>
</tr>
<tr>
<td>Bibiloni et al, 40 2005</td>
<td>O 6 wk</td>
<td>VSL3 (3.6 × 10^9 CFU) n = 32</td>
<td>None</td>
<td>Mesalamine, steroids, or immunosuppressants</td>
<td>Remission (UCDAI ≤2) achieved in 18, response (UCDAI ≥3) achieved in 8 whereas 3 did not have a response and 3 others worsened</td>
</tr>
<tr>
<td>Furrie et al, 47 2005</td>
<td>DB, R, C 1 mo</td>
<td><em>B. longum</em> and Synergy 1 n = 8</td>
<td>Placebo n = 8</td>
<td>Mesalamine, immunosuppressants, steroids</td>
<td>NSD re sigmoidoscopy scores</td>
</tr>
</tbody>
</table>

(continued on next page)
<table>
<thead>
<tr>
<th>First Author, Year</th>
<th>Design Duration</th>
<th>Probiotic</th>
<th>Comparator</th>
<th>Concomitant Therapy</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tsuda et al, 2007</td>
<td>O 4 wk</td>
<td>BIO-THREE n = 20</td>
<td>None</td>
<td>Mesalamine or 6-mercaptopurine</td>
<td>Remission achieved in 9/20 patients, no response in 8/20, and worsening in 1/20</td>
</tr>
<tr>
<td>Miele et al, 2009</td>
<td>DR, R, C 8 wk</td>
<td>VSL3 (weight-based dosing) n = 19</td>
<td>Placebo n = 10</td>
<td>Corticosteroids, immunosuppressants, mesalamine</td>
<td>Remission achieved in 92% of probiotic-treated patients</td>
</tr>
<tr>
<td>Huynh et al, 2009</td>
<td>O</td>
<td>VSL3 (weight-based dosing) n = 18</td>
<td>None</td>
<td>Patients were failing standard ulcerative colitis induction therapy</td>
<td>Remission achieved in 56% of probiotic treated-patients</td>
</tr>
<tr>
<td>Sood et al, 2009</td>
<td>DB, R, C 12 wk</td>
<td>VSL3 (3.6 x 10^9 CFU) n = 77</td>
<td>Placebo n = 70</td>
<td>Oral mesalamine and immunosuppressants</td>
<td>43% Achieved remission in probiotic group (P&lt;.001)</td>
</tr>
<tr>
<td>Tursi et al, 2010</td>
<td>DB, R, C 8 wk</td>
<td>VSL3 (3.6 x 10^9 CFU) n = 71</td>
<td>Placebo n = 73</td>
<td>5-ASA or immunosuppressants</td>
<td>Remission achieved in 48% for the probiotic group</td>
</tr>
<tr>
<td>Ishikawa et al, 2011</td>
<td>R, C 1 y</td>
<td>B breve strain Yakult (3 x 10^9 CFU) and galacto-oligosaccharide (5.5 g) n = 21</td>
<td>Placebo n = 20</td>
<td>Salazosulfapyridine, mesalamine, steroids</td>
<td>Endoscopic score was significantly reduced in probiotic group compared with baseline (P&lt;.05)</td>
</tr>
</tbody>
</table>

**Ulcerative colitis: maintenance of remission**

<p>| Kruis et al, 1997 | DB, DD, R 3 mo | E coli Nissle 1917 (CFU &gt;10^{10}) n = 50 | Mesalazine (1.6 g) n = 53 | None | NSD for relapse rates, CAI scores, global assessment |</p>
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Design</th>
<th>Duration</th>
<th>Treatment 1</th>
<th>Treatment 2</th>
<th>Treatment 3</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rembacken et al, 42 1999</td>
<td>DB, R, C</td>
<td>1 y</td>
<td>E coli Nissle 1917 (CFU &gt; 10^10)</td>
<td>Mesalamine (1.6 g) n = 44</td>
<td>Prednisolone (tapered to nil over 4 mo)</td>
<td>NSD</td>
<td></td>
</tr>
<tr>
<td>Venturi et al, 85 1999</td>
<td>O</td>
<td>1 y</td>
<td>VSL3 (1 x 10^{11} CFU) n = 20</td>
<td>None</td>
<td>None</td>
<td>75% Maintained clinical and endoscopic remission</td>
<td></td>
</tr>
<tr>
<td>Ishikawa et al, 51 2003</td>
<td>R, C</td>
<td>1 y</td>
<td>BFM n = 11</td>
<td>Placebo n = 10</td>
<td>Salazosulfapyridine, mesalazine, and steroids</td>
<td>Reduced exacerbation of symptoms (P &lt; .01)</td>
<td></td>
</tr>
<tr>
<td>Cui et al, 86 2004</td>
<td>DB, C</td>
<td>8 mo</td>
<td>BIFICO (1.26 g) (1 x 10^7 CFU) n = 15</td>
<td>Placebo n = 15</td>
<td>Sulphasalazine and glucocorticoids</td>
<td>P &lt; .01 Where 93% of placebo relapsed vs 20% of active treatment group</td>
<td></td>
</tr>
<tr>
<td>Kruis et al, 50 2004</td>
<td>DB, R, C</td>
<td>1 y</td>
<td>E coli Nissle 1917 (2.5–25 x 10^9 CFU) n = 162</td>
<td>Mesalamine (1.6 g) n = 165</td>
<td>None</td>
<td>As effective as mesalamine at maintaining remission (SE, P = .003)</td>
<td></td>
</tr>
<tr>
<td>Zocco et al, 53 2006</td>
<td>O</td>
<td>1 y</td>
<td>L rhamnosus GG (1.8 x 10^{10} CFU) n = 65</td>
<td>Mesalazine (2.4 g) n = 60</td>
<td>Mesalazine and LGG n = 62</td>
<td>NSD in relapse rates at 12 months; but probiotic more effective than mesalazine for prolonging duration of remission (P &lt; .05)</td>
<td></td>
</tr>
<tr>
<td>Wildt et al, 54 2011</td>
<td>DB, R, C</td>
<td>1 y</td>
<td>L acidophilus La-5 and B animalis and Lactis BB n = 20</td>
<td>Placebo n = 12</td>
<td>None</td>
<td>Insignificant number of patients achieved remission (P = .37)</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** B infantis, B infantis 356,234; BFM, commercial product containing Yakult live strains of B breve, B bifidum, and L acidophilus YIT 0168; BIFICO, commercial probiotic capsule containing Enterococci, Bifidobacteria, and Lactobacilli triple therapy; C, controlled; CAI, clinical activity index; DB, double blind; L acidophilus, L casei, L delbrueckii subsp bulgaricus, L plantarum, and Streptococcus salivarius subsp thermophilus; NSD, no significant difference; O, open label; R, randomized; SE, significant equivalence; VSL3, commercial mixture containing B longum, B infantis, and B breve.
[5-ASA], 6-mercaptopurine, azathioprine, and antidiarrheal agents) for 6 weeks, evaluating for the presence of probiotic bacteria in tissue samples, as well as UCDAI as an intent-to-treat analysis. This analysis demonstrated that remission was achieved in 53% (n = 18) of patients; response in 24% (n = 8) of patients; no response in 9% (n = 3) of patients; worsening in 9% (n = 3) of patients; and 5% (n = 2) did not have final sigmodinoscopic assessment. This yielded a combined induction of remission/response rate of 77%. Some components of the VSL3 bacteria were identified in 3 patients in remission. No adverse events were identified.

A Japanese study investigated BIO-THREE probiotics (each tablet containing 2 mg of Streptococcus faecalis, 10 mg Clostridium butyricum, and 10 mg Bacillus mesentericus) in an open-label study of 23 patients with mild to moderate distal ulcerative colitis, which was refractory to medical therapy (oral mesalamine, sulfasalazine, 6-mercaptopurine, and mesalamine enema). For 4 weeks, 9 tablets were administered daily. The UCDAI scores were evaluated and fecal microflora were identified by terminal restriction fragment length polymorphism analysis. Remission was observed in 45% (9/20) of patients; response (decrease in UCDAI ≥3 but final score >3) in 10% (2/20); no response in 40% (8/20); and worsening in 5% (1/20). There was an overall increase in fecal bifidobacteria counts.

An early single-center, randomized, double-dummy study investigated induction of remission in 116 patients with ulcerative colitis randomized to either standard mesalamine therapy or E coli Nissle 1917. After a run-in course of tapering prednisolone for moderate to severe disease as well as oral gentamicin for existing microbial floral suppression, no significant differences in induction rates at 4 months were identified (75% and 68% in each group, respectively). Nevertheless, this study was not powered for equivalence.

The use of probiotics in pediatric populations has demonstrated similar encouraging results. For example, an open-label trial using VSL3 twice daily in 18 eligible pediatric patients (ages 3–17) for 8 weeks was completed. Patients were evaluated by the simple clinical colitis activity index and the Mayo ulcerative colitis endoscopic score as well as various serologic and histologic profiling, completed at weeks 0 and 8. This trial demonstrated induction of remission in 56% of subjects (n = 10), response in 6% (n = 1), and no change or worse in 39% of subjects (n = 7). Five patients withdrew due to lack of response to therapy.

Likewise, in a small Italian pediatric trial using VSL3, 29 patients (mean age 9.8 years, range 1.7–16.1 years) with newly diagnosed ulcerative colitis, were randomized to receive VSL3 (weight-based dose, range 450–1800 billion bacteria/d) or placebo. Concomitant steroid induction treatment, consisting of oral methylprednisolone (1 mg/kg/d, maximum 40 mg/d) and oral mesalamine maintenance treatment (50 mg/kg/d), was permitted. The Lichtiger colitis activity index as well as a physician’s global assessment measured disease activity. Follow-up occurred at 0, 6, and 12 months as well as whenever relapse occurred. Remission was achieved in 13 patients (92.8%) in the VSL3 group whereas 4 patients (36.4%) treated with placebo and IBD therapy had successful induction of remission (P < .001).

A Cochrane review was recently performed to delineate the role of probiotics in the induction of remission in ulcerative colitis. The objectives of this review were to analyze and compare the efficacy of probiotics versus placebo or standard medical treatment (eg, corticosteroids, sulfasalazine, or 5-ASA agents) for the induction of remission in active ulcerative colitis. In addition, secondary outcome evaluation included (1) proportion of patients achieving disease improvement, (2) steroid withdrawal, (3) biochemical markers of inflammation, (4) histology scores, (5) progression to surgery, (6) clinical scores, (7) symptomatic severity (stool frequency or abdominal
pain), (8) quality-of-life scores, (9) time to remission/improvement, and (10) withdrawal due to adverse events. From a total of 119 references reviewed, 4 randomized controlled trials met the inclusion criteria whereas 2 were excluded. A formal meta-analysis was not performed due to heterogeneity in probiotic types, methodology, and outcomes. The results of this review showed that none of the studies included demonstrated any meaningful differences in remission induction rates in probiotic-treated cohorts compared with placebo or other comparator groups. The investigators concluded, “Conventional therapy combined with a probiotic does not improve overall remission rates in patients with mild to moderate ulcerative colitis.” With respect to safety concerns, however, one of the studies included showed that there was no statistically significant difference in the incidence of adverse events, between a group treated with probiotics and the placebo group (relative risk [RR] 0.75; 95% CI, 0.3–1.88).

In keeping with the Cochrane review, a meta-analysis performed by Sang and colleagues selected 13 randomized control trials that studied the efficacy of probiotics in the induction and maintenance of remission in ulcerative colitis. Seven of the trials examined induction of remission rates in 219 patients who received probiotics as an auxiliary therapy compared with 180 patients treated with placebo or standard therapy. Again, there was no statistically significant difference in the overall induction of remission rates between the 2 groups, although the investigators concluded that the results were subject to heterogeneous bias. Furthermore, heterogeneity was also identified in a subgroup analysis with respect to probiotic type and disease severity (mild, middle, or active disease) and for treatment of less than 12 months in duration.

Optimizing the effects of probiotic organisms, Furrie and colleagues sought to evaluate the effect of the combination of probiotics and prebiotics (synbiotics) containing Bifidobacterium longum and Synergy 1 (6 g of prebiotic fructooligosaccharide/inulin mix) in a double-blind randomized controlled trial using 18 patients (N = 9, study group) with active ulcerative colitis for a period of 1 month. The patients’ standard therapy at the time of entry into the study remained unchanged (steroids and/or immunosuppressants and/or 5-ASA). The results demonstrated a systemic anti-inflammatory response with a decrease in serum TNF-α (P = .018), interleukin 1 (P = .023), and mRNA levels of defensins 2 and 4. Nevertheless there were no significant differences in sigmoidoscopy or clinical disease activity indices.

Similarly, Ishikawa and colleagues in a randomized controlled trial evaluated 41 patients with mild to moderate ulcerative colitis administered synbiotics. This trial used a B breve strain; Yakult (9 × 10⁹ CFU/g) was administered in divided doses 3 times daily in combination with galacto-oligosaccharide (5.5 g once daily, for 1 year) in comparison to placebo. Both groups were allowed standard medical therapy. Endoscopic evaluation of disease activity was performed at 1 year as well as evaluation of a colonic lavage solution for myeloperoxidase activity. Mean endoscopic disease activity score of patients receiving synbiotics decreased significantly (P<.05) relative to placebo. Furthermore, myeloperoxidase activity in the treatment group significantly decreased (P<.05).

In summary, the existing evidence does not support the broad use of probiotics in the induction of remission in patients with active ulcerative colitis. Not all probiotics are the same and randomized controlled trials of each individual probiotic preparation are required to determine its efficacy. Nevertheless, emerging data from 2 double-blind randomized controlled trials and 3 open-label trials with the probiotic preparation VSL3 are supportive of its efficacy in the induction of remission of ulcerative colitis. In addition, a single trial with E coli Nissle 1917 suggests it may be as effective as mesalamine. These trials, however, were underpowered to be statistically confirmatory.
Probiotics and ulcerative colitis: induction of remission recall points

- Currently, there are insufficient data to support the broad use of probiotics in inducing remission in patients with acute ulcerative colitis.
- Nevertheless, underpowered randomized controlled trials with the probiotic preparation VSL3 have demonstrated its efficacy over placebo in the induction of remission, and *E. coli* Nissle 1917 may be as effective as mesalamine.

**Maintenance of remission**

Kruis and colleagues\(^4^9\) first examined remission maintenance in ulcerative colitis in 120 patients who previously achieved a mesalamine-induced remission. These patients were subsequently randomized to 1600 mg of mesalamine or *E. coli* Nissle 1917. Similar efficacy was identified in both groups at 3 months, with 89% and 84% of the respective groups in remission. Subsequently, the same investigators completed a multicenter, randomized noninferiority trial comparing mesalamine (1600 mg daily) versus *E. coli* Nissle 1917 in 327 patients over a 12-month period.\(^5^0\) *E. coli* Nissle was found statistically noninferior (*P* = .013), with relapse rates of 34% in the mesalamine group and 36% in the *E. coli* Nissle 1917 group.

A prospective, noninferiority trial by Rembacken found similar results in a study comparing oral mesalamine (1600 mg daily) to *E. coli* Nissle 1917 in 116 patients.\(^4^2\) After 12 months, 25% and 26% of the respective groups were found in remission. Furthermore, the rates of remission were found similar to known rates of remission achieved with placebo.

In a randomized, placebo-controlled trial in 21 patients, Ishikawa and colleagues\(^5^1\) examined the effect of fermented milk, which contained live *Bifidobacteria* and *L. acidophilus* in patients with quiescent ulcerative colitis. Clinical remission was sustained over 1 year in 73% of patients taking the probiotic versus 10% in the placebo arm (*P* = .0184). No endoscopic differences, however, were noted.

Shanahan and von Wright\(^5^2\) compared *L. salivarius* subsp. *salivarius* UCC118, *B. infantis* 35,624 (1 × 10\(^9\) CFU/d) or placebo for 1 year in patients with ulcerative colitis in clinical remission (n = 157 patients). There was no significant difference in time to relapse when placebo was compared with either treatment arm. Nevertheless, the probiotics demonstrated an anti-inflammatory effect.

Another prospective randomized trial by Zocco and colleagues\(^5^3\) compared *Lactobacillus* GG (1.8 × 10\(^9\) viable bacteria/d) to delayed-released mesalamine (2400 mg daily) or both in 187 patients with ulcerative colitis. Based on UCDAI scores, relapse rates were similar at 6 months (*P* = .44) and at 12 months (*P* = .77) in all 3 groups, *Lactobacillus* GG did prolong relapse-free time more effectively than mesalamine (*P* < .05).

A recent trial out of Denmark sought to investigate the clinical effects of a combination of *L. acidophilus* La-5 and *B. animalis* subsp. *lactis* BB (Probio-Tec AB-25) in maintenance of remission in a randomized double-blind placebo-controlled trial in 32 patients with ulcerative colitis.\(^5^4\) These patients included those with left-sided ulcerative colitis in remission, including proctitis. All patients had at least one relapse within the year preceding the trial. Twenty patients received Probio-Tec AB-25 whereas 12 received placebo. After 1 year of treatment, 5 patients (25%) in the Probio-Tec AB-25 group and 1 patient (8%) in the placebo group were in remission (*P* = .37). The median times to relapse were 125.5 days (11–391 days) and 104 days (28–369 days), respectively (*P* = .683). Although encouraging, the study was of small size and did not reach statistical significance.

A Cochrane database review in 2011 was performed by Naidoo and colleagues\(^5^5\) to evaluate the role of probiotics in the maintenance of remission in patients with...
ulcerative colitis. Four studies (n = 587) with study duration from 3 to 12 months were included. There were no statistically significant differences between the probiotic-treated and mesalamine-treated patients (40.1% vs 34.1%, respectively; 3 studies; 555 patients; odds ratio [OR] 1.33; 95% CI, 0.94–1.90) and in adverse events (26% vs 24%, respectively; 2 studies; 430 patients; OR 1.21; 95% CI, 0.80–1.84). The investigators identified risk of bias due to lack of blinding and incomplete outcome data (2 studies), and unclear methods of allocation in all 4 studies.

In summary, there is adequately powered randomized controlled trial evidence to support that \textit{E coli} Nissle 1917 is as effective as mesalamine in maintaining remission in patients with mild to moderate ulcerative colitis. Not all probiotics are the same and randomized controlled trials of each individual probiotic preparation are required to determine their efficacy.

Probiotics and ulcerative colitis: maintenance of remission recall point

- \textit{E coli} Nissle 1917 is as effective as mesalamine in maintaining remission in patients with mild to moderate ulcerative colitis.

\textbf{Pouchitis}

In patients with ulcerative colitis in whom medical management fails, total colectomy and construction of an ileal pouch–anal anastomosis (IPAA) is the surgical approach of choice (Table 2). More than half of these patients develop inflammation of the pouch, leading to pouchitis, with symptoms of pain, diarrhea, and often fecal incontinence. A summary of the clinical trials that examined probiotics in the induction and maintenance of remission in pouchitis is in Table 2.

\textbf{Induction and maintenance of remission}

An early, randomized, double-blind, placebo-controlled trial by Gionchetti and colleagues\textsuperscript{56} demonstrated successful maintenance of remission with probiotics in 40 patients. These patients first underwent a successful induction of remission of their pouchitis with antibiotics and then were randomized to VSL3 or placebo. After 9 months, 85% of the VSL3-treated patients versus 0% of those on placebo were in remission. Relapse of pouchitis occurred within 3 months in those patients who had their VSL3 discontinued.

In a follow-up, double-blind, placebo-controlled trial Gionchetti sought to examine primary prevention of pouchitis in patients who had recently undergone an IPAA operation.\textsuperscript{57} In 40 consecutive patients, immediately after IPAA construction, 20 were randomized to VSL3 (9 \times 10^9 CFU/d whereas 20 received placebo for 12 months. Every 3 months, clinical, endoscopic, and histologic evaluations were performed. At 12 months, 90% of VSL3-treated patients and 60% of placebo-treated patients were in remission (log-rank test, z = 2.273; \textit{P}<.05).

Similar to the early trial by Gionchetti, Mimura and colleagues\textsuperscript{58} also examined the maintenance of remission after inducing pouchitis into remission with antibiotics. The trial compared VSL3 to placebo in a double-blind randomized controlled study. Remission rates after 12 months were 85% in the VSL3-treated group versus 6% in the placebo-treated arm, supporting the previous findings by Gionchetti.

In an open-label trial, using \textit{Lactobacillus} GG, Gosselink and colleagues\textsuperscript{59} also demonstrated the ability of another probiotic to maintain remission after induction of pouchitis remission with antibiotics. In this study, 93% of patients treated with \textit{Lactobacillus} GG were in remission at 12 months. Divergent from this maintenance of remission data with \textit{Lactobacillus} GG, Kuisma and colleagues\textsuperscript{60} did not find \textit{Lactobacillus} GG able to induce remission in patients with acute pouchitis. Over a 3-month period,
### Table 2
Evidence for the effect of probiotic treatments in pouchitis

<table>
<thead>
<tr>
<th>First Author, Year</th>
<th>Design Duration</th>
<th>Probiotic</th>
<th>Comparator</th>
<th>Concomitant Therapy</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pouchitis: induction of remission</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kuisma et al, 60 2003</td>
<td>DB, R, C 3 mo</td>
<td>Lactobacillus GG (1 x 10^{10} CFU) n = 10</td>
<td>Placebo n = 10</td>
<td>Not indicated</td>
<td>No difference in pouch disease activity index</td>
</tr>
<tr>
<td>Laake et al, 87 2004</td>
<td>O 4 wk</td>
<td>L acidophilus and B lactis–fermented milk (500 mL) n = 51</td>
<td>None</td>
<td>Loperamide</td>
<td>Improved pouch disease activity index; no difference in histology</td>
</tr>
<tr>
<td>Pronio et al, 36 2008</td>
<td>O 1 y</td>
<td>VSL3 n = 31</td>
<td>None</td>
<td>None</td>
<td>Reduction in pouch disease activity index</td>
</tr>
<tr>
<td><strong>Pouchitis: maintenance of remission</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gionchetti et al, 88 2000</td>
<td>DB, R, C 9 mo</td>
<td>VSL3 (6 g) n = 20</td>
<td>Placebo n = 20</td>
<td>None</td>
<td>Increased duration of remission (P &lt; .001)</td>
</tr>
<tr>
<td>Gionchetti et al, 57 2003</td>
<td>DB, R, C 1 y</td>
<td>VSL3 (1 x 10^{11} CFU) n = 20</td>
<td>Placebo n = 20</td>
<td>None</td>
<td>Increased duration of remission (P &lt; .05)</td>
</tr>
<tr>
<td>Gosselink et al, 59 2004</td>
<td>R, C 3 y</td>
<td>L rhamnosus GG (CFU &gt; 10^{10}) n = 78</td>
<td>Placebo n = 39</td>
<td>Not indicated</td>
<td>Increased duration of remission (P = .011)</td>
</tr>
<tr>
<td>Mimura et al, 58 2004</td>
<td>DB, R, C 1 y</td>
<td>VSL3 (6 g) n = 20</td>
<td>Placebo n = 16</td>
<td>Not indicated</td>
<td>Increased duration of remission (P &lt; .0001)</td>
</tr>
</tbody>
</table>

**Abbreviations:** C, controlled; DB, double blind; L acidophilus, L casei, L delbrueckii subsp bulgaricus, L plantarum, and Streptococcus salivarius subsp thermophilus; O, open label; R, randomized; VSL3, commercial mixture containing B longum, B infantis, and B breve.
only 40% of patients with acute pouchitis treated with *Lactobacillus* GG were colonized with the *Lactobacillus* GG and no clinical benefit was realized in the treatment group compared with the placebo group.

Given the efficacy of VSL3 in maintenance of remission of pouchitis, studies have been performed to document changes in mucosal inflammation and characterize the associated changes in the mucosal and systemic immune systems and luminal microbial profiles. An Italian study by Pronio and colleagues\(^3\) examined the effects of VSL3 in 31 IPAA patients in an open-label trial lasting 1 year. This demonstrated an expansion in CD4\(^+\) T lymphocytes expressing CD25 (CD4\(^+\) CD25 high), CD4\(^+\) latency-associated peptide (CD4\(^+\) LAP), interleukin-1\(\beta\) in peripheral blood mononuclear cells, and mucosal biopsies, all indices demonstrating enhanced anti-inflammatory effects. Accordingly, patients experienced a reduction in their pouch activity index. Studies of pouch biodiversity have shown reduction in both species type and absolute colony count in those patients who have undergone IPAA for ulcerative colitis when compared with those who have undergone IPAA for familial adenomatous polyposis.\(^6\) In addition, in a murine model of colitis induced by 2,4,6-trinitrobenzenesulfonic acid, VSL3 reduced mucosal inflammation in association with a reduction in biodiversity.\(^6\)

In summary, there are randomized controlled studies supporting VSL3 and *Lactobacillus* GG in the maintenance of remission of pouchitis after IPAA or antibiotic-induced remission, respectively. Not all probiotics are the same and randomized controlled trials of each individual probiotic preparation are required to determine its efficacy.

**Probiotics and pouchitis: recall points**
- Probiotics have been shown effective in maintenance of remission of patients with pouchitis.

**Crohn Disease**

**Induction of remission**

Table 3 summarizes the clinical trials that examined probiotics in the induction and maintenance of remission in Crohn disease.

A recent clinical trial by Steed and colleagues\(^6\) evaluated mucosal TNF-\(\alpha\) levels and remission rates in 35 patients with Crohn disease, who were randomized to either placebo or a synbiotic comprising *B longum* and Synergy 1 while on concurrent immunomodulation or immunosuppression. There were significant improvements in mean CDAI scores in the synbiotic group (start 219 ± 74.6, finish 147 ± 74; *P* = .020) but not in the placebo group (start 249 ± 79.4, finish 233 ± 155; *P* = .810) after 6 months. Similar improvements in mean histologic scores in the synbiotic group (*P* = .018) were also seen over the same time. A significant initial reduction in mucosal TNF-\(\alpha\) levels (*P* = .041) at 3 months was not maintained at 6 months.

These encouraging data, however, have not been the rule. In 2008, Butterworth and colleagues\(^6\) completed a Cochrane review of the role of probiotics in the induction of remission of active Crohn disease and confirmed that a favorable therapeutic response in these patients remains to be seen. Included in this analysis were small open-label trials because no randomized placebo-controlled trials existed. In 2004, Schultz and colleagues\(^6\) used *Lactobacillus* GG in patients with active Crohn disease who were initially treated with concurrent steroids and antibiotics for 1 week and then randomized to receive either *Lactobacillus* GG or placebo. Of the 5 of 11 patients who completed the trial, the time to relapse was similar between treatment and the placebo groups (12 wk vs 16 wk, *P* = .5). Another open-label trial by Fujimori and colleagues\(^6\) in 2007 showed improvement in CDAI scores in 7 of 10 patients treated with
### Table 3

**Induction and maintenance of remission in Crohn disease: a summary of evidence investigating the effect of probiotic treatments**

<table>
<thead>
<tr>
<th>First Author, Date</th>
<th>Design Duration</th>
<th>Group (dose/d)</th>
<th>Comparator</th>
<th>Concomitant Therapy</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Crohn disease: induction of remission</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gupta et al,68 2000</td>
<td>O 6 mo</td>
<td>LGG (2 × 10^10 CFU) n = 4</td>
<td>None</td>
<td>Prednisone, immunomodulatory agents, metronidazole</td>
<td>Improved CDAI scores compared with baseline (P &lt; .05)</td>
</tr>
<tr>
<td>McCarthy et al,67 2001</td>
<td>O N/A</td>
<td>L salivarius UCC118</td>
<td>None</td>
<td>N/A</td>
<td>Improved CDAI scores</td>
</tr>
<tr>
<td>Schultz et al,65 2004</td>
<td>DB, R, C 6 mo</td>
<td>LGG (2 × 10^9 CFU) n = 5</td>
<td>Placebo n = 6</td>
<td>Ciprofloxacin, metronidazole, corticosteroids</td>
<td>NSD</td>
</tr>
<tr>
<td>Fujimori et al,66 2007</td>
<td>O 13 ± 4.5 mo</td>
<td>B breve (3 × 10^10 CFU), L casei (3 × 10^10 CFU), B longum (1.5 × 10^10 CFU), Psyllium (9.9 g) n = 10</td>
<td>None</td>
<td>Aminosalicylate, prednisolone, home enteral nutrition</td>
<td>Improved CDAI and IOIBD scores compared with baseline (255–136, P = .009, and 3.5–2.1, P = .03, respectively). 60% (6/10) achieved remission</td>
</tr>
<tr>
<td>Steed et al,63 2010</td>
<td>DB, R, C 6 mo</td>
<td>B longum (4 × 10^11 CFU) and Synergy 1 (12 g) n = 13</td>
<td>Placebo n = 11</td>
<td>Steroids and/or immunomodulators</td>
<td>Reductions in TNF-α expression and CDAI at 3 months (P = .041)</td>
</tr>
<tr>
<td><strong>Crohn disease: maintenance of remission</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malchow et al,89 1997</td>
<td>DB, R, C 1 y</td>
<td>E coli Nissle 1917 (5 × 10^10 CFU) n = 16</td>
<td>Placebo n = 12</td>
<td>Prednisolone</td>
<td>NSD</td>
</tr>
<tr>
<td>Guslandi et al,69 2000</td>
<td>R, C 6 mo</td>
<td>S boulardii (1 g) and mesalamine (2 g) n = 16</td>
<td>Mesalamine (3 g) n = 16</td>
<td>Not indicated</td>
<td>Increased duration of remission (P &lt; .05)</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Duration</td>
<td>Treatment</td>
<td>Placebo</td>
<td>Adjunct Therapy</td>
</tr>
<tr>
<td>-----------------------</td>
<td>-----------</td>
<td>----------</td>
<td>------------</td>
<td>-----------</td>
<td>-------------------------------------------</td>
</tr>
<tr>
<td>Prantera et al, 2002</td>
<td>DB, R, C</td>
<td>1 y</td>
<td>LGG (1.2 × 10^{10} CFU) n = 22</td>
<td>Placebo n = 23</td>
<td>Loperamide, cholestyramine</td>
</tr>
<tr>
<td>Bousvaros et al, 2005</td>
<td>DB, R, C</td>
<td>2 y</td>
<td>LGG (4 × 10^{10} CFU) n = 39</td>
<td>Placebo n = 36</td>
<td>Aminosaliclylates, 6-mercaptopurine, azathioprine, corticosteroids</td>
</tr>
<tr>
<td>Marteau et al, 2006</td>
<td>DB, R, C</td>
<td>6 mo</td>
<td>L johnsonii LA1, Nestle (2 × 10^{9} CFU) n = 43</td>
<td>Placebo n = 47</td>
<td>Loperamide, cholestyramine, corticosteroids tapered to nil by wk 3</td>
</tr>
<tr>
<td>Chermesh et al, 2007</td>
<td>DB, R, C</td>
<td>2 y</td>
<td>Synbiotic 2000 n = 7</td>
<td>Placebo n = 2</td>
<td>Not indicated</td>
</tr>
<tr>
<td>Vilela et al, 2008</td>
<td>R, C</td>
<td>3 mo</td>
<td>S boulardii (1.2 × 10^{9} CFU) n = 14</td>
<td>Placebo n = 17</td>
<td>Mesalamine, immunosuppressants, thalidomide</td>
</tr>
</tbody>
</table>

Abbreviations: C, controlled; DB, double blind; LGG, L rhamnosus GG; N/A, not available; NSD, no significant difference; O, open label; R, randomized; *, special note.
a combination of *Lactobacillus* and *Bifidobacterium* species. Another uncontrolled open-label trial in 2001 also showed an improvement in CDAI scores in patients with Crohn disease treated with *L salivarius* UCC118.67 In 2000, Gupta and colleagues68 evaluated the possible benefits of twice-daily dosing of *Lactobacillus* GG in a 6-month open-label trial in 4 pediatric patients with Crohn disease taking concomitant glucocorticoid and/or immunomodulator therapy.68 By the end of the first week, the Pediatric Crohn Disease Activity Index (PCDAI) score had improved and this effect was maintained throughout the study period. At 4 weeks, 3 patients had a PCDAI score of less than 10 (median PCDAI score = 5, range 0–12.5), 73% lower than baseline. Glucocorticoid tapering was achieved in 3 patients, whereas 3 patients experienced clinical relapses, 4 to 12 weeks after discontinuing the probiotic.

In summary, there is no evidence for the use of probiotics in induction of remission in Crohn disease. The existing clinical trials are small and open label. Not all probiotics are the same and randomized controlled trials of each individual probiotic preparation are required to determine its efficacy.

Probiotics and Crohn disease: induction of remission recall points
- There is insufficient evidence to support probiotic use in inducing remission in patients with Crohn disease.

**Maintenance of medically induced remission**

In an early small trial69 using *Saccharomyces boulardii*, 32 patients with Crohn disease were randomized to either mesalamine (1 g 3 times a day) or mesalamine (1 g 2 times a day) in addition to a preparation of *S boulardii* (1 g daily). Clinical remission was observed in 94% and 62% of patients, respectively (*P = .04*).

Given that mucosal permeability is increased in Crohn disease, Vilela and colleagues70 examined the effects of *S boulardii* or placebo in 34 patients with Crohn disease in remission, measuring intestinal permeability with lactulose/mannitol ratios. Again, current therapeutic regimen remained unaltered. In the placebo group, there was worsening of the intestinal permeability with an increase in the lactulose/mannitol ratio by 0.004 ± 0.010 (*P = .12*) at the end of the third month. In contrast, in the *S boulardii*–treated group, there was an improvement in intestinal permeability, with a decrease in the lactulose/mannitol ratio by 0.008 ± 0.006 (*P = .0005*). Complete normalization of intestinal permeability, however, was not achieved.

Most studies in Crohn disease, however, are not supportive of a probiotic effect. Bousvaros and colleagues71 found no difference in relapse rates in 75 pediatric Crohn disease patients receiving either *Lactobacillus* GG or placebo over a period of 24 months (71% vs 83%, respectively). Similarly, other studies have demonstrated results for *Lactobacillus* that are in keeping with this.72,73

A Cochrane review in 200674 failed to demonstrate any benefit for probiotics as maintenance therapy in patients with Crohn disease; however, the investigators observed that due to low patient enrollment, statistical power may have been affected. In 2008, Rahimi and colleagues75 conducted a meta-analysis, which included 8 randomized controlled trials evaluating the role of probiotics in the maintenance of remission and in Crohn disease. No significant differences were noted for either clinical relapse (OR = 0.92 [0.52–1.62]) or endoscopic relapse (OR = 0.97 [0.54–1.78]).

In 2009, Shen and colleagues,76 in a meta-analysis, evaluated *Lactobacillus* species with respect to efficacy and adverse events as maintenance therapy in patients with Crohn disease. They included 6 trials (359 patients) comparing *Lactobacilli* with placebo; the RR of clinical relapse rate was 1.15 (95% CI, 0.90–1.48) and the RR of endoscopic relapse rate was 1.31 (95% CI, 0.57–3.00), whereas the pooled RR of
adverse events was 0.83 (95% CI, 0.61–1.12). They suggested that *L. rhamnosus* GG might actually increase the relapse rate in patients with Crohn disease.

In summary, there is no evidence for the use of probiotics in maintenance of medically induced remission in Crohn disease. The existing clinical trials are small and open label. Not all probiotics are the same and randomized controlled trials of each individual probiotic preparation are required to determine its efficacy.

**Probiotics and Crohn disease: maintenance of medically induced remission recall points**

- There is insufficient evidence to support probiotic use in maintenance of medically induced remission in patients with Crohn disease.

**Maintenance of surgically induced remission**

There remains to be definitive evidence to support the use of probiotic organisms as maintenance therapy in patients with Crohn disease who have had remission induced via surgical means. Prantera and colleagues\(^72\) used *Lactobacillus* GG in 45 patients versus placebo, administered within 10 days postoperatively to patients undergoing intestinal resection for their Crohn disease. At 12 months, no significant endoscopic or clinical differences were realized between the 2 groups. Furthermore, Marteau and colleagues\(^73\) performed a randomized, placebo-controlled trial comparing *Lactobacillus johnsonii* LA1 (2 \(\times\) \(10^9\) CFU/d) to placebo and found no clinical or endoscopic differences (98 patients) at 6 months.

A meta-analysis in 2009 by Doherty\(^78\) confirmed the ineffectiveness of probiotics versus placebo in the control of surgically induced remission in patients with Crohn disease: RR of clinical recurrence with any probiotic = 1.41 (95% CI, 0.59–3.36) and RR of endoscopic recurrence = 0.98 (95% CI, 0.74–1.29).

In hopes of improving the efficacy of probiotics, Chermesh and colleagues\(^77\) sought to evaluate a mixture of 4 prebiotics (nondigestible foodstuffs used to stimulate the activity of bacteria within the gastrointestinal tract) and 4 probiotics (Synbiotic 2000) to placebo in postoperative patients with Crohn disease. Again, no discernible endoscopic or clinical differences were noted.

In summary, there is little evidence to support the use of probiotics in the setting of postoperative patient with Crohn disease in hopes of preventing clinical or endoscopic relapse.

**Probiotics and surgical patients with Crohn disease: maintenance of surgically induced remission recall points**

- There are insufficient data to support probiotic use in maintaining surgically induced remission in patients with Crohn disease in the postoperative state

**SUMMARY**

The presence of a diverse microbial population within the gastrointestinal tract and the changes that occur during IBD provide reasonable support for the use of probiotic organisms in the treatment of ulcerative colitis, pouchitis, and Crohn disease.\(^79\)

Double-blind, randomized controlled studies support the therapeutic role of some, but not all, probiotics in the treatment of ulcerative colitis and pouchitis but not yet Crohn disease. Nonetheless, challenges remain. Not all probiotics are the same and thus properly powered and controlled clinical trials are needed for each probiotic preparation before it can be accepted as a therapeutic modality. There does not seem to be a “class” effect for probiotics. Despite this, the human gastrointestinal tract represents a dynamic environment for the microbe, with changes in host
anatomy, physiology, and disease states affecting microbe diversity and, in turn, microbe diversity affecting the host and disease states. There is much to be done in the field of probiotic research, both at the microbial and mechanism of action levels and also within the clinical trial realm. Specifically, future large scale prospective trials are required to move beyond the prevalence of current small uncontrolled trials with probiotics. For probiotic treatment to advance and become mainstream, they need to be seen and treated as clinically significant pharmacotherapeutic agents, with appropriate consideration given to their efficacy and safety profiles.

REFERENCES


