Efficacy of probiotic use in acute diarrhea in children: a meta-analysis

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Authors' objectives
To determine the efficacy of probiotic use in reducing the duration of increased stool output in children with acute diarrhoeal illness.

Searching
MEDLINE, EMBASE and CINAHL were searched from 1966 to December 2001. The search terms were reported in the article. In addition, abstracts from relevant major meetings and reference lists were searched, and experts were contacted.

Study selection
Study designs of evaluations included in the review
Only randomised controlled trials (RCTs) were included in the meta-analysis.

Specific interventions included in the review
Inclusion was limited to studies of probiotics as therapy. The specific probiotics included were Lactobacillus GG, L. acidophilus, L. bulgaricus, S. thermophilus, L. rhamnosus, Yalacta (L. rhamnosus, L. delbruckii, L. bulgaricus), L. reuteri, Enterococcus SF68, S. boulardii, S. subtilis, B. bifidum and B. infantis.

Participants included in the review
Children with acute diarrhoea (less than 1 week in duration), who were otherwise healthy, were included.

Outcomes assessed in the review
Inclusion was limited to studies that reported the duration of diarrhoea as an outcome variable.

How were decisions on the relevance of primary studies made?
Three investigators identified 300 references from three different literature searches.

Assessment of study quality
The validity of the included studies was not assessed using a formal checklist, but study characteristics (e.g. details of randomisation and blinding) were extracted from these studies.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. Data were extracted on the first author, year of publication and study design. The latter included details on randomisation, whether the participants and investigators were blinded to the intervention, the number of patients in each treatment group, the type and amount of probiotic used, the length of treatment and follow-up, and the outcome of treatment (measured as duration of diarrhoea in days).

Methods of synthesis
How were the studies combined?
Each arm of the included studies was counted as a separate study arm compared to control. All 26 arms were initially pooled, then meta-analyses of the following were performed: studies mainly involving hospitalised patients; only double-blind studies; only studies evaluating lactobacilli; and studies not evaluating Lactobacillus GG. The meta-analyses were performed using a random-effects model.
Publication bias was investigated using Begg's test, Egger's test and funnel plots.

How were differences between studies investigated?
Heterogeneity between the studies was examined using Cochran's Q test.

**Results of the review**
A total of 18 RCTs (n=1,917) were included.

Overall effect of probiotic therapy on the duration of diarrhoea (26 comparisons): the pooled estimate was -0.8 days of diarrhoea (95% confidence interval, CI: -1.1, -0.6, P<0.001). There was significant heterogeneity between the studies (Q=204.1, P<0.001). Twenty-two of the 26 comparisons indicated a shorter duration of diarrhoea in probiotic-treated patients than in placebo-treated patients. No evidence of publication bias was found using the methods suggested by Begg (P=0.22) or Egger (P=0.86).

Subanalysis of in-patient trials (23 comparisons): the pooled estimate was -0.7 days (P<0.001). There was significant heterogeneity between the studies (Q=48.1, P<0.001).

Subanalysis of double-blinded, randomised, placebo-controlled trials (9 comparisons): the pooled estimate was -0.6 days (95% CI: -1.0, -0.3, P<0.001). There was significant heterogeneity between the studies (Q=34.0, P<0.001).

Subanalysis of lactobacilli therapy: the pooled estimate was -1.1 days (95% CI: -1.3, -0.8, P<0.001). There was significant heterogeneity between the studies (Q=133.5, P<0.001).

Subanalysis of Lactobacillus GG therapy: the pooled estimate was -1.2 days (95% CI: -1.6, -0.8, P<0.001). There was significant heterogeneity between the studies (Q=52.8, P<0.001).

Subanalysis of studies evaluating probiotics other than Lactobacillus GG: the pooled estimate was -0.6 days (95% CI: -0.9, -0.3, P<0.001). There was significant heterogeneity between the studies (Q=115.9, P<0.001).

**Authors’ conclusions**
The meta-analysis provided confirmatory evidence of the efficacy of probiotic supplements in reducing the duration of symptoms among children up to 5 years old with acute, nonbacterial diarrhoea. Probiotics, particularly lactobacilli, reduced the duration of an acute diarrhoeal episode in an infant or child by approximately one day.

**CRD commentary**
The meta-analysis was based upon a broadly defined question that may be responsible for the observed heterogeneity in the findings. The researchers conducted an adequate search of databases, which was supplemented by searches of relevant conference abstracts and contact with experts in the field. Though some aspects of validity were investigated, there was no in-depth investigation of the influence of study validity on the results, with the exception of a subanalysis of double-blinded studies. The statistical methods used to combine the studies seemed appropriate, though details of the trials themselves were sparse. The authors' broad conclusion that probiotics are superior to placebo in reducing the duration of diarrhoea in children does, however, appear to be supported by the evidence presented in the meta-analysis.

**Implications of the review for practice and research**
Practice: The authors did not state any implications for practice.

Research: The authors stated that further clinical study is recommended to address the question of cost-effectiveness of using probiotics to treat children with acute diarrhoea, to further delineate the groups (out- versus in-patient, older versus younger) deriving greatest clinical benefit from probiotic therapy, and to determine the most effective dosing schedule.
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