

# Probiotics and remission of ulcerative colitis: a systematic review

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## ABSTRACT

**Background:** Ulcerative colitis (UC) is an acute and inflammatory disease of the large bowel of unknown aetiology. The use of probiotics for this disease remains controversial. The objective of this systematic review was to identify studies based on randomised controlled trials comparing the effect of probiotics to the effect of anti-inflammatory drugs or placebo in the remission of UC.

**Methods:** We conducted a systematic review of clinical trials comparing the effect of probiotics to the effect of anti-inflammatory treatment or placebo in the remission of UC. PubMed, ScienceDirect, Cochrane, Google Scholar, metaRegister of Controlled Trials and National Institutes of Health were searched.

**Results:** Nine studies met the inclusion criteria. These studies present a significant heterogeneity concerning their methodology and their results. The improvement in UC remission and the frequency of adverse effects do not differ significantly between probiotic and control groups.

**Conclusions:** There are a limited number of randomised trials published in the field of probiotics used for the remission of UC, and they present many methodological differences. The existing studies suggest a similar safety and efficacy of probiotics in comparison with anti-inflammatory drugs.

## KEYWORDS

Clinical trials, probiotics, ulcerative colitis, randomised

## INTRODUCTION

Ulcerative colitis (UC) is a relapsing disease of the colon of unknown aetiology. Clinical studies and experiments

in animals suggest that genetic factors, agents such as viruses or other micro-organisms, reactions to allergens (milk proteins and bacterial polysaccharides), autoimmune phenomena or a combination of these may have a role in the aetiology of this condition. Its annual incidence is about 10 new cases per 100,000 white adults at risk.<sup>1</sup>

An attractive therapy for UC manipulation is to reduce the inflammatory effectiveness of colonising bacteria. Antibiotics are one option to eliminate the species involved in inducing the inflammation.<sup>2</sup>

Antibiotics are generally not effective for acute UC.<sup>1</sup> In spite of this, aminosalicylates are recommended for maintenance treatment.<sup>3</sup> However, there is considerable intolerance not only to classic aminosalicylate sulphalazine<sup>4</sup> but also to sulphur-free compounds such as mesalazine or olsalazine.<sup>5</sup> Current 5-aminosalicylate formulations have positive results in the majority of patients but they are associated with a number of limitations such as inconvenient dosing regimens and poor patient acceptance leading to noncompliance with prescribed therapy.<sup>6</sup>

An alternative is to use probiotic bacteria that interact with the host epithelium to resolve inflammation. Probiotics have been defined as live microbial feed supplements that beneficially affect the host by improving the intestinal microbial balance. Theoretically, probiotics can modify the composition and some metabolic activities of microflora by preventing overgrowth of potentially pathogenic bacteria.<sup>7,8</sup> The relationship between intestinal inflammation and pathogenic bacteria is perplexing. Similarly, the field of probiotics is complex and in need of rigorous research.<sup>8,9</sup> If bacteria participate in the pathogenesis of ulcerative colitis and in resistance to antibiotics, probiotics may offer an alternative useful way to manipulate the microflora in chronic diseases.<sup>10</sup> Several studies suggest that selected probiotic preparations have a positive influence

in gastrointestinal diseases including UC.<sup>11-13</sup> The most widely used probiotics in humans are *Bifidobacteria* and *Lactobacilli*. However, data are based on relatively small studies, which are not sufficient to determine if they are definitely helpful, and the benefits and harms implicated are still poorly understood.<sup>14</sup>

The objective of this systematic review was to identify studies based on data of randomised controlled trials comparing the effect of probiotics with the effect of anti-inflammatory drugs or placebo in the remission of UC in order to compare their methodology and summarise their results.

## MATERIALS AND METHODS

### Criteria for study selection

Abstracts and full articles of all citations and retrieved studies comparing the effects of probiotics with those of anti-inflammatory drugs or placebo, published before 9 October 2007 were reviewed and rated for inclusion. Full articles were retrieved if specific treatments were given to treat the disease of interest. The inclusion criteria were randomised, controlled trials in humans addressing probiotic use for the induction of remission and/or maintenance of remission. Exclusion criteria were preclinical studies, case reports or case series, phase I studies in volunteers and not in the disease being studied.

### Data sources and data extraction

The databases searched for unrestricted dates and languages until 9 October 2007 were PubMed, ScienceDirect, Cochrane and Google Scholar. Two on-line clinical trial registers were searched: metaRegister of Controlled Trials ([www.controlled-trials.com/mrct](http://www.controlled-trials.com/mrct)), and National Institutes of Health ([www.clinicaltrials.gov](http://www.clinicaltrials.gov)). A secondary hand search of reference lists, authors, associated diseases and meeting abstracts was also performed. The key words used to search in PubMed were (lactobacillus OR probiotics OR saccharomyces OR bifidobacterium OR yeasts OR yogurt OR dairy products) AND ulcerative colitis. In ScienceDirect and Google Scholar we used probiotics and ulcerative colitis and in Cochrane, metaRegister of Controlled Trials and National Institutes of Health the keyword was probiotics. Search strategies were broad-based initially, and then narrowed to the disease of interest.

Data on general characteristics of patients, patients at the start of the study, number of completed subjects, treatment type and duration, outcomes and adverse effects were extracted into a standardised table. One researcher completed the search and checked all titles and abstracts of relevant studies. Two authors reviewed the full text of relevant studies for their eligibility for inclusion. When discrepancies occurred a third author resolved them. Two trials had multiple arms.<sup>15,16</sup> In one trial the two

groups of patients receiving anti-inflammatory drugs were considered as one control group.<sup>15</sup> The second trial included two probiotic groups.<sup>16</sup> Each one of them was compared with the control group separately.

### Methodological quality

Each study included in the systematic review was evaluated on the following items: inclusion and exclusion criteria for patients, co-treatment/concomitant medication use, and outcome measurement. For inclusion/exclusion criteria we examined if inclusion and exclusion criteria are clearly stated in the text. For co-treatment we examined if concomitant medication was used in the probiotic group. For the outcome measurement we examined if a clinical activity index and/or an endoscopy index were used at entry and at the end of the study for each patient.

### Statistical analysis

Summary statistics were performed using the software Lau-Meta-analyst.EXE. Relative risks with 95% confidence intervals were computed as summary statistics. Heterogeneity across trials was evaluated using Cochran's Q test. Regardless of whether the studies were homogeneous or not, a random effects model was used and a pooled relative risk was calculated using the DerSimonian and Laird method. P values <0.05 were considered statistically significant.

## RESULTS

### Results of searching

A total of 24 articles were initially identified, comparing the effect of probiotics with the effect of anti-inflammatory drugs or placebo (*table 1*). The other papers contained general information about probiotics and inflammatory bowel disease. All these papers were found in PubMed using the key words mentioned above. As shown in *table 1*, 15 articles failed to meet one or more of the inclusion criteria. Five studies were not randomised controlled trials,<sup>19,21,29,30,36</sup> four referred to pouchitis,<sup>19,28,33,34</sup> one referred to inflammatory bowel disease,<sup>23</sup> one to colonic surgery,<sup>32</sup> three to Crohn's disease<sup>25,26,38</sup> and one<sup>27</sup> was published twice. Nine studies met the inclusion criteria and provided data on 972 enrolled subjects. The number of patients in each of these studies ranged from 18 to 327 (median 103). The included studies are presented in *table 2*. One study used a synbiotic compared with placebo in patients with active UC.<sup>22</sup> One study used balsalazide and VSL#3 compared with mesalazine and balsalazide in patients with mild to moderate UC.<sup>15</sup> One study used *Lactobacillus* GG compared with mesalazine and with *Lactobacillus* GG plus mesalazine.<sup>16</sup> Three studies used *E. coli* compared with mesalazine in active and in inactive UC<sup>18,20,31</sup> and

**Table 1. Studies on probiotics and inflammatory bowel disease**

Authors	Year	Disease	Randomised controlled trial	Probiotic
Tursi <i>et al.</i> <sup>15</sup>	2004	Ulcerative colitis	Yes	Yes
Zocco <i>et al.</i> <sup>16</sup>	2006	Ulcerative colitis	Yes	Yes
Ishikawa <i>et al.</i> <sup>17</sup>	2002	Ulcerative colitis	Yes	Yes
Kruis <i>et al.</i> <sup>18</sup>	2004	Ulcerative colitis	Yes	Yes
Braegger <i>et al.</i> <sup>19</sup>	2003	Pouchitis	No	Yes
Rembacken <i>et al.</i> <sup>20</sup>	1999	Ulcerative colitis	Yes	Yes
Bibiloni <i>et al.</i> <sup>21</sup>	2005	Ulcerative colitis	No	Yes
Furrie <i>et al.</i> <sup>22</sup>	2005	Ulcerative colitis	Yes	Yes
Annese <i>et al.</i> <sup>23</sup>	2004	Inflammatory bowel disease	Yes	No
Kato <i>et al.</i> <sup>24</sup>	2004	Ulcerative colitis	Yes	Yes
Schultz <i>et al.</i> <sup>25</sup>	2004	Crohn's disease	Yes	Yes
Teml <i>et al.</i> <sup>26</sup>	2003	Crohn's disease	Yes	No
Cui <i>et al.</i> <sup>27</sup>	2003	Ulcerative colitis	Yes	Yes
Gionchetti <i>et al.</i> <sup>28</sup>	2000	Pouchitis	Yes	Yes
Folwaczny <sup>29</sup>	2000	Ulcerative colitis	No	Yes
Faubion <i>et al.</i> <sup>30</sup>	2000	Ulcerative colitis	No	Yes
Kruis <i>et al.</i> <sup>31</sup>	1997	Ulcerative colitis	Yes	Yes
Everett <i>et al.</i> <sup>32</sup>	1969	Colonic surgery	Maybe	No
Kuhbacher <i>et al.</i> <sup>33</sup>	2006	Pouchitis	Maybe	Yes
Gionchetti <i>et al.</i> <sup>34</sup>	2003	Pouchitis	Yes	Yes
Cui <i>et al.</i> <sup>35</sup>	2004	Ulcerative colitis	Yes	Yes
Bai <i>et al.</i> <sup>36</sup>	2006	Ulcerative colitis	No	Yes
Shibata <i>et al.</i> <sup>37</sup>	2007	Ulcerative colitis	Yes	Yes
Van Gossum <i>et al.</i> <sup>38</sup>	2007	Crohn's disease	Yes	Yes

three studies used *Bifidobacteria* compared with placebo in mild to moderate and in active UC.<sup>17,24,35</sup> Concerning the methodological quality, the studies present significant differences, and only four of them combine clear inclusion and exclusion criteria, exclusive use of probiotics in the experiment group, and adequate outcome measurement (table 3).

#### Clinical success of experiment-control group

Among nine randomised, controlled studies providing adequate data, two reported a significantly higher remission in UC for the probiotics compared with the control group.<sup>17,35</sup> Two studies showed a trend for increased efficacy and five trials did not show any significant difference between probiotic and control groups.<sup>15,22</sup> The pooled relative risk for the nine randomised-controlled trials was 1.51 (95% CI 0.79-2.87,  $p=0.21$ ) (table 4), showing no statistically significant difference between probiotic and control groups. A significant heterogeneity was found ( $Q=28.61$ ). The normal heterogeneity for 9 degrees of freedom (df) according to the  $\chi^2$  distribution is 14,684.

#### Adverse effects

Seven of the nine (77.8%) trials presented data on adverse reactions.<sup>15,17,18,20,22,24,31</sup> The pooled relative risk of adverse effects for the seven studies was: 1.17 (0.81-1.70),  $p=0.40$ .

A nonsignificant heterogeneity was found ( $Q=5.47$ ). The normal heterogeneity for 6 df according to the  $\chi^2$  distribution is 10,645.

#### Subgroups of studies

##### *Induction of remission vs maintenance of remission*

Three randomised, controlled studies estimated induction of remission as an outcome measure. One of them reported significantly improved remission in UC for the probiotics compared with the control group.<sup>22</sup> The other two studies had a trend for increased efficacy.<sup>15,24</sup> The pooled relative risk was 2.27 (95% CI 1.00-5.14,  $p=0.049$ ), showing a significant difference between probiotic and control group. A nonsignificant heterogeneity was found ( $Q=0.20$ ) as the normal heterogeneity for 2 df according to the  $\chi^2$  distribution is 4605.

Six randomised, controlled studies provided adequate data for the maintenance of remission. Two of them reported significantly higher remission in UC for the probiotics compared with the control group.<sup>17,35</sup> The other four trials did not find any significant difference between the probiotic and control group.<sup>16,18,20,31</sup> The pooled relative risk was 1.37 (95% CI 0.62-3.04,  $p=0.44$ ) showing no significant difference between probiotic and control group. A significant heterogeneity was found ( $Q=24.26$ ) as the normal heterogeneity for 6 df according to the  $\chi^2$  distribution was 10,645.

**Table 2.** Characteristics of nine randomised controlled trials assessing the effect of probiotics in ulcerative colitis remission

Authors, year	Probiotic	Control group	Dose (n of probiotic/day)	Treatment duration	N (probiotic/control group)	Disease severity	Induction or maintenance of remission N (probiotic/control group)	Outcome measures
Tursi <i>et al.</i> <sup>15</sup> 2004	Balsalazide/ VSL#3	Mesalazine/ balsalazide	900 x 10 <sup>8</sup>	8 weeks	30/30/30	Mild-to-moderate	Induction of remission 24/21/16	1. Patients in symptomatic remission based on clinical evaluation and diary card 2. Time to symptomatic remission, proportion of patients with improvement in endoscopic and histological score
Zocco <i>et al.</i> <sup>16</sup> 2006	<i>Lactobacillus</i> GG	Mesalazine	18 x 10 <sup>9</sup>	12 months	65/60/62	Inactive UC	Maintenance of remission 55/48/52	1. Number of patients suffering relapse among the 3 groups 2. To evaluate the variations of clinical, endoscopic and histological scores and the relapse-free time as index of drug efficacy
Ishikawa <i>et al.</i> <sup>17</sup> 2002	<i>Bifidobacterium breve</i> <i>Bifidobacterium bifidum</i> <i>Lactobacillus acidophilus</i> YIT 0168	BFM without these <i>Bifidobacteria</i>	10 x 10 <sup>8</sup>	12 months	11/10	Mild Moderate	Maintenance of remission 8/1	Exacerbation of clinical symptoms
Kruis <i>et al.</i> <sup>18</sup> 2004	<i>E. coli</i> Nissle 1917	Mesalazine	2.5-25 x 10 <sup>9</sup>	12 months	162/165	Inactive	Maintenance of remission 89/104	Comparison of number of patients with relapse of UC between the two groups
Rembacken <i>et al.</i> <sup>20</sup> 1999	<i>E. coli</i> Nissle 1917 serotype O6: K5: H1	Mesalazine	5 x 10 <sup>10</sup>	12 months	57/59	Active	Maintenance of remission 39/44	1. Time and rate of relapse 2. Time and rate of remission in patients treated with topical or systemic steroids in addition to the non-pathogenic <i>E. coli</i> or mesalazine
Furrie <i>et al.</i> <sup>22</sup> 2005	Symbiotic ( <i>Bifidobacterium longum</i> + inulin-oligofructose)	Potato starch and sachet of 6 g powdered maltodextrose	4 x 10 <sup>11</sup>	4 weeks	9/9	Active	Induction of remission 5/3	1. Clinical improvement in symbiotic vs placebo group 2. Effects of symbiotic in mucosa
Kato <i>et al.</i> <sup>24</sup> 2004	<i>Bifidobacterium breve</i> strain Yakult <i>Bifidobacterium bifidum</i> strain Yakult <i>Lactobacillus acidophilus</i>	BFM without <i>B. bifidum</i> and <i>L. acidophilus</i>	10 <sup>9</sup>	12 weeks	10/10	Mild-to-moderate active	Induction of remission 4/3	Clinical improvement (indicated by a decrease in CAI score of ≥3 points)
Cui <i>et al.</i> <sup>27</sup> 2004	<i>Bifidobacteria</i>	Starch	1.26 g/d	8 weeks	15/15	Active	Maintenance of remission 12/1	Effects of probiotics on intestinal mucosae and role of probiotics in preventing relapse of UC
Kruis <i>et al.</i> <sup>31</sup> 1997	<i>E. coli</i> Nissle 1917 serotype O6: K5: H1	Mesalazine	50 x 10 <sup>9</sup>	12 weeks	50/53	Inactive UC	Maintenance of remission 42/51	Prove equivalence of the CAI score under the <i>E. coli</i> and mesalazine

N = number of patients.

**Table 3. Methodological quality of the nine studies**

Authors, year	Inclusion/exclusion criteria	Description of the patients	Co-treatment/concomitant medication (probiotic group)	Outcome measurement
Tursi <i>et al.</i> <sup>15</sup> 2004	Both	Patients with newly diagnosed or recently relapsed (within 4 weeks) mild-to-moderate UC confirmed by endoscopic evaluation	Probiotic + balsalazide	CAI by Lennard/EI score/HI score
Zocco <i>et al.</i> <sup>16</sup> 2006	Both	Patients with UC in clinical, laboratory and endoscopic remission of ≤12 months before admission	1 group: probiotic 2 group: probiotic + mesalazine	CAI according to Rachmilewitz/EI by Baron/HI by Truelove-Richard
Ishikawa <i>et al.</i> <sup>17</sup> 2002	Inclusion criteria	Patients who had been diagnosed with UC ≥1 year previously based on clinical grounds and colonoscopic findings	Probiotic only	Not mentioned
Kruis <i>et al.</i> <sup>18</sup> 2004	Both	Patients aged 18-70 with UC in remission (CAI ≤4, EI ≤4 and no signs of acute inflammation on histological examination)	Probiotic only	Scores according to Rachmilewitz
Rembacken <i>et al.</i> <sup>20</sup> 1999	Inclusion criteria	Patients aged 18-80 years with clinically active UC (≥4 liquid stools a day for the last 7 days with or without blood) with at least erythema on sigmoidoscopy and histological confirmation of active UC	Probiotic only	Scores according to Rachmilewitz
Furrie <i>et al.</i> <sup>22</sup> 2005	Inclusion criteria	Patients with active UC aged 24-67 who had not received antibiotics in the last 3 months and were not taking commercially available probiotic preparations	Probiotic + prebiotic (synbiotic)	CAI by Walmsley/SI by Baron
Kato <i>et al.</i> <sup>24</sup> 2004	Both	Patients with active UC; diagnosis confirmed by characteristic clinical, endoscopic and histological features	Probiotic only	CAI by Lichtiger/EI by Harig, Scheppach/HI by Matts
Cui <i>et al.</i> <sup>27</sup> 2004	Not mentioned	Active UC patients	Probiotic only	Not mentioned
Kruis <i>et al.</i> <sup>31</sup> 1997	Both	Patients >17 years, presence of chronic UC, previously diagnosed by endoscopic and histological criteria and now in remission	Probiotic only	Scores according to Rachmilewitz

CAI = clinical activity index; SI = sigmoidoscopy index; EI = endoscopy index; HI = histology index.

**Table 4. Total random effects (clinical success and adverse effects) from nine randomised controlled trials**

Outcome	Patients (n)	Probiotic		Control		Odds ratio	95% CI		p	Q	p (Q)
		N in remission	Total	N in remission	Total		Low	High			
Clinical success	972	330	471	340	501	1.51	0.79	2.87	0.21	28.61	14,684
Adverse effects	710	86	337	83	373	1.17	0.81	1.70	0.40	5.47	10,645

**Probiotics vs anti-inflammatory drugs and vs placebo**

Trials that compared the effects of probiotics with the effect of placebo (*Bifidobacteria* vs placebo, synbiotic vs placebo) gave better results than studies that compared the effect of probiotics with the effect of anti-inflammatory drugs. Among five randomised, controlled studies comparing probiotics with anti-inflammatory drugs, Tursi's trial showed a trend for increased efficacy.<sup>24</sup> The other four studies did not find any significant difference between probiotics and anti-inflammatory agents.<sup>16,18,20,31</sup> The pooled relative risk was 0.95 (95% CI 0.58-1.55, p=0.84), showing no significant difference between probiotic and anti-inflammatory treatment. A nonsignificant heterogeneity was found (Q=9.63) as the normal heterogeneity for 5 df according to the  $\chi^2$  distribution was 9236.

Among four randomised, controlled studies with probiotics with placebo, two trials reported significantly higher remission in UC for patients receiving probiotics.<sup>17,35</sup> The other two trials showed a trend for increased efficacy of probiotic compared with placebo.<sup>22,24</sup> The pooled relative risk was 7.32 (95% CI 1.37-39.13, p=0.020), showing a significant difference between probiotic and placebo. A significant heterogeneity was found (Q=7.42).

**Type of probiotic and ulcerative colitis**

Significant differences in effectiveness have also been reported for different types of strains in species of bacteria and yeasts. Depending on the type of probiotic, the clinical success of the *Bifidobacteria* treatment combined with one synbiotic was significantly more effective compared with

the control group in contrast to the studies with *E. coli*, which did not present significantly improved effect for the probiotic group: *Bifidobacteria* vs control group: odds ratio 7.32 (1.37-39.13), *E. coli* vs control group: odds ratio 0.66 (0.43-1.02). The type of UC does not seem to influence the results: mild-to-moderate UC: odds ratio 3.39 (0.97-11.87), active UC: odds ratio 3.79 (0.37-39.01), nonactive UC: odds ratio 1.26 (0.64- 2.46) (table 4).

#### Adverse effects into subgroups of studies

In all subgroups mentioned above the frequency of adverse effects did not differ significantly between the probiotic and the control group. The pooled relative risks of adverse effects for each subgroup were: probiotics vs anti-inflammatory drugs: 1.12 (0.69-1.83), probiotics vs placebo: 0.72 (0.10-5.30), induction of remission: 0.29 (0.06-1.45), maintenance of remission: 1.27 (0.86-1.86). The pooled relative risks of adverse effects for the different species of probiotics and types of UC were: *Bifidobacteria*: 0.72 (0.10-5.30), *E. coli*: 1.25 (0.85-1.84). For different types of UC the pooled relative risks for adverse effects were: active UC: 0.83 (0.12-5.94), nonactive UC: 1.16 (0.77- 1.74), mild to moderate UC: 0.60 (0.12-3.08).

## DISCUSSION

According to the results of this systematic review, there are only few randomised trials assessing the effectiveness and safety of probiotics used for the remission of UC. These studies suggest that probiotics do not differ significantly from anti-inflammatory drugs for UC remission, concerning both effectiveness and safety. A significant heterogeneity of results was found among studies. The contradictory results of randomised trials may arise from methodological differences between studies, such as the type of probiotic being investigated, or differences in duration of treatment.

Significant differences in effectiveness have been reported for different types of strains in species of bacteria and yeasts.<sup>8,39</sup> For UC, additional factors may influence the results, including the type of UC, medication compliance and patient behaviour. Another source of heterogeneity for probiotic trials is the use of antibiotics together with probiotics, the differences in control groups, the outcome measures, and the number of patients included in each study.

According to the results of the present study *Bifidobacteria* are likely to give the best results. The efficacy of the *Bifidobacteria* may be related to the increased concentrations of faecal (luminal) short chain fatty acids (SCFAs), and these probiotics may improve epithelial function via production of SCFAs.<sup>24</sup> SCFAs, particularly butyrate, are the major energy source for colonocytes and

appear to function in immunological regulation including the suppression of proinflammatory cytokines through the inhibition of NF- $\kappa$ B activation. *Bifidobacteria*-fermented milk (BFM) supplements may also reduce exacerbation of UC through the normalisation of the intestinal flora and may lead to a significant decrease in the relative number of *B. vulgatus* (percentage) in *Bacteroidaceae* in faeces.<sup>17</sup> However, another explanation for the improved results of *Bifidobacteria* could be that all studies using *Bifidobacteria* as a probiotic used placebo (and no anti-inflammatory drugs) for the control group. In addition, these studies are based on small numbers of patients.

The results of our study suggest no significant difference in effectiveness between *E. coli* and anti-inflammatory drugs. Several factors may be related to this finding. A recent controlled trial suggests an effectiveness of ciprofloxacin in complicated UC.<sup>40</sup> Oral tobramycin was shown to eliminate pathogenic *E. coli* strains; this was related to significant clinical and histological improvement of UC. However, when tobramycin was stopped, pathogenic adhesive *E. coli* recolonised, and relapses occurred in some patients.<sup>41</sup> We hypothesise that this may also happen with other drugs, such as mesalazine, giving another possible explanation for the results of these trials. It should be pointed out that all three trials for *E. coli* included in the systematic review compared the probiotic group with a control group receiving mesalazine and not placebo, while trials for *Bifidobacteria* used placebo in the control group. As a consequence, it is difficult to conclude that *E. coli* is less effective than *Bifidobacteria* in UC remission.

Trials using probiotics vs placebo are likely to give better results than trials using probiotics vs antibiotics. The difference may be related to the fact that all the trials comparing probiotics with placebo used *Bifidobacteria*, as a probiotic, with clearly better results in effectiveness than other probiotics mentioned above. The trials comparing probiotics with anti-inflammatory drugs, use *E. coli* or VSL#3 or *Lactobacillus* as a probiotic, and did not show a significant difference in effectiveness between probiotic and control groups. However, this finding may be related to a similar effectiveness of probiotics and anti-inflammatory drugs, and not to a lower effectiveness of the specific probiotics used in these trials.

The present study found that trials assessing induction of remission as an outcome measure give better results for patients receiving probiotics than the trials assessing maintenance of remission. Why this occurred is not clearly understood. We hypothesise that the type of probiotic (most of the trials assessing induction of remission as outcome measure used *Bifidobacteria*) may be related to this finding.

Another limitation in the interpretation of our results could be related to the antibiotics the patients took before

entering the study. The trials that had patients taking antibiotics before entering the study (three studies using *Bifidobacteria* as a control group)<sup>17,24,35</sup> showed better results than the trials with patients who did not use antibiotics.<sup>15,16,22</sup> The explanation of this finding is not clear. The type of UC, the antibiotic, the dose of the antibiotic and other factors must be taken into consideration. Concerning the adverse effects, they do not present significant differences between probiotics and the placebo or pharmaceutical treatment. The results of adverse effects did not present significant heterogeneity among studies. The type of probiotic, the type of UC, or other methodological differences of the studies are not likely to influence the adverse effects to a significant level. Concerns about the safety of probiotics have been raised. As probiotics are living organisms given to ill patients, the threat for adverse reactions exists. Some intestinal bacteria have been shown to translocate from the intestine to other organs and antibiotic-resistance gene acquisition is also a concern. Considering that, globally, millions of doses of probiotics are taken a year, the risk of adverse effects due to probiotics is extremely low.<sup>41</sup> Compared with many pharmaceutical agents, serious adverse effects from probiotics rarely occur because they are well tolerated and safe.<sup>42</sup> While most of the species and genera, especially *Lactobacilli* and *Bifidobacteria* are apparently safe, certain micro-organisms may be problematic, particularly the *Enterococci*, which are associated with nosocomial infections and harbour transmissible antibiotic resistance determinants.<sup>43</sup> However, prolonged safety issues have not been addressed in studies.

Positive results from the use of probiotics have been suggested by meta-analysis published by McFarland on travellers diarrhoea,<sup>39</sup> Souza *et al.* on antibiotic associated diarrhoea,<sup>44</sup> van Niel *et al.* on acute infectious diarrhoea in children.<sup>45</sup> Sazawal *et al.* on acute diarrhoea<sup>46</sup> and McFarland on antibiotic-associated diarrhoea.<sup>41</sup> There are also positive results in meta-analysis published by Huang *et al.* on acute diarrhoea in children and Cremonini *et al.* on antibiotic-associated diarrhoea.<sup>47,48</sup> A meta-analysis by Szajewska and Mrukowicz found moderately effective results for *Saccharomyces boulardii* in the prevention of antibiotic-associated diarrhoea.<sup>49</sup>

A micro-organism classified as a probiotic has to have the following properties: exhibit non-pathogenic characteristics, be viable in delivery vehicles, be stable in acid and bile, adhere to target epithelial tissue, persist within the gastrointestinal tract, produce antimicrobial substances, modulate the immune system and influence metabolic activities. The variety of micro-organisms that have these requirements may or may not have similar impacts on specific health outcomes.<sup>46</sup> The main advantage of probiotic therapies is that they are therapeutically active but they do not disrupt the re-establishment of the

protective normal microbial flora.<sup>39</sup> The way in which probiotics affect the gut is of much interest. To overcome the problems of gastrointestinal infection, a probiotic must be nonpathogenic and must act against pathogens in ways different than antibiotics, for example, by competition. Moreover, probiotics should have a rapid onset of action and survive the challenges of gastric acid, bile, or concurrent antibiotics. It is also important that they modify immune processes to help destroy the invading organism.<sup>45</sup> The results of the present review suggest that probiotics, in general, are not more safe and effective than anti-inflammatory drugs in the remission of UC. But according to the type of probiotic or the type of UC they may be effective in the remission of UC. However, the systematic review showed that the number of studies published on this field is limited, with many methodological differences and a significant heterogeneity of results.

In conclusion, we can say that whether the use of probiotics can actually reduce the relapse of UC, and whether they are safer and more effective than anti-inflammatory drugs are issues that need to be further studied in clinical trials. The bacteria chosen, the dose of bacteria, and the duration of therapy all require further clarification. Continued investigation into the ways by which appropriate bacteria may prevent or ameliorate the chronic inflammatory state is necessary.

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