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Melissa Maloof

*James Madison University*

Grace Berardini

*James Madison University*

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**PROBIOTICS AS AN ADJUNCT TREATMENT TO STANDARD  
THERAPY IN ULCERATIVE COLITIS.**

Grace Berardini PA-S and Melissa Maloof PA-S  
James Madison University  
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## **ABSTRACT**

**Objective:** To determine the effectiveness of probiotics in addition to traditional therapy for patients with ulcerative colitis (UC) using a systematic review. **Methods:** PubMed and Cochrane Library databases were queried to evaluate patient clinical trials within the past five years using the search terms probiotics and ulcerative colitis. **Results:** Three trials met inclusion criteria. Two of three studies found no significant improvement in their primary endpoint with probiotics. Yoshimatsu, et al. found that after one year 56.6% of the placebo group remained in remission, whereas 69.5% of the probiotic group remained in remission ( $p > 0.05$ ).<sup>9</sup> Tursi, et al. found no significant difference ( $p = 0.069$ ) in UC remission after 8 weeks of using probiotics.<sup>10</sup> Palumbo, et al. did find a significant difference ( $p < 0.05$ ) in the UC disease activity index (UCDAI), stool frequency, intestinal mucosa, and rectal bleeding after two years of using a probiotic blend.<sup>11</sup> **Conclusion:** This systematic review did not show strong evidence in support of probiotic supplementation in UC patients. However, due to trial design and limited number of patients, a potential benefit to probiotics may exist. While it appears that probiotics do not pose any additional risk to individuals with UC, until large randomized trials are performed, we cannot recommend or discourage the use of probiotics.

## **INTRODUCTION**

Ulcerative colitis (UC) is a form of inflammatory bowel disease that causes an estimated 6 cases per 100,000 individuals annually.<sup>1</sup> UC is characterized by relapsing-remitting episodes affecting the mucosal layer of the colon.<sup>2</sup> It consistently involves the rectum and may extend proximally as far as the left colic flexure.<sup>2</sup> A small subset of patients have continuing symptoms and are unable to arrive at complete symptomatic remission.<sup>2</sup> UC is commonly diagnosed in patients aged 15-35 years old, however it can present at any age and in either gender.<sup>2</sup>

The cause of UC is poorly understood and is still under examination. While no single etiology has been identified, several ideas have been studied. It is believed that many factors contribute to the development of UC, including a genetic predisposition, environmental factors, and the immune system.<sup>3</sup> In normal hosts, phagocytic cells do not attack the enteric bacteria.<sup>3</sup> However, in patients with UC, phagocytes begin to mount a response to the normal microflora and secrete interleukin – 25, a proinflammatory cytokine, favoring a type 2 helper T cell (Th2) and mast cell immune response.<sup>3</sup> This results in inflammation and injury to the mucosal layer.<sup>3</sup>

In contrast to the cellular level, at the organismal level there is evidence to believe that the enteric bacteria in individuals with UC is less diverse than in healthy patients.<sup>3</sup> Individuals with inflammatory bowel disease have an increased rate of gut pathogens.<sup>3</sup> While several pathogenic bacteria, such as *Pectinatus*, *Sutterella*, and *Fusobacterium*, are often present in UC, there is no evidence to prove these are causative bacteria of the disease.<sup>3</sup>

There are three classifications of severity in UC, including: mild, moderate, and severe. Mild UC is characterized as intermittent rectal bleeding, associated with fewer than four episodes of diarrhea per day, and may also present with periods of crampy abdominal pain, tenesmus, and constipation. Symptoms associated with moderate UC include up to 10 episodes of diarrhea per day, mild abdominal pain, and a low-grade fever. Mild anemia may also be seen in moderate disease.<sup>2</sup> Severe UC, however, is distinguished as greater than 10 episodes of diarrhea per day, severe crampy abdominal pain, fever, and anemia often requiring a blood transfusion.<sup>2</sup> These patients may also suffer unintentional weight loss and develop poor nutrition.<sup>2</sup>

The diagnosis of UC is made based on a person having chronic diarrhea for more than 4 weeks, evidence of inflammation on endoscopy, and chronic inflammatory changes on biopsy.<sup>2,4</sup> Because these criteria aren't specific for UC, other conditions must be ruled out based on patient history and other lab studies.<sup>2,4,5</sup> Patients with UC can have a wide variety of findings on endoscopy and biopsy.<sup>2,4</sup> Endoscopic findings that support the diagnosis of UC include engorged, granular, erythematous mucosa, petechiae, spontaneous bleeding, edema, and erosions in the mucosa.<sup>2,4</sup> Biopsy findings can include "crypt abscesses, crypt branching, shortening and disarray, and crypt atrophy" as well as others.<sup>2</sup>

No medication can cure UC so the goal of medication therapy is to reduce symptoms and to induce and maintain remission.<sup>5,6</sup> Treatment of UC largely depends on the location and severity of the disease, however most initial treatment for people with mild to moderate disease begins with the use of 5-aminosalicylic acid (5-ASA) containing medications called aminosalicylates.<sup>5,6</sup> Topical and oral 5-ASA formulations, such as sulfasalazine and mesalamine, are available and are used for their anti-inflammatory and immunosuppressive properties.<sup>6,7</sup> Other medications are available for more severe cases of UC and include oral and intravenous corticosteroids, immunomodulators, and biologic agents.<sup>5,6</sup>

In the addition to standard 5-ASA treatment, probiotics have been used as an adjunct therapy for UC.<sup>7,8</sup> Probiotics are supplements of live microorganisms, such as *Lactobacillus*, *Bifidobacterium*, *Saccharomyces*, *Escherichia coli*, *Enterococcus*, *Streptococcus*, *Pediococcus*, and *Leuconostoc*, that are beneficial to the human gut.<sup>7,8</sup> Probiotics are believed to decrease the amount of pathogenic microorganisms that are able to colonize the gut, improve the ability of the gut to act as a barrier, and reduce proinflammatory cytokines.<sup>8</sup> For the aforementioned reasons, the use of probiotics has been studied for efficacy in the adjunct treatment of several gastrointestinal disorders, including UC.<sup>7,8</sup> Three different probiotic formulations and their ability to aid in the prolongation of remission and reduction of symptoms in UC are reviewed here.

### **PICO**

*Population:* In patients older than 13 years old with UC

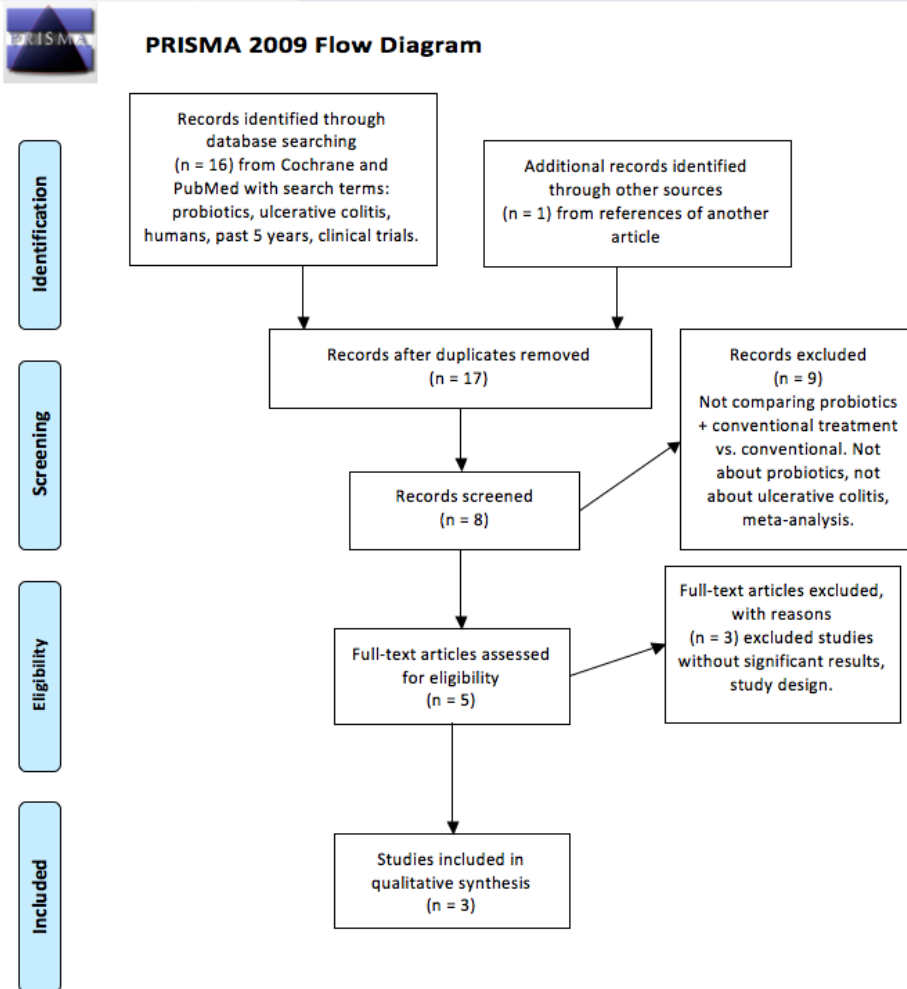
*Intervention:* Combination of probiotic and conventional treatment

*Control:* Conventional treatment alone

*Outcome:* Prolonged remission

### **CLINICAL QUESTION**

In patients older than 13 years old with UC, does probiotic and conventional treatment as compared to conventional treatment alone prolong remission?



**Figure 1: PRISMA flow diagram**

Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med* 6(7): e1000097. doi:10.1371/journal.pmed1000097

## **METHODS**

In September 2017 the PubMed and Cochrane Library databases were searched using the key terms: probiotics, ulcerative colitis, humans, within five years, and clinical trials. This search yielded a total of 16 articles. One additional resource was identified by searching within the references of one of the previously found articles. Of these 17 articles, nine were excluded because they either did not compare probiotics to conventional treatment, weren't specifically about probiotic supplements, were not primarily about ulcerative colitis, or were meta-analyses. The eight remaining articles were reviewed, of which three were excluded due to failure of significant results or poor study design. There were three remaining articles that met all the necessary criteria which included: *Effectiveness of probiotic therapy for the prevention of relapse in patients with inactive Ulcerative Colitis. Yoshimatsu et al.*; *Treatment of relapsing mild-to-moderate Ulcerative Colitis with the probiotic VSL#3 as adjunctive to a standard pharmaceutical treatment: a double-blind, randomized, placebo-controlled study. Tursi et al.*;

and *The long-term effects of probiotics in the therapy of Ulcerative Colitis: A clinical study.* Palumbo *et al.* Figure 1 provides a diagram of this article screening process.

## **RESULTS**

### **Study 1**

*Effectiveness of probiotic therapy for the prevention of relapse in patients with inactive Ulcerative Colitis.* Yoshimatsu *et al.*<sup>9</sup>

**Study Objective:** To determine if the use of probiotics in addition to conventional UC treatment was more effective in maintaining remission in patients with inactive UC as compared to conventional treatment alone over the course of 12 months.

**Study Design:** In this randomized, double-blind, placebo-controlled study, 60 patients were randomly divided into one of two groups: Bio-Three probiotic tablets and identical placebo tablets. Both groups took three tablets of the respective preparations, three times by mouth daily for twelve months. Further, both groups were allowed to continue taking ongoing remission maintenance therapies including mesalazine and salazosulfapyridine for the entire duration of the study. Throughout the trial patients were monitored by assessing: exacerbation of symptoms monthly, and fecal samples every three months for bacterial DNA analysis and bacterial composition of fecal flora.

Table 1. Inclusion and Exclusion Criteria for Study Participation.	
Inclusion Criteria	Exclusion Criteria
<ol style="list-style-type: none"> <li>1. Patients in remission from UC</li> <li>2. Patients receiving outpatient treatment at Sakura Medical Center, Toho University, Japan.</li> <li>3. Age 13 and older</li> <li>4. UC Clinical Activity index of five or less while receiving mesalazine, salazosulfapyridine, or steroids</li> <li>5. No medication changes within four weeks of starting the trial</li> </ol>	<ol style="list-style-type: none"> <li>1. Serious cardiac disease</li> <li>2. Serious renal disease</li> <li>3. Hypotension (Systolic <math>\leq</math> 80 mmHg)</li> <li>4. History of shock extracorporeal circulation</li> <li>5. Serious infections such as sepsis or pneumonia</li> <li>6. Serum hemoglobin less than 10g/dL</li> <li>7. Treatments that were just recently begun including: leukocytapheresis, granulocyte adsorptive apheresis, and immunosuppressant therapy with drugs such as 6-mercaptopurine, azathioprine, and cyclosporine</li> <li>8. Milk allergy</li> <li>9. UC Clinical Activity Index of six or higher.</li> <li>10. Pregnancy</li> </ol>

**Results:** Of the 60 randomized patients, 23 patients in the Bio-Three group, and 23 patients in the placebo group completed the entire one year trial. The number of patients who experienced relapse in the Bio-Three and placebo groups were respectively 0 vs 4 patients at 3 months ( $p=0.036$ ), 2 vs 6 patients at 6 months ( $p=0.119$ ), 5 vs 8 at 9 months ( $p=0.326$ ), and 7 vs 10 patients at 12 months ( $p=0.248$ ). At the end of the 12 month study, 56.6% of the placebo group (12 patients), remained in remission, whereas 69.5% of the Bio-Three group (16 patients) maintained in remission.

**Number Needed to Treat (NNT):** 8. The Bio-Three and placebo groups were used in order to calculate the NNT. The NNT demonstrates that 8 patients must be treated over 12 months in order for one patient to achieve remission maintenance.

**Critique:** Strengths of this study include that it was a randomized trial, used double blinding of patients and researchers, and included a wide age range of patients. These features helped to minimize bias and could apply to a wide range of patients suffering from UC. Some weaknesses of this study included that it had a limited number of participants in each study group, the follow up was only one year, and that the results of this patient population might not be able to be generalized to other patient populations. Another notable weakness of the study was the high dropout rate of participants from 60 participants at the start to a total of 46 participants who completed the study. The authors explained that the dropout of 7 participants from each group, after randomization, was due to the fact that they met exclusion criteria such as age at onset of disease and use of prohibited drugs. The authors did not account for the high dropout rate in their analysis, even though this could affect how the results of the study can be extrapolated to patients in clinical practice. The results of this study were not statistically significant overall which may be due to having a very small sample size and only a short period of follow up used. If in the future, this study was done on a much larger scale with a several year follow up, results may show statistically significant decreases in relapse rate. Further, the population used in this study was from a single outpatient center in Japan, making it less likely to apply to patients in the US due to factors such as differing diets and environmental exposures.

## Study 2

*Treatment of relapsing mild-to-moderate Ulcerative Colitis with the probiotic VSL#3 as adjunctive to a standard pharmaceutical treatment: a double-blind, randomized, placebo-controlled study. Tursi et al.<sup>10</sup>*

**Study Objective:** To investigate if probiotic VSL#3 as an adjunct to standard therapy is more effective in treating mild-to-moderate UC compared to UC standard therapy alone.

**Study Design:** In this multicenter, double-blind, randomized control trial, 144 patients were randomly assigned to receive VSL#3 probiotic mixture or placebo two times by mouth daily for 8 weeks in addition to their mesalazine maintenance therapy for the entire duration of the study. The VSL#3 treatment group received sachets containing 900 billion bacteria, including strains of *lactobacilli*, *bifidobacteria*, and *streptococcus* with a daily dose of 3,600 billion bacteria per day.

The primary endpoints were the change in baseline in the UCDAI score (with higher scores indicating worse quality of life), stool frequency, intestinal mucosa, and rectal bleeding.

Inclusion Criteria	Exclusion Criteria
<ol style="list-style-type: none"> <li>1. Greater than 18 years old</li> <li>2. Diagnosis of UC established by previous colonoscopy, with consistent histology and clinical course</li> <li>3. UC involving at least the rectosigmoid region; confirmed by colonoscopy</li> <li>4. Mild-to-moderate relapsing UC</li> <li>5. Relapsing episodes for &lt; 4 weeks before the study</li> <li>6. <u>Greater than or equal to</u> 3 UCDAI score at screening</li> <li>7. Use of 5-ASA at least 4 weeks before the study and/or azathioprine or 6-mercaptoprine at least 3 months before the study</li> </ol>	<ol style="list-style-type: none"> <li>1. Crohn's disease or pouchitis</li> <li>2. Greater than &gt; 8 UCDAI score</li> <li>3. Use of oral steroids within last 4 weeks before the study</li> <li>4. Use of antibiotics within last 2 weeks before the study</li> <li>5. Change in dose of 5-ASA within last 4 weeks and throughout the 8 week study period or a change in azathioprine dose within 3 months before the study</li> <li>6. Use of rectal 5-ASA or steroids within 1 week beforehand or throughout 8 week study period</li> <li>7. Use of probiotics within 2 weeks before the study</li> <li>8. Use of NSAIDs for 1 week before or through the study</li> <li>9. Pregnancy</li> </ol>

ASA, aminosalicylic acid; UC, ulcerative colitis; UCDAI, Ulcerative Colitis Disease Activity Index.

**Results:** 144 patients underwent randomiz 65 patients in the VSL#3 and 66 patients placebo group) completed the entire study. As compared with the use of mesalazine, the use of probiotic VSL#3 was associated with lower disease activity scores, but not with a higher incidence of remission. Improvement in UCDAI scores was 63.1% with VSL#3 and 40.8% with placebo ( $p = 0.010$ ). After a followup time of 8 weeks, the remission rate was 47% with probiotic VSL#3 and 32% with placebo, meaning remission was not significantly lower with probiotic VSL#3 than with placebo. While there was no significant improvement with VSL#3 in stool frequency and endoscopic scores, there was reduction in the frequency of rectal bleeding. Furthermore, 6 patients in the VSL#3 group and 7 patients in the placebo group were requested to withdraw



from the study due to protocol violation, lost to follow up, or clinical deterioration. There were no adverse events reported in either group.

**Number Needed to Treat (NNT):** 5. The VSL#3 treatment group and placebo group were used in order to determine the NNT. The NNT demonstrates that 5 patients must be treated over 12 months in order for one patient to achieve decreased UC disease activity.

**Critique:** The randomizing of assigned individuals to a study and control group is a significant strength of the study as it controls confounding variables. The participants and investigators were both blinded to the treatment, which helped to prevent bias. Groups were well balanced as there was no major difference in demographic characteristics (age, male-to-female ratio, and UCDAI score). The investigators also determined an optimal sample size for the study by using a statistical power of 80% and a statistical significance of 95% while also anticipating subject dropouts. The follow up period occurred at 8 weeks, however, long term outcomes were not assessed. The study drop out rate was 9% (13 of 144 patients). Due to the dropout of patients, the study included intention to treat and per protocol outcomes.

The improvement in UCDAI score of 50% or more was higher in the VSL#3 group compared to the placebo group (per protocol (PP)  $P=0.010$ ; intention to treat (ITT)  $P=0.031$ ). Significant results with VSL#3 are demonstrated with an improvement of three points or more in the UCDAI score (PP  $P=0.017$ ; ITT  $P=0.046$ ), whereas remission after 8 weeks (PP  $P=0.069$ ; ITT  $P=0.132$ ) did not show a significant difference. This may be due to the notion that the study was underpowered and included a short follow up period. Furthermore, this study was funded by VSL Pharmaceuticals, which may contribute to outcomes favouring the sponsor.

One potential weakness in the study is the patient population was from a multicenter in Italy, making it more difficult to apply these results to patients in the United States due to differing diets and environmental factors.

### Study 3:

*The long-term effects of probiotics in the therapy of Ulcerative Colitis: A clinical study. Palumbo et al.*<sup>11</sup>

**Study Objective:** To evaluate if the long-term effects of a combination therapy of mesalazine plus a probiotic blend compared to mesalazine alone is more effective in treating UC.

**Methods:** In this randomized control trial, 60 patients with moderate-to-severe UC were randomly assigned to receive mesalazine 1200 mg once daily or a combination of mesalazine 1200 mg and a probiotic blend twice daily. The probiotic group received strains of *Lactobacillus salivarius*, *Lactobacillus acidophilus* and *Bifidobacterium bifidus* strain BGN4. The primary endpoint was the change from baseline in in the disease activity according to the the Modified Mayo Disease Activity Index (MMDAI) at 24 months. The study compared the efficacy of

treatment by analyzing the proportion of patients who noticed clinical improvements at months 6, 12, 18 and 24.

Inclusion Criteria	Exclusion Criteria
<ol style="list-style-type: none"> <li>1. Older than 18 years old</li> <li>2. Diagnosis of UC established by clinical course, colonoscopy, and histology</li> <li>3. Moderate-to-severe disease (MMDAI score: 8-12)</li> </ol>	<ol style="list-style-type: none"> <li>1. Steroid dependence</li> <li>2. Renal impairment</li> <li>3. Pregnancy</li> <li>4. Lactation</li> <li>5. Established low compliance</li> </ol>

**Results:** A total of 60 randomized patients underwent randomization (30 patients in the mesalazine group and 30 patients in the combination mesalazine and probiotic blend group) completed the two year trial. Throughout the study, patients in the combined treatment group achieved a significant reduction in disease activity, stool frequency, and rectal bleeding at 6 months, as well as improvement in endoscopic findings at 18 months ( $p < 0.05$  for each parameter). There were no adverse events reported in either group.

**Critique:** The randomizing of assigned individuals to a study and control group is a significant strength of the study as it controls confounding variables. One strength of this study is that groups were well balanced as there was no significant difference in demographics (mean age and male-to-female ratio). Several weaknesses of this study included failure to double-blind patients to the control and treatment groups and the study had a limited number of patients in each group. Another weakness of the trial was setting up the potential for bias due to lack of blinding patients and researchers. In other words, patients may have become aware of their allocated treatment group because the placebo group received a single daily administration of mesalazine while the treatment group received the mesalazine plus a double daily administration of probiotic blend. This may have led to an increased attrition rate, demonstrated by a poor compliance rate of 85% among subjects. The study also failed to define several medical and statistical terms used to describe results and criteria for endoscopic scores. Furthermore, the researchers failed to report the study dropout rate, per protocol outcomes, and how the study was funded.

## **DISCUSSION**

This review focused on the clinical significance of the use of probiotics as an adjunct therapy for the treatment of ulcerative colitis. The current studies demonstrate conflicting results on whether or not adding probiotics to the treatment regimen for UC is efficacious. Table 4 summarizes the results of the systematically reviewed studies.

<b>Table 4. Summary of studies reviewed</b>
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	<b>Study #1 Yoshimatsu, et al.<sup>9</sup></b>	<b>Study #2 Tursi, et al.<sup>10</sup></b>	<b>Study #3 Palumbo, et al.<sup>11</sup></b>
<b>Objective</b>	To determine if the use of probiotics in addition to conventional UC treatment was more effective in maintaining remission in patients with inactive UC as compared to conventional treatment alone over the course of 12 months.	To investigate if probiotic VSL#3 as an adjunct to standard UC therapy is more effective in treating mild-to-moderate UC compared to standard therapy alone.	To evaluate if the long-term effects of a combination therapy of mesalazine plus a probiotic blend as compared to mesalazine alone is more effective in treating UC.
<b>Study Type</b>	Double-blinded RCT	Double-blinded RCT	RCT
<b>Sample Size</b>	n = 46 (23, 23)	n = 144 (71,73)	n= 60 (30,30)
<b>Study Treatments</b>	Bio-Three  ( <i>Streptococcus faecalis</i> , <i>Clostridium butyricum</i> , <i>Bacillus mesentericus</i> )	VSL#3  ( <i>Lactobacillus</i> , <i>Bifidobacteria</i> , <i>Streptococcus thermophilus</i> )	Probiotic blend  ( <i>Lactobacillus</i> , <i>Bifidobacterium bifidus</i> )
<b>Standard Treatment</b>	Mesalazine & Salazosulfapyradine	Mesalazine	Mesalazine
<b>Follow Up Period</b>	12 months	8 weeks	2 years
<b>Conclusion</b>	After 12 months, 56.6% of the placebo group (12 patients), remained in remission, whereas 69.5% of the Bio-Three group (16 patients) remained in remission ( $p>0.05$ ).	After 8 weeks, 63.1% of the VSL#3 group reported improvement in $>50\%$ of UCDAI score, compared to 40.8% of the placebo group ( $p<0.05$ ). Furthermore, there was no significant difference in remission ( $p>0.05$ ).	After 2 years, there was a significant difference in MMDAI, stool frequency, endoscopic scores, and rectal bleeding ( $p<0.05$ ).
<b>NNT</b>	NNT= 8	NNT = 5	NNT= unobtainable

The three studies were similar in some aspects, however there were also distinct differences between them as well. One similarity was that all three studies observed the effect of the addition of a probiotic to a standard 5-ASA (mesalazine) treatment.<sup>9,10,11</sup> This was important because the point of this research was not to see if using probiotics would replace the use of standard therapy, but rather to see if there were additional benefits to using the probiotics in combination with standard therapy. Another quality the three studies had in common was that they all were randomized control trials which helped to decrease bias and confounding variables

in each study. The studies done by Yoshimatsu, et al. and Tursi, et al. both studied patients who were suffering from mild to moderate disease that was in remission at the time of study.<sup>9,10</sup> In contrast, the third study observed patients that had moderate to severe disease.<sup>11</sup> It was helpful to see the different impacts that the adjunct use of probiotics had on different severities of UC, but ultimately was a major difference in the patient population which made it difficult to make a final conclusion on this topic. Tursi, et al. and Palumbo, et al. used objective symptom score tools as a measured outcome in the studies.<sup>10,11</sup> Tursi, et al. used the UCDAI score, while Palumbo, et al. used the MMDAI score, both of which included observation of stool frequency, endoscopic scores, and rectal bleeding.<sup>10,11</sup> In contrast, Yoshimatsu, et al. measured remission rates and fecal cluster analysis as the main outcomes of the study.<sup>9</sup> Further differences between the study included use of three different probiotic formulas (Bio-Three, VSL#3, and a probiotic blend), patient populations and sample sizes, and length follow up periods.<sup>9,10,11</sup> Overall these studies display heterogeneous results due to different outcomes studied, and differing patient populations.

Each of the studies varied in their strengths and weaknesses in regards to sample size, patient population, and duration of the study. Yoshimatsu, et al. is a double-blinded RCT and enrolled patients with a wide age range.<sup>9</sup> However, the study used a small sample size of only 46 individuals, used a short follow up period of 12 months and as a result makes it difficult to conclude if the findings may be generalized to other patient populations.<sup>9</sup> On the other hand, Tursi, et al. is a double-blinded RCT with a large sample size, but included the shortest follow up period of 8 weeks.<sup>10</sup> Because the patient population is fairly homogeneous it is not reflective of the overall patient population with UC.<sup>10</sup> The third study, Palumbo, et al. is a RCT, but failed to blind both subjects and investigators in order to eliminate possible bias.<sup>11</sup> As a result of this potential bias and an extensive 2 year follow up period, the study reported a high dropout rate of patients, suggesting a major limitation in the study.<sup>11</sup> For all of the reasons just discussed, Palumbo, et al. is determined to have the most limitations of the three studies while Tursi, et al. is believed to be the most reliable.

The presented studies offer some evidence to support supplementation of probiotics for improvement of several clinical outcomes. First, in the study done by Tursi, et al., the UCDAI symptom score increased by at least 50% in the VSL#3 group, which was statistically significant.<sup>10</sup> Also, Yoshimatsu, et al. did show some improvement, but not statistical significance, in maintenance of UC remission in those using probiotics compared to placebo. Another important result was in the Palumbo, et al. study, demonstrated significant improvement in UC disease activity index, stool frequency, intestinal mucosa, and rectal bleeding. So while not all studies show statistically significant improvements in all UC outcomes, there do not appear to be any adverse events associated with taking probiotics along with standard medications. Therefore, we do not discourage patients to take the probiotics, as they may see improvement in symptoms and remission with little associated risk.

There are limitations of this systematic review due to the heterogeneity between the three studies with regards to the probiotic of choice, endpoints and final clinical outcomes. Specifically, Yoshimatsu, et al. investigated remission rates while Tursi, et al. examined UCDAI scores and Palumbo, et al. studied MMDAI scores.<sup>9,10,11</sup> Both the UCDAI and MMDAI included similar criteria of stool frequency, rectal bleeding, endoscopic findings, and physician global assessment of the disease.<sup>10,11</sup>

Overall, additional large randomized controlled double-blind studies on the effectiveness of probiotics in UC is necessary to determine their potential benefits and increased remission rates.

## **CONCLUSION**

This systematic review does not show strong evidence in support of probiotic supplementation in UC patients. However, due to trial design, limited variety of probiotic strains tested, and small sample sizes, a potential benefit to probiotics may still exist. The bacterial composition of the probiotic blends used in these studies represent only a few of the many available blends in the market today. *Lactobacillus* and *bifidobacterium* species are the most commonly used probiotics on the market and both of these species are represented in the probiotic blends in the studies that are a part of this review.<sup>11</sup> There are several commonly available probiotic blends that have shown benefits in human trials. Examples of the most effective probiotics to treat UC include Mutaflor and VSL#3, which consist of *E.coli* Nissle 1917, strains of *Streptococcus*, *Bifidobacterium* and *Lactobacillus*.<sup>11</sup>

It is important to consider risks associated with the use of probiotics in order to determine if their usage would be beneficial for all patients. Common side effects are gas and bloating, however, for most patients probiotic use is considered safe and associated with rare complications. Therefore, while it appears that probiotics do not pose any serious additional risk to individuals with UC, until large randomized trials are performed, we cannot recommend or discourage the use of probiotics.

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