Meta-analysis: the effect and adverse events of Lactobacilli versus placebo in maintenance therapy for Crohn disease

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CRD summary
The review evaluated efficacy and adverse events for Lactobacilli compared with placebo in maintenance therapy for Crohn disease and found that both Lactobacillus johnsonii and Lactobacillus rhamnosus strain GG (LGG) had no benefit for relapse; LGG significantly increased relapse, but only in children. The extent to which the conclusions are reliable is unclear due to the limited evidence available.

Authors' objectives
To evaluate the efficacy and adverse events of Lactobacilli compared with placebo in maintenance therapy for Crohn disease.

Searching
MEDLINE (from 1966 to June 2007), EMBASE (from 1980 to June 2007), BIOSIS Previews (from 1996 to December 2006) and Cochrane Central Register of Controlled Trials (CENTRAL) (first quarter 2007) databases were searched. OVID (from 1950 to June 2007) was searched. Abstracts of gastroenterological meetings were handsearched. Search terms were reported.

Study selection
Randomised controlled trials (RCTs) with at least two arms in adults or children with Crohn disease were eligible for inclusion. Eligible studies included a control group that received placebo with/without aminosalicylates, steroids and/or azathioprine for maintenance of remission and a Lactobacilli (intervention) group that received Lactobacilli or Lactobacilli plus the same treatment as the control group. Full papers and studies in abstracts or meeting reports where the full paper had not been published were eligible for inclusion. Interventions in included studies were with Lactobacillus johnsonii (LA1) and Lactobacillus rhamnosus strain GG (LGG). Length of follow-up in the included studies ranged from three to 24 months. Included studies were in adults and children, but no other participant details were provided. Outcomes of interest were clinical relapse rates and adverse events. Clinical relapse was defined as Crohn Disease Activity Index over different standards that ranged from 100 to 200.

Two independent researchers were involved in study selection. Disagreements were resolved by a third reviewer.

Assessment of study quality
Methodological quality was assessed by two reviewers independently using the method developed by Jadad and Schulz to give a quality rating of 0 to 5. Criteria included randomisation and blinding. RCTs were considered to be low quality if their score was less than 3. Disagreements were resolved by consensus or consultation with a third reviewer.

Data extraction
The number of events for each outcome were extracted in order to calculate rate difference and 95% confidence intervals (CI). The authors reported the type of data extracted, but not how data were extracted for the review and how many reviewers performed the extraction.

Methods of synthesis
Pooled relative risks (RR) and 95% CI were calculated using a fixed-effect model and intention to treat. P<0.05 (two sided) was considered to be significant. Between-study heterogeneity was determined with I² tests and visually with funnel plots. Subanalyses were performed for adults and children and the different Lactobacilli subtypes. Sensitivity analyses were performed.

Results of the review
Six relevant RCTs were identified (n=359, range nine to 98). All six RCTs were placebo-controlled. Five RCTs were
double-blind. Two studies were in children (n=150) and four studies were in adults (n=209). LA1 was used in two studies and LGG in four studies; both the studies in children used LGG.

**Relapse rates:**

*Lactobacilli* administration compared to placebo did not significantly affect overall relapse rates. There was some heterogeneity among the studies (I^2=43.6%). A sensitivity analysis found no difference in overall relapse rates after the omission of one unpublished study. Funnel plots showed evidence for publication bias.

Subanalyses that assessed studies in adults and children separately found no significant benefit for *Lactobacilli*. There was significant heterogeneity (I^2=43.9%) for the meta-analysis in adults and no heterogeneity for the meta-analysis in children (I^2=0%).

Subanalyses for the different *Lactobacilli* subtype interventions gave a significant benefit in relapse rate for placebo compared to LGG (RR 1.68, 95% CI 1.07 to 2.64, I^2=0%), but no significant difference in relapse rate between LA1 and placebo.

Three RCTs (all in adults) reported endoscopic relapse rates. Meta-analysis showed no significant benefit for administration of *Lactobacilli* versus placebo and little heterogeneity (I^2=0%).

**Adverse events:**

There was no significant difference in the number of adverse events for *Lactobacilli* administration versus placebo (five RCTs).

**Authors’ conclusions**

Administration of LGG and LA1 as maintenance therapy for Crohn disease was inefficacious in reducing the incidence of relapse; LGG may have increased incidence of relapse. There was no evidence for a significant benefit of LGG and LA1 in maintenance therapy in both adults and children with Crohn disease; similar and few adverse events were observed.

**CRD commentary**

The review addressed a well-defined question in terms of participants, interventions and study design, but definitions of relevant outcomes were less clear. Relevant databases were searched and unpublished studies were considered. It appeared that searches were carried out only for publications in English, so some relevant studies may have been missed. Publication bias was assessed. Study quality was assessed with suitable criteria, but few details of study quality of individual RCTs were reported. Study selection and validity assessment were carried out with efforts to reduce error and bias; it was not reported whether this process applied to data extraction. Minimal study details were reported, with limited details of the interventions and no data relevant to the placebos used, no details of the age and sex of participants and no details of loss to follow-up. Statistical heterogeneity was assessed and there was evidence for heterogeneity with some outcomes. The statistical method used for the meta-analysis of the RCTs may not have been appropriate as a fixed-effects model was used to derive relative risks and there was evidence of heterogeneity. A sensitivity analysis was carried out. The extent to which the authors’ conclusions are reliable is unclear, chiefly due to the small number of relevant studies identified and the small number of participants.

**Implications of the review for practice and research**

**Practice:** The authors stated that it could not be assumed that all *Lactobacilli* were inefficacious in the maintenance therapy of Crohn disease.

**Research:** The authors identified a need for further more rigorous well-designed and larger RCTs in children to confirm these results.

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