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# Probiotics and Crohn's Disease

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## Abstract

Crohn's disease (CD) is a chronic inflammatory condition that can affect any part of the gastrointestinal tract. The human gut microbiome is altered in patients with Crohn's disease. This knowledge has led to research directed at altering the microbiome for therapeutic potential. Probiotics are an attractive therapy, both from a researcher's perspective and also from the patients' perspective. In this chapter, we will review the current clinical evidence for the use of probiotics in the treatment of Crohn's disease. These studies are divided into three categories: induction of remission, maintenance of medically induced remission, and maintenance of surgically induced remission. Unfortunately, there is insufficient evidence to support the use of probiotics in the management of Crohn's disease at this time.

**Keywords:** Crohn's disease, remission, post-operative recurrence, CDAI

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## 1. Introduction

Crohn's disease (CD) is one of the inflammatory bowel diseases (IBD) that can affect any part of the intestinal tract, from the gums to bum. This disease was first described in 1932 as regional ileitis; at that time, treatment was palliative [1]. It was known even then that this disease could cause perforation and fistulas. Crohn's disease is characterized by transmural inflammation, ulceration—from superficial aphthous ulcers to those that are deep and cause penetration, with skip lesions, and granulomas on pathological specimens. The pathogenesis of Crohn's disease is multifactorial—genetic susceptibility, altered host immune response, interplay with the environment, and altered gut microbiome.

The mainstay of treatment for Crohn's disease is medical with surgical intervention reserved for managing strictures and fistulas and for medically refractory disease. While there is no cure

for Crohn's disease, therapies are used to induce remission and maintain remission. When surgery is used to induce remission, strategies to prevent post-operative recurrence are important. Standard therapies for Crohn's disease focus on altering the immune system with corticosteroids, immunosuppressants, and biologic therapies that are directed at altering the immune system. Knowledge of the role of the enteric bacteria in the pathogenesis of Crohn's disease has led to interest in using probiotics for the treatment of this disease.

## 2. The altered microbiome in Crohn's disease

The microbiome of patients with Crohn's disease is known to be different than healthy controls. This difference is frequently called dysbiosis. The faecal microbiota in patients with CD has less complexity compared to the healthy controls [2]. Further, the temporal stability of dominant species of bacteria is lower in patients with CD compared to the controls [3]. Biopsy specimens of patients with IBD showed an abundance of *Enterobacteriaceae* compared to the controls [4]. Interestingly, in another study, biopsies from affected and unaffected areas of tissue of patients with IBD show significant differences in diversity [5]. It is uncertain whether the changes in the microbiota in IBD contribute to the disease development or the reverse is true. The Genetics, Environmental, Microbial (GEM) Project is looking for insight into this question by recruiting healthy first-degree siblings and offspring of patients with CD ([www.gemproject.ca](http://www.gemproject.ca)). Alterations of the microbiome may prove to be an effective approach for the treatment of IBD, especially if these changes in microbiome precede the onset of the disease.

Altering the microbiome as a way to treat active Crohn's disease (induce remission) or maintain remission induced by surgery or medications is being explored. Current methods to alter the microbiome include diet, antibiotics, probiotics, and more recently faecal microbial transplantation.

The use of enteral nutrition (EN) to induce remission in children with Crohn's disease has long been described [6]. In the recent ECCO/ESPGHAN guidelines, exclusive enteral nutrition is recommended as first-line therapy to induce remission in children with active luminal CD [7]. Recently, a systematic review of EN to maintain remission has also shown that EN is associated with a lower risk of relapse compared to a regular diet (34% vs. 64%,  $p < 0.01$ ) [8]. Dietary therapy has rapid effects on microbiota composition and reduces inflammation [9].

Antibiotic exposure is known to be associated with dysbiosis, and this dysbiosis has been shown to be decreased with reduced intestinal inflammation in CD [9]. There are several studies looking at the antibiotics for the treatment of luminal Crohn's disease with some evidence to support the use of ciprofloxacin and metronidazole in treating luminal disease [10]. In surgically induced remission, antibiotics, in particular metronidazole and ornidazole, can reduce recurrence rates at 1 year [10].

Finally, probiotics are being used to attempt to alter the microbiome in patients with IBD. To date, the studies looking at probiotics to treat Crohn's disease have shown a rather modest

benefit [11]. Nevertheless, patients and physicians alike remain interested in the potential of probiotics for use in the management of IBD. In a focus group study of patients with IBD and IBS conducted at the Cleveland Clinic, patients viewed probiotics favourably and understood them as a natural, low-risk option [12]. In addition to this, they had many unanswered questions about the use of probiotics. This further supports the need for health care providers to know and understand the evidence for the use of probiotics in the treatment of Crohn's disease.

### 3. Probiotic therapy in Crohn's disease

Medical treatment of Crohn's disease is often classified into the following categories: (1) induction of remission, (2) maintenance of medically induced remission, and (3) maintenance of surgically induced remission. The results of the available randomized and open-label clinical trials examining the effectiveness of probiotics will be presented for each of these three categories. In Crohn's disease, traditionally, clinical indices have been used to assess clinical efficacy for the treatment of Crohn's disease, with an emphasis on improving patient's symptoms and quality of life. The Crohn's disease activity index (CDAI) is most commonly used with values <150 being associated with remission and scores >450 indicating severe disease [13]. More recently, mucosal healing has emerged as an important and objective treatment endpoint in evaluating the efficacy for the treatments of Crohn's disease [14]. The majority of the studies of probiotics in Crohn's disease have used clinical endpoints, with the exception of the post-operative recurrence studies [15].

#### 3.1. Induction of remission

The data to support the use of synbiotics or probiotics to treat active Crohn's disease are limited. In an open-label trial, Fujimori et al. examined the effect of synbiotic therapy (*Bifidobacterium breve*, *Lactobacillus casei*, *Bifidobacterium longum*, and *psyllium*) in 10 CD patients with active disease, the CDAI significantly improved (255-136,  $P = 0.009$ ) with only two of the six responders successfully discontinuing steroid therapy in 13 months [15]. In a randomized controlled study of a different synbiotic (*Bifidobacterium longum* and Synergy 1 [inulin and oligofructose]), the CDAI of 35 patients with active CD also significantly improved at 6 months in the treatment group ( $219 \pm 78$  vs.  $147 \pm 74$ ,  $p = 0.02$ ) but not in the placebo group ( $249 \pm 78$  vs.  $233 \pm 155$ ,  $p = 0.81$ ) [16]. A criticism of this study is that baseline CDAI of the treatment group was lower than the placebo group, even though this difference was not statistically different ( $p = 0.35$ ). Schultz et al. treated 11 CD patients with antibiotics and a tapering course of steroids. At 2 weeks, antibiotics were discontinued and the subjects were randomized to receive either *Lactobacillus GG* or placebo but found no difference in remission rates between the groups (80% vs. 83%) [17]. Twenty-five patients with mild/moderately active CD taking 5-acetylsalicylic acid (5-ASA) were treated in an open-label study with *Lactobacillus salivarius* for 6 weeks which resulted in significant improvement in clinical disease activity (217 vs. 150,  $p < 0.05$ ) [18]. In a small open-label study of four paediatric CD patients using *Lactobacillus GG* for

6 months, Gupta et al. [19] showed a significant improvement in paediatric CDAI scores ( $p < 0.05$ ) and 3/4 were able to taper their steroids.

In a recent meta-analysis that included 12 randomized trials studying remission induction in active IBD, subgroup analyses for CD showed no significant benefit with probiotics for inducing remission or response in active disease ( $p = 0.35$ ,  $RR = 0.89$ ) [20]. Overall, based on current evidence, probiotics cannot be recommended for use to induce remission in patients with active Crohn's disease.

### 3.2. Maintenance of medically induced remission

To date, the only study that demonstrated a statistically significant prolongation of medically induced remission in CD was that of Guslandi et al. [21], who compared *Saccharomyces boulardii* plus mesalamine versus mesalamine alone for 6 months. In this study, only 6.25% patients treated with probiotic plus mesalamine had a clinical relapse compared to 37.5% treated with mesalamine alone ( $p = 0.04$ ). Prior to this, Malchow [22] completed a randomized, double-blind, placebo-controlled study of *Escherichia coli* Nissle 1917 in a group of 28 patients with active colonic CD with corticosteroid-induced remission. In this study of the patients that were able to successfully wean from steroids, 30% of the probiotic group relapsed compared to 70% of the controls; this difference was not statistically different.

Currently, in regards to *Lactobacillus*, there continues to only be one randomized, placebo-controlled trial in the adult population to evaluate if *Lactobacillus* GG is effective in inducing or maintaining medically induced remission [17]. All patients received a 2-week course of ciprofloxacin and metronidazole, along with a 12-week tapering course of corticosteroids starting at 60 mg. Eleven patients with moderate to active CD were initially enrolled to receive probiotic, LGG ( $2 \times 10^9$  CFU/day), or placebo at week 2 of the study for six months. The primary endpoint was sustained remission defined as the absence of relapse at the 6-month follow-up visit. Relapse was defined as an increase in CDAI of  $>100$  points. This study did not identify a benefit of *Lactobacillus* GG in maintaining remission in CD. However, a limitation of this study was inadequate power as the sample size was only 11 patients with only 5/11 patients completing the study. Of the five patients who remained in the study, two patients in each of the placebo and the probiotic groups had sustained remission. Systematic reviews and meta-analyses have also identified no benefits of *Lactobacillus* as a single probiotic agent in maintaining remission or preventing clinical or endoscopic relapses [20, 23, 24].

Bousvaros et al. [25] conducted a study in which 75 paediatric CD patients in remission were randomly assigned to receive either *Lactobacillus rhamnosus* strain GG (LGG) or placebo for 2 years. There were no significant differences between the groups with respect to the median time to relapse (9.8 vs. 11.0 months,  $p = 0.24$  for the LGG and placebo groups, respectively) or the number of patients who relapsed ( $p = 0.18$ ).

Most recently, Bourreille et al. [26] have conducted the only randomized-controlled trial (FLORABEST) in 165 patients with corticosteroid- or aminosalicylate-induced remission; patients were randomized to *Saccharomyces boulardii* or placebo for 1 year. The rate of relapse

was similar between the groups (47.5% were in the *S. boulardii* group vs. 53.2% were in the placebo group,  $p > 0.05$ ) with no difference in the median time to relapse.

In a recent meta-analysis from 2014, subgroup analyses assessing seven studies recruiting CD patients revealed no significant difference in maintaining clinical remission with probiotics and placebo. The strains assessed included *E. coli* Nissle and *Bifidobacterium longum* [20]. Study limitations include the lack of consistency with probiotic, dose, concurrent IBD medications and the absence of endoscopic assessment of remission. Thus, there remains inconclusive evidence to support the use of probiotics to maintain remission in Crohn's disease and well-designed studies are required.

### 3.3. Maintenance of surgically induced remission

Recurrence of Crohn's disease post-resection continues to be an ongoing challenge in its management. The Rutgeerts score is a widely accepted scoring system for assessment of endoscopic recurrence post-ileocolonic resection. A number of studies have looked at different probiotics to prevent disease recurrence in CD patients with surgically induced remission.

Campieri et al. [27] reported in an abstract, a study of 40 patients treated with either rifaximin for 3 months followed by VSL#3 for 9 months versus mesalamine for 12 months, endoscopic recurrence rates at 1 year (80% for the probiotic group vs. 60% mesalamine group, no statistics reported). In another study of VSL#3, this combination product significantly reduced CD post-operative recurrence when the probiotic was administered immediately after surgery but not when administered some months after surgery [28]. In this multicenter study, 120 patients were randomly assigned to receive VSL#3 or placebo for 90 days, after 90 days of randomized treatment, all patients demonstrating either no or mild endoscopic recurrence were given VSL#3 for the remainder of this 365-day study. Colonoscopy was performed at days 90 and 365 to assess for endoscopic recurrence. At day 90, rates of severe endoscopic recurrence were similar (9.3% for the VSL#3 vs. 15.7 for placebo,  $p = 0.19$ ). Endoscopic assessment at 365 days showed a trend toward less severe endoscopic recurrence if treated with VSL#3 for the year than those treated later (10% vs. 26.7%,  $p = 0.09$ ).

In a randomized, double-blind trial by Prantera et al. [29], 40 patients received either *Lactobacillus* GG versus placebo following surgical resection for 1 year, there were no significant differences in clinical recurrence (16.6% vs. 10.5%,  $p = 0.948$ ), or endoscopic recurrence (60% vs. 35.2%,  $p = 0.297$ ) between the two groups. In 2006, Marteau et al. [30] conducted a larger trial ( $n = 98$ ) over 6 months to investigate the efficacy of a single probiotic strain (*Lactobacillus johnsonii* LA1) to prolong the time to relapse in CD patients. The per protocol analysis confirmed that there was no significant difference between the two cohorts regarding endoscopic recurrence of disease at 6 months (64% vs. 49%,  $p = 0.15$ ). Similarly, Van Gossum et al. [31] examined the efficacy of this same probiotic *Lactobacillus johnsonii* LA1 in a multicenter randomized controlled trial to prolong the time to relapse following elective ileocecal resection. Subjects were randomized to probiotic or placebo for 12 weeks at which time endoscopic recurrence was assessed; the proportion of patients with severe recurrence was similar (21% vs. 15%,  $p = 0.33$ ).



In 2007, Chermesh et al. [32], conducted a small trial of Synbiotic 2000 (a commercial mixture containing four probiotics and four prebiotics) versus placebo. A total of 30 subjects were randomized 2:1 to probiotic: placebo. During the 2-year study, 21 subjects dropped out leaving only nine patients for analysis. No significant difference was found.

In summary, the evidence to support the use of probiotics to prevent recurrence in surgically induced remission is lacking.

#### 4. Conclusion

The role of the microbiome as part of the pathogenesis of Crohn's disease has provided the impetus for much of the research at ways to influence the microbiome in patients with Crohn's disease. Probiotics, along with antibiotics, diet, and faecal microbial transplant, are being studied as options to treat this chronic inflammatory disease. Probiotics are appealing to patients likely due to them being perceived as natural, low-risk therapies for the treatment of IBD, in contrast to standard therapy which focuses on modulating the immune system. To date, the evidence to support the use of probiotics to induce and maintain remission in Crohn's disease is disappointing. Problems with probiotic research include the lack of knowledge about which probiotic to choose and at what dose. For probiotics to have a role in the management of Crohn's disease, more research is needed to align the pathogenic mechanism of the disease with the actions of the probiotics.

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