

REVIEW ARTICLE

Probiotic Use in Gastrointestinal Conditions: An Overview of Efficacy and Evidence

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ABSTRACT: Probiotics are collections of live bacteria that are meant to be ingested for beneficial purposes. Many different preparations are widely available over-the-counter and used to improve or stabilize gastrointestinal flora. Studies have shown promise for probiotic use in a number of gastrointestinal diseases, treating medication side effects, and in healthy individuals with minor GI upset. Investigators continue to evaluate the effects the gastrointestinal microbiome has on homeostasis and methods by which probiotics may beneficially influence the microbiome. Long term efficacy, choice of species, dosage, and concentration of available preparations also remain areas of evolving study. This article will discuss probiotic regulation and formulations, review current understanding of mechanisms of action, and summarize recent study data in regards to clinically relevant GI disorders.

INTRODUCTION

Probiotics are collections of bacterial flora that are meant to be ingested for beneficial purposes. Most varieties of probiotics are normally present in healthy gastrointestinal tracts and have become a popular research target over the past two decades for the treatment of nearly every gastrointestinal issue. Probiotics come in many forms, including pills, additives in water, cultured milk, yogurt, and other foods. They are currently treated as a supplement, and thus are not required to prove safety or efficacy to be sold to consumers.¹ The FDA has not approved any probiotics for the treatment of disease.

Probiotic research runs parallel to the effects of the gut microbiome on overall health. Healthy GI flora has been shown to play a role in metabolism, immune response, cardiovascular disease, and even mental health. A study of Americans not taking antibiotics found that most patients have stable levels of the same fecal bacteria over at least five years, while other studies indicate these bacteria levels may stay steady over an individual's lifetime. The effects of diet, race, and genetic factors on the microbiome requires more research. However, if the healthy microbiome becomes affected by antibiotics or disease, we may be able to return it to baseline with probiotic supplementation and have positive effects on overall health.²

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MECHANISM OF ACTION

There is no consistently-proposed mechanism of action by which probiotics exert their effects, although several hypotheses have been put forth.^{3,4} It is thought that beneficial bacteria contained in probiotics compete for nutrients, starving out pathogens, or that they are able to bind invaders for a direct antagonistic effect. Probiotics may be able to exert antimicrobial effects on harmful bacteria, or stimulate an immune response to better fight off pathogens with the proper antibody response, increasing mucosal immune products such as IgA. Some species may be able to aid in digestion of products such as gliadins in gluten and decrease inflammation in autoimmune disease. They may be able to repair defects in GI permeability, or simply compete for adhesion sites, affecting which bacteria survive.^{3,4,10}

FIGURE 1 :

Proposed Mechanisms of Action⁴³

Downregulation of proinflammatory cytokines in the GI tract
Strengthening or enhancing the epithelial barrier in the GI tract
Displacing pathogenic bacterial species or competing for adhesion sites
Beneficial changes to GI flora through acidification and fermentation of nutrients

DOSING

There is little consensus about the ideal concentration for probiotics, and studies vary in the number of colony forming units (CFUs) studied. Most over-the-counter preparations contain around 106 CFUs. (Figure 2) Study treatment times have ranged

anywhere from one week to three months, raising the question of long term viability of probiotics as a treatment. Due to the wide variation of data, it is difficult to determine which species, preparation, concentration, and duration of probiotic treatment to use specific GI disorders. Most studies are small and have poor outcomes regarding efficacy, but there are some promising formulations for certain diseases. Generally, broad spectrum combinations such as VSL#3 and products containing 10 billion CFUs appear to be most effective.

FIGURE 2 :

Commonly found formulations and pricing

Brand	Culture	CFUs	Price
Align	<i>B. infantis</i>	1x10 ⁷	\$50/ 56 count package
Culturelle	<i>L. rhamnosus</i>	1x10 ¹⁰	\$30-\$40/ 60 capsules
DanActive	<i>L. casei</i>	1x10 ¹⁰	\$4-\$5/bottle
Florastor	<i>S. boulardii</i>	5x10 ⁹	\$25/ 20 capsules
Mutaflor	<i>E. coli</i>	1x10 ⁹	\$75/ 60 capsules
VSL#3	<i>Bifidobacterium breve</i> , <i>B. longum</i> , <i>B. infantis</i> , <i>Lactobacillus acidophilus</i> , <i>L. plantarum</i> , <i>L. paracasei</i> , <i>L. bulgaricus</i> , <i>Streptococcus thermophilus</i>	1x10 ¹¹ 9x10 ¹¹	\$60 for 60 capsules \$50-\$90 for 60 capsules

SPECIFIC CONDITIONS

Antibiotic-Associated Diarrhea

Diarrhea is an extremely common side effect of antibiotic use. The clinical impact of antibiotic-associated diarrhea (AAD) ranges from mild, self-limited disease to life-threatening illness such as *Clostridium difficile* diarrhea. Probiotics are effective in maintaining gut flora during antibiotic treatment in children and adults and can be prescribed with the antibiotic course to increase patient compliance.

A Cochrane database review of twenty-three studies targeting children assessed the use of probiotics during antibiotic administration on prevention of AAD. Various probiotic formulations were used, including eight different strains across studies. The incidence of AAD in the treatment group was 8% compared to 19% in the control group. Analysis of this meta-analysis noted that this evidence was only moderate quality.⁵

A meta-analysis of adult and pediatric patients prescribed *Lactobacillus* for prevention of AAD during antibiotic treatment showed that those receiving *Lactobacillus* had a significantly lower risk of AAD (reported NNT ranging from 8-13). Subgroup analysis found this to be effective for adults but not pediatric patients.⁶

Acute Pancreatitis

Patients suffering from acute pancreatitis incur a risk of necrosis and subsequent infection and mortality. Studies analyzing the effect of probiotics on acute pancreatitis have been inconclusive or show increases in mortality and complications. They generally conclude that probiotics are not effective in treatment of acute pancreatitis.

One multicenter, randomized, double-blind, placebo-controlled study involved patients with APACHE II severe acute pancreatitis. Patients received probiotics or placebo within three days of symptom onset. Infectious complications occurred at a higher rate in the probiotics group compared to placebo. In addition, 16% of patients in the probiotics group died compared with 6% in the placebo group. Some patients in the probiotic group developed bowel ischemia while none in the placebo group did.^{7,8}

Clostridium difficile Associated Diarrhea

Clostridium difficile associated diarrhea (CDAD) remains a troublesome inpatient and outpatient issue causing considerable mortality and health care spending. Probiotic use in CDAD remains controversial due to inconsistent evidence regarding treatment initiation and variability in data collection.

A meta-analysis of nineteen studies consisting of a cohort receiving probiotics and antibiotics and a control group receiving antibiotics alone showed decreased incidence of CDAD in the probiotic group. Results showed 1.6% of patients in the probiotic group contracted CDAD vs. 3.9% in the control group ($p < 0.001$). The most benefit was seen when probiotics were given within two days of antibiotic administration.⁹

In 2012, a meta-analysis of 20 trials involving adult and pediatric patients was performed to assess prevention of CDAD with the use of probiotics. Probiotic administration reduced CDAD by 66%. Those treated with probiotics also experienced less adverse events at 9.3% compared to 12.6% in the control group. In a population experiencing an incidence of CDAD at 5%, it was extrapolated that the use of probiotics for prophylaxis may prevent 33 episodes of CDAD per every 1000 patients. There was missing outcome data in 13 of the trials with up to 45% of data missing for some patients.⁹

Celiac Disease

Trials of probiotics for celiac disease have assessed probiotics' ability to hydrolyze gliadins in preventing symptoms. VSL#3 probiotics were used to pre-digest gliadins and compared to laboratory digestion of gliadins. Celiac jejunal biopsies were exposed to the pre-digested VSL#3 gliadin and showed a decrease in inflammatory cell infiltration, indicating possible benefits and immune modulation.¹⁰

Another study involved 22 patients with laboratory confirmed celiac disease. They were randomized to receive *B. infantis* or placebo two times a day for three weeks. Baseline intestinal permeability was not significantly affected by either treatment arm, but there was subjective improvement in symptoms.¹¹ Using probiotics in patients with celiac disease may provide subjective

improvement if patients have failed other options as adverse effects are minimal.

Constipation

Constipation can be induced by medication or diet. Although it is often self-limited, constipation can cause significant impairment through impaction or obstruction. Probiotics are effective in increasing stool frequency and are well tolerated although treatment with polyethylene glycol (PEG) may be just as effective.

A systematic review and meta-analysis of 21 studies that involved patients treated with either *Lactobacillus* or *Bifidobacterium* determined there was an increase in weekly stool frequency ($p < 0.001$) although the effects varied depending on which ROME criteria was used. The meta-analysis observed high heterogeneity and publication bias, and when corrected for this, the effects on stool frequency were less apparent.¹²

Treatment of constipation with probiotics in pediatric patients was studied using *Lactobacillus reuteri* in a trial involving 121 patients ages 3-7. Patients with functional constipation were treated with a *Lactobacillus* formulation or PEG. There was no significant difference in number of bowel movements at two months and no difference in reported abdominal pain, pain with defecation, withholding, or hard stool.¹³

Healthy Patients

Patients without chronic gastrointestinal conditions may be prescribed probiotics to maintain healthy gut flora and prevent general GI upset. The available data involved non-primary outcomes and featured small sample sizes, but probiotics remain a viable and safe choice for healthy patients looking to use them as a supplement.

Two identical trials that involved treatment of healthy female patients with mild GI upset using *Bifidobacterium lactis* in fermented milk were assessed in 2013. Study groups were given fermented milk containing the probiotic or a control dairy drink for four weeks. A repeat study was designed to emulate the original study. No significant difference in GI wellbeing between the treatment and control groups was observed, but there was improvement when both studies were included in pooled analysis.¹⁴

A 2017 study that involved healthy elderly patients assessed the effects of *Bifidobacterium lactis* on cellular immune function. There was an increase in PMN phagocyte capability and NK cell tumoricidal activity, though no patient-oriented outcomes were assessed. Data quality was low, as only four studies were included in the final meta-analysis.¹⁵

Hepatic Encephalopathy

Lactulose and Rifaximin are proven therapies for hepatic encephalopathy (HE), and probiotics have been proposed as an adjunctive treatment. Probiotics are well tolerated and effective in improving symptoms and quality of life, but data is low quality with high associated bias and should be interpreted in this light.

A meta-analysis that included 21 trials compared probiotic with placebo or no treatment. Some of the trials also compared lactulose to probiotics. VSL#3 was the most commonly used probiotic, and duration of treatment was highly variable. There was low quality evidence of no effect on all-cause mortality in the treatment group. There was moderate quality evidence of incomplete or no resolution of HE symptoms in the treatment group. Adverse events were lower in the treatment group, quality of life was better, and ammonia levels were lower.¹⁶

A study from the *American Journal of Gastroenterology* in 2012 assessed lactulose vs. probiotics vs. placebo for secondary prophylaxis in cirrhotic patients who had already recovered from HE. Patients treated with lactulose probiotics saw a significant benefit when compared with placebo. There was no difference between patients treated with lactulose vs. probiotics.¹⁷

In a 2004 study, 97 patients with cirrhosis were randomized to receive either placebo or a "synbiotic" treatment of probiotics with fiber. The treatment group had a significant increase in stool *Lactobacillus* species and a decrease in *E. coli*, *Staphylococcus* species, and blood ammonia levels.¹⁸

H. Pylori Infection and Eradication

Helicobacter pylori is commonly encountered in primary care and ensuring eradication is central to preventing further gastric mucosal damage. Current studies show risk of bias, and show only modest benefit to using probiotics in conjunction with recommended treatment.

Infectious Diarrhea

Probiotic use has been shown to have beneficial effects on infectious causes of diarrhea and can decrease severity and duration of symptoms. Use in treatment of rotavirus induced diarrhea has produced inconsistent results.

A Cochrane review in 2010 collected 63 trials comparing probiotics with placebo in patients with acute infection diarrhea. Fifty-six studies enrolled infants and children. There was wide variation in species, dosage, and patient medical characteristics. Mean duration of diarrhea was reduced by 24.76 hours, and there was a reduction in stool frequency by day 2 in the treatment groups. There were no adverse events reported in the treatment group.²¹

A meta-analysis that included 12 studies showed that *Saccharomyces boulardii*, *Lactobacillus acidophilus*, and *Bifidobacterium bifidum* had statistically significant effects on reducing or preventing traveler's diarrhea ($P < 0.001$). There were no adverse events reported across all 12 trials.²²

One meta-analysis collected 14 studies that involved treatment of children with acute diarrhea due to rotavirus. *Lactobacillus rhamnosus* significantly reduced duration of diarrhea in some studies while others did not show any significant difference.²³

A multi-center, randomized controlled trial evaluated *Lactobacillus reuteri* use in children with acute infectious diarrhea in an outpatient setting. One group was treated with oral rehydration

solution (ORS) and probiotics and compared to a control group receiving ORS alone. Duration of diarrhea was reduced by 15 hours in the treatment group ($p < 0.05$). There was no difference in the percentage of children with diarrhea after 72 hours. There were no reported adverse effects related to probiotic administration.²⁴

Inflammatory Bowel Disease

Probiotics have been heavily targeted for treatment and symptomatic relief of IBD to promote beneficial immune modulation in the GI tract and help maintain healthy mucosal barrier function. They are effective for symptom control in patients with ulcerative colitis (UC) and are well tolerated. Their use in Crohn's disease (CD) has been shown to be ineffective, so probiotics should not be used in this patient population.

A meta-analysis of 23 randomized controlled trials looked at the effect of probiotics on inducing remission and maintaining therapy in UC, CD, and pouchitis. Remission rates were found to be significantly higher in patients with active UC treated with probiotics than with placebo. Subgroup analysis found that only VSL#3 probiotics significantly increased the remission rates compared to controls in patients with active UC. VSL#3 was beneficial for maintaining remission in patients with pouchitis, and probiotics can provide the similar effect as 5-aminosalicylic acid on maintaining remission of UC without additional adverse events.²⁵

Analysis of 18 trials revealed that VSL#3 had significant effect ($P < 0.01$) in patients with UC. In children with IBD, the combination of Lactobacillus with VSL#3 probiotics had significant positive effect ($P < 0.01$). In conclusion, it was stated that probiotics are beneficial in IBD, especially the combination ones in UC.²⁶

Review of 22 RCT's showed that with the exception of VSL#3, probiotics held no benefit over placebo in inducing remission in active UC. They concluded that VSL#3 may be effective in inducing remission in active UC and that probiotics may be as effective as 5-ASAs in preventing relapse of quiescent UC. There was no benefit of probiotics in inducing remission of active CD, in preventing relapse of quiescent CD, or in preventing relapse of CD after surgically induced remission.²⁷

Irritable Bowel Syndrome

Probiotics are a safe option for treatment of IBS and have been shown to be somewhat effective. Available trials are short in duration, have low sample sizes, and show mixed results or only modest benefit. When treating IBS with probiotics, patients should be instructed to continue treatment symptomatically as needed.

One study that involved 122 patients randomized to receive placebo vs. Bifidobacterium bifidum once daily for four weeks resulted in beneficial response in 57% of patients receiving Bifidobacteria compared to only 21% in the placebo group.²⁸

Another study involved 100 subjects randomized to receive placebo or a combination of probiotics for four weeks. The placebo group did not experience relief of symptoms compared with the probiotic combination, and there was a decrease in subjective abdominal pain in the treatment group.²⁹

A trial in which 25 patients with IBS were randomly assigned treatment with VSL#3 or placebo twice a day for eight weeks showed no significant difference in GI transit, bowel function scores, or global symptom relief. There was statistically significant relief of abdominal bloating in the treatment group.³⁰

Another study enrolled 70 patients with IBS and randomly assigned them to receive Lactobacillus plantarum and Bifidobacterium breve, Lactobacillus plantarum and Lactobacillus acidophilus, or a placebo powder for four weeks. Pain score and IBS severity scores decreased significantly in the treatment group after 14 weeks compared to placebo.³¹

Seventy-seven patients with IBS were randomized to receive Lactobacillus salivarius, Bifidobacterium infantis or placebo for eight weeks. Patients receiving B. infantis reported reduction in symptoms with easier bowel movements and less abdominal discomfort compared to placebo. In addition, patients with IBS had abnormal IL-10/IL-12 ratios at baseline that were found to be normalized in patients receiving B. infantis.³²

One large study involving 362 patients with IBS were randomized to get placebo or a freeze-dried B. infantis for four weeks. Patients were given three different CFU concentrations. Only the middle-concentration group receiving a concentration of 1×10^8 CFU of B. infantis had significantly reduced symptoms. The lack of benefit observed at other dosage levels indicates the need for more trials regarding formulation.³³

A study performed in early 2018 was the first to assess probiotic efficacy on small intestinal bacterial overgrowth (SIBO) in patients with IBS. Five patients with IBS and SIBO and 21 patients with IBS without SIBO were enrolled. Patients were given a capsule containing Saccharomyces boulardii, Bifidobacterium lactis, Lactobacillus acidophilus and Lactobacillus plantarum twice a day for 30 days. There was a 71% decrease in total IBS score in the IBS plus SIBO group compared to a 10.6% decrease in the IBS group. The IBS scoring is highly subjective, sample size was small, and results should be interpreted carefully.³⁴

Lactose Intolerance

A systematic review performed to evaluate the role of probiotics in lactose intolerance involved 10 RCTs. The researchers concluded that probiotics did not alleviate symptoms of lactose intolerance. There were some strains and concentrations that may be effective, but further research is necessary.³⁵

Necrotizing Enterocolitis in Preterm Infants

Neonatal necrotizing enterocolitis (NEC) is a condition of ischemic necrosis of the bowel due to the proliferation of enteric gas-forming microorganisms. It occurs in approximately 1–3 infants per 1,000 live births,^{36,37,38} and is much more common in preterm infants.³⁹ It is thought that administration of probiotics should reduce the development of the altered gut microbiome that predisposes preterm infants to NEC.

Two meta-analyses have reviewed the usefulness of probiotics for preventing severe NEC. They concluded that probiotics led to a reduction in the incidence of NEC and mortality associated

with NEC in very-low birth weight (VLBW) infants. They also found that feeding with human breast milk worked synergistically with probiotics to protect against NEC. Based off a subgroup analysis, Thomas et al. concluded that Lactobacillus and Bifidobacterium species led to the best reduction in NEC-related mortality and all-cause mortality. They did not find that probiotics prevented the incidence of surgical NEC.⁴¹ Given the fragility of the patient population most at risk for NEC (VLBW and preterm infants), there is a magnification of common problems facing probiotics, including poor quality control and lack of standardization of the specific products offered.^{40,41} Considering the current state of evidence, probiotics have not been routinely adopted as a preventive strategy for the development of NEC.

Pouchitis

An ileal pouch-anal anastomosis is performed in some patients that require a total proctocolectomy. Inflammation of this pouch can occur, and treatment with probiotics has been shown to be effective in reducing inflammatory cytokines and improving stool consistency.

A study performed in 2017 used Lactobacillus acidophilus to treat pouchitis in rats that had undergone a colectomy and ileal pouch-anal anastomosis. Dextran sulfate sodium was administered to the rats to induce pouchitis. End points involved reduced weight loss associated with pouchitis (p<0.05), rate of hematochezia disappearance and stool consistency. There was an observed reduction of pro-inflammatory factors such as TNF-alpha, IL-1B, and IL-6 in the treatment group (p<0.05).⁴²

CONTRAINDICATIONS

Probiotic preparations carry minimal risk of side effects and are well tolerated. Clinicians should prescribe probiotics when indicated in generally healthy patients if there is the possibility of symptom relief. There are situations in which probiotics are contraindicated, as there have been reported incidences of sepsis and fungal overgrowth. Those with acute pancreatitis should not receive probiotics as they may increase mortality.^{7,8} Patients with immunocompromising conditions such as cancer and those on immunosuppressive drugs like transplant recipients should not receive probiotics.⁴³ Further studies are needed to assess other areas where probiotics may be contraindicated, if clinicians have concern for harm or mortality they should not be prescribed.

CONCLUSION

When used in conjunction with standard treatment, probiotics can be useful in symptom management of several frequently encountered GI disorders. Although cost remains an issue, probiotics have minimal side effects and are well tolerated by most patients. What species to use should be taken into consideration when choosing to prescribe probiotics for patients with specific GI disorders.^{Fig.4} VSL#3 probiotics may be effective in the short-term for treatment of pouchitis. Patients with ulcerative colitis who cannot tolerate traditional treatments may respond well to E. coli probiotics. There has been no benefit seen in trials involving

patients with Crohn's disease. Adult and pediatric patients who are assumed to have infectious diarrhea may respond to probiotic treatment with Lactobacillus GG and S. boulardii. Results of trials analyzing treatment of IBS with probiotics have been inconclusive as to which formulation may be effective. There are very few studies on lactose intolerance, and no benefit has been seen so far. Trials of probiotic use for patients with hepatic encephalopathy have shown no benefit in regards to mortality. Probiotics should be avoided in patients who are critically ill or have immunocompromising conditions.⁴³

FIGURE 3 :

Probiotic efficacy by disease type ^{25,43,44,45}
Evidence ratings of A through D per GRADE rating scale

Condition	Efficacy	Evidence rating
Antibiotic associated diarrhea	May be effective for treatment and prevention	A ⁴⁴
Clostridium difficile colitis	May be effective for prevention but not treatment	A ⁴⁴
Infectious diarrhea	May be effective for treatment	A ⁴⁴
Ulcerative Colitis	May be effective for treatment	A ²⁵
Crohn's disease	No proven benefit	C ⁴⁴
Pouchitis	May be effective for treatment	C ²⁵
Irritable Bowel Syndrome	May be effective for symptom relief	B ⁴⁵
Lactose intolerance	No proven benefit	Insufficient studies to provide rating
Hepatic encephalopathy	No proven benefit, may decrease hepatic encephalopathy but no more effective than lactulose and rifaximin	C ⁴⁴
Necrotizing Enterocolitis	No proven benefit, but may reduce mortality in very low birth weight infants	C ⁴⁴

AUTHOR DISCLOSURES:

No relevant financial affiliations

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FIGURE 4 :

Strains that may be effective for certain conditions

Condition	Probiotic strain
Antibiotic- associated diarrhea ⁴⁴	Lactobacillus acidophilus, L. casei, L. rhamnosus, Saccharomyces Boulardii
Clostridium difficile associated diarrhea ⁴⁴	Lactobacillus acidophilus, L. casei, L. rhamnosus
Celiac disease ^{10,11}	Bifidobacterium breve, B. longum, B. infantis, Lactobacillus acidophilus, L. plantarum, L. paracasei, L. bulgaricus, Streptococcus thermophilus
Infectious diarrhea ⁴⁴	Lactobacillus reuteri, L. protectis, L. casei, Saccharomyces. Boulardii
Irritable Bowel Syndrome ⁴³	Bifidobacterium spp., Lactobacillus spp.
Necrotizing enterocolitis ⁴¹	Bifidobacterium spp., Lactobacillus acidophilus, L. casei, L. rhamnosus
Pouchitis ⁴³	Bifidobacterium breve, B. longum, B. infantis, Lactobacillus acidophilus, L. plantarum, L. paracasei, L. bulgaricus, Streptococcus thermophilus
Ulcerative colitis ⁴³	Bifidobacterium longum, B. breve, B. bifidum, E. coli Nissle 1917, Lactobacillus acidophilus, L. GG

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