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### Probiotics and prebiotics in Crohn's disease therapies



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Therapeutic manipulation of gut microbiota has proven valuable in the management of ulcerative colitis and pouchitis. Despite some similarities among the various inflammatory bowel conditions, the probiotics investigated thus far seem to confer little benefit in Crohn's disease. In this review, we aim to bring together the evidence available on the clinical effect of probiotics and prebiotics in Crohn's disease patients, and to clarify the place of probiotic treatment in current Crohn's therapeutic regimens.

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#### Introduction

A variety of in vitro experiments and animal models show that probiotic strains could reshape gut immune parameters [1–4]. Correlation of these findings with physiological events taking place within the human body, however, is far from unequivocal [5]. Results from controlled clinical trials are not always consistent with preclinical findings, especially in the immunologically diverse field of inflammatory bowel disease: for example, though probiotics have proven to be fairly advantageous in pouchitis and UC, those investigated thus far seem to confer little benefit in Crohn's disease.

In this review, we aim to clarify the evidence available on the clinical effect of probiotics and prebiotics in current therapeutic regimens for Crohn's disease. In doing so, we take into consideration different treatment endpoints (induction of remission vs. prevention of relapses), anatomical nuances

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(ileal vs. colonic disease), choice of specific microorganism(s), dosages, modes of administration, and duration of therapy.

### Induction of clinical remission

Four relatively small studies [6–9] examined the use of probiotics as an adjunct therapy to conventional treatments, in the induction of clinical remission in Crohn's patients (Table 1).

In a pioneering study by Plein and Hotz in 1993 [6], 20 Crohn's patients treated conventionally, yet with some residual diarrhea (bowel movements  $5.0 \pm 1.4$  evacuations/day) and moderate complaints (CDAI  $193 \pm 32$ ), were also administered the yeast preparation *Saccharomyces boulardii* for two weeks. A modest yet statistically significant reduction in the frequency of bowel movements ( $5.0 \pm 1.4$  vs.  $4.1 \pm 2.3$  evacuations/day;  $p < 0.01$ ) and in CDAI ( $193 \pm 32$  vs.  $168 \pm 59$ ;  $p < 0.05$ ) was reported in the open-labeled, uncontrolled induction phase of the study.

In a small (4 patients) open-label uncontrolled pilot by Gupta et al. [10], a lactic acid-producing *Lactobacillus rhamnosus* GG (previously known as *L. acidophilus* GG) administered for 6 months was observed to ameliorate clinical activity in children with mildly to moderately active Crohn's disease. These results were challenged by a subsequent study by Schultz et al. [7], where 11 adult patients with active Crohn's disease were treated with a combination of corticosteroids (60 mg/day) and antibiotics, and then randomized for addition of LGG or placebo to the treatment regimen. No difference in clinical remission rates was observed during the 6 month-long treatment period.

Steed et al. [8] randomized 35 patients with active Crohn's disease to receive a synbiotic regimen comprising *Bifidobacterium longum*, oligofructose and inulin, or placebo, for 6 months, in tandem with stable doses of conventional medications. Almost half of the patients from both experimental and control arms were lost to follow-up. Bearing in mind this limitation, significant clinical improvement in the rest of the synbiotic group was reported, a finding supported by simultaneous improvement in their histological scores, and reductions in serum levels of pro-inflammatory TNF- $\alpha$ .

In addition to those randomized controlled studies, Fujimori et al. [9] reported results from a small open-label, uncontrolled trial involving 10 active and steroid-refractory Crohn's patients treated with psyllium (*Plantago ovata*), and a probiotic preparation consisting of *Bifidobacterium breve*, *Bifidobacterium longum*, and *Lactobacillus casei*. Over the 13 months of synbiotic therapy, 7 out of 10 patients reported symptomatic improvement. However, only 2 of them were able to discontinue corticosteroid treatment, and laboratory markers of inflammation did not improve.

Overall, there is no convincing evidence that probiotics – either alone, or in combination with prebiotic preparations – display a significant ability to effectively augment conventional treatments in inducing clinical remission in Crohn's patients [11–15].

### Maintenance of medically induced remission

Nine studies examined the ability of various probiotic regimens to support the maintenance of medically induced clinical remission in such patients [6,7,16–22] (Table 2).

**Table 1**  
Use of probiotics to induce clinical remission in Crohn's patients.

Study	No. of patients	Duration (months)	Probiotic strain	Control	Outcome
Plein, 1993 [6]	17	½ month	<i>S. boulardii</i>	Open-labeled; uncontrolled	Modest symptomatic improvement
Schultz et al., 2004 [7]	11	6	LGG + Corticosteroids	Placebo + Corticosteroids	No benefit
Steed et al., 2010 [8]	35 (16 lost to follow-up)	6	<i>B. longum</i> + "Synergy 1"	Placebo	Symptomatic improvement
Fujimori et al., 2007 [9]	10	13	<i>B. longum</i> , <i>B. breve</i> , <i>L. casei</i> + <i>Plantago ovata</i>	Open-labeled; uncontrolled	Symptomatic improvement

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