Lactobacillus therapy for acute infectious diarrhea in children: a meta-analysis
Van Niel C W, Feudtner C, Garrison M M, Christakis D A

Authors' objectives
To determine whether treatment with Lactobacillus improves clinical outcomes in children with acute infectious diarrhoea.

Searching
MEDLINE, EMBASE, the Cochrane Controlled Trials Register, DARE and CINAHL were searched from 1966 to 2000; AMED, MANTIS, the Complementary and Alternative Medicine Citation Index and AltHealthWatch were searched from 1985 to 2000. No language restrictions were applied and the search terms were reported. The reference sections of clinical trials and review articles were also checked, and researchers in the field were contacted. The Medical Editors Trial Amnesty was searched for unpublished trials.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) with blinding of the participants, care providers and outcome assessors were eligible for inclusion. Studies where participants were either excluded or reallocated after randomisation were excluded.

Specific interventions included in the review
Studies comparing Lactobacillus with a placebo were eligible for inclusion. Any species or strain of Lactobacillus was considered suitable. Studies using killed Lactobacillus as the placebo were excluded.

Participants included in the review
Studies involving children with infectious diarrhoea by any definition were eligible for inclusion. Children with bloody or non-bloody diarrhoea were included. Studies in which children had received recent antibiotics were excluded. Most of the included studies were conducted in developed countries.

Outcomes assessed in the review
Studies that reported diarrhoea intensity were eligible for inclusion. The primary outcomes were duration (number of days), frequency (number of stools per day) and amount of diarrhoea (volume). The secondary outcomes included the requirement for intravenous fluids and adverse effects.

How were decisions on the relevance of primary studies made?
Two reviewers, blind to the author and source, independently assessed the relevance of studies for inclusion. Two other reviewers resolved any disagreements by discussion.

Assessment of study quality
Randomisation and blinding were among the selection criteria. Randomisation was not assessed further.

Two reviewers independently assessed the methodology of the primary studies, resolving any disagreements by discussion.

Data extraction
The data were extracted independently by two reviewers and verified by a third. Data that best approximated duration, frequency and amount of diarrhoea were extracted from each study. Duration was converted into days.

Methods of synthesis
How were the studies combined?
The studies were combined using a random-effects meta-analysis, weighted by the inverse of the variance, to obtain a pooled weighted difference in the mean duration and mean number of stools on day 2.

Publication bias was investigated using an adjusted rank correlation test (Begg and Mazumdar) and a regression asymmetry test (Egger et al.).

How were differences between studies investigated?
Subgroup analyses were predefined for age, use of additional therapy (oral rehydration or intravenous fluid), strain of Lactobacillus, dose and duration of Lactobacillus treatment, location of population, whether patients were in-patients or not, and the infectious agent causing the diarrhoea, when reported in three or more studies.

Results of the review
Nine RCTs (n=765) were included in the review.

Duration: 7 studies provided a measure of variance. A meta-analysis of these studies showed a reduction in the duration of diarrhoea of 0.7 days (95% confidence interval, CI: 0.3, 1.2) for those treated with Lactobacillus compared with placebo. A positive significant linear association between the logarithm of the Lactobacillus dose and reduction in diarrhoea duration was reported (P<0.01).

Frequency: 3 studies provided a measure of variance. A meta-analysis of these studies showed a reduction in the frequency of diarrhoea on day 2 of 1.6 fewer stools per day (95% CI: 0.7, 2.6) for those treated with Lactobacillus compared with placebo.

Volume: no data were found for changes in the volume of diarrhoea.

Subgroup analyses: the authors planned 7 a priori subgroup analyses. The results of two were reported, while a third was not undertaken due to the heterogeneity of the included studies.

Five studies carried out in developed countries showed a reduction in the duration of diarrhoea of 0.8 days (95% CI: 0.1, 1.5) for those treated with Lactobacillus compared with placebo. Six studies using live Lactobacillus preparations showed a reduction in the duration of diarrhoea of 0.8 days (95% CI: 0.3, 1.3 days) for those treated with Lactobacillus compared to placebo. Due to heterogeneity between the studies, the effects of different strains of Lactobacillus could not be determined.

Adverse reactions: overall, these were similar in both the control and treatment groups. Two studies reported a decrease in vomiting in children given Lactobacillus. One study reported myoclonic jerks in two patients, one in each arm of the trial.

Publication bias: the results of the tests were not statistically significant.

Cost information
The authors stated that a 48-hour course of Lactobacillus is commercially available for approximately $10. On average, this could save approximately 17 hours of caring for a sick child and 1 to 2 diapers.

Authors’ conclusions
Lactobacillus seems safe and reasonably effective in reducing the duration and frequency of diarrhoea.

CRD commentary
The authors undertook an extensive search for published research. They attempted to locate unpublished research and did not apply any language restrictions, therefore minimising the potential for publication and language bias. The review methodology was sound, with clear inclusion criteria, independent assessment of relevance and study design, and...
independent data extraction. However, potential limitations included the lack of an assessment of the adequacy of randomisation in the included studies, and the pooling of studies that were clinically dissimilar. The conclusions drawn by the authors are consistent with the evidence presented.

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

**Practice:** The authors stated that Lactobacillus can be recommended in the treatment of children with infectious diarrhoea.

**Research:** The authors recommended a large RCT, funded by a non-vested party, to test whether high-dose Lactobacillus is an effective treatment for infectious diarrhoea in ambulatory children. They also recommended the use of standardised measurements of diarrhoea intensity to aid interpretation of the results.

**Bibliographic details**


**PubMedID**

11927715

**Original Paper URL**

http://pediatrics.aappublications.org/cgi/content/full/109/4/678

**Other publications of related interest**


**Indexing Status**

Subject indexing assigned by NLM

**MeSH**

Administration, Oral; Child, Preschool; Diarrhea /etiology /therapy; Gastroenteritis /complications /therapy; Humans; Infant; Lactobacillus; Probiotics /administration & dosage

**AccessionNumber**

12002000895

**Date bibliographic record published**

31/10/2004

**Date abstract record published**

31/10/2004

**Record Status**

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