Probiotics in prevention of antibiotic associated diarrhoea: meta-analysis

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Authors' objectives
To evaluate the efficacy of probiotics in the prevention and treatment of diarrhoea associated with the use of antibiotics.

Searching
MEDLINE was searched from 1966 to 2000 using the terms 'probiotics', 'biotherapeutic agents', 'lactobacilli', antibiotic associated diarrhoea' and 'Clostridium difficile'. The search included only published literature that had an English abstract. The Cochrane Controlled Trials Register and the Cochrane Database of Systematic Reviews were also searched. Trials without an English abstract were identified using the review papers found by the MEDLINE and Cochrane database searches.

Study selection
Study designs of evaluations included in the review
Only randomised double-blind placebo-controlled trials were included.

Specific interventions included in the review
Only studies where probiotic therapy for the prevention of diarrhoea was compared with placebo (both given in combination with antibiotics) were included. There were 4 yeast trials that used the probiotic Saccharomyces boulardii (S. boulardii). This was administered as either 4 capsules/day with a variable duration of treatment; 1 g/day with a variable duration of treatment; 1 g/day for 49 days; or 113 mg twice a day for 14 days. There were 5 non-yeast trials: 2 used L. acidophilus and L. bulgaricus (1 sachet of Lactinex 4 times a day for 5 or 10 days); one used E. faecium SF68 (1 capsule twice a day for 7 days); one used L. acidophilus and Bifidobacterium longum (fermented milk with cultures, 250 mL twice a day for 21 days); and, one used Lactobacillus GG (1 to 2 capsules/day for 10 days). Trials that looked at the treatment of diarrhoea were excluded.

Participants included in the review
Individuals receiving antibiotic treatment. Further exclusion and inclusion criteria relating to the participants were not specified. In 6 of the studies the participants were receiving a mixture of different antibiotics. Ampicillin alone was received in one study; amoxicillin alone in another study, and clindamycin alone in a further study. Two of the studies were of children and 7 were of adults.

Outcomes assessed in the review
The outcome was the absence of diarrhoea.

How were decisions on the relevance of primary studies made?
The articles and abstracts were independently assessed by the four authors.

Assessment of study quality
The authors state that only randomised double-blind trials were included. Further details of the validity assessment were not reported.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the reviewers performed the data extraction.

The abstracted data included the sample size, treatment regimens, and the numbers of patients in the treatment and...
placebo groups who were without diarrhoea. The odds ratio (OR) and 95% confidence interval (CI) were calculated for absence of diarrhoea.

**Methods of synthesis**

How were the studies combined?
The 4 yeast trials and 5 non-yeast trials were combined both separately and all together using the Mantel-Haenszel method, and the summary ORs and 95% CIs were calculated. Publication bias was assessed using a funnel plot (see Other Publications of Related Interest no.1), the Begg and Mazumdar adjusted rank correlation test (see Other Publications of Related Interest no.2) and the regression asymmetry test (Egger et al.).

How were differences between studies investigated?
Three separate tests of homogeneity were carried out for all 9 trials, the 4 yeast trials and the 5 non-yeast trials.

**Results of the review**

Nine randomised controlled trials (n=1,214) were included.

The tests for homogeneity were non significant across all 9 trials (p=0.246), across the 4 yeast trials (p=0.065), and across the 5 non-yeast trials (p=0.573).

The combined OR was 0.39 (95% CI: 0.25, 0.62) for the 4 yeast trials and 0.34 (95% CI: 0.19, 0.61) for the 5 non-yeast trials. The overall OR for the 9 trials was 0.37 (95% CI: 0.26, 0.53).

Tests for publication bias did not show significant results.

**Authors' conclusions**

The meta-analysis suggested that probiotics can be used to prevent antibiotic-associated diarrhoea, and that S. boulardii and lactobacilli have the potential to be used in this situation. The efficacy of probiotics in treating antibiotic-associated diarrhoea remains unproven.

**CRD commentary**

The review presented a clearly stated research question and the authors’ conclusions follow from the results presented. However, there were some limitations. For example, although the review question was clear, the type of participant considered was unspecified and the patient demographic and disease characteristics were not reported. The literature search was restricted to two databases, there was no mention of checking the references of retrieved articles, and no attempt was made to identify unpublished studies. In addition, non-English publications were excluded from the MEDLINE search and were only identified from review articles and the Cochrane database. It is therefore possible that some articles were missed. Publication bias was assessed.

The authors used fairly stringent inclusion criteria for study design but there was no systematic assessment of study quality. It is therefore unclear whether all the studies were of the same quality. The results were pooled appropriately given the evidence of homogeneity. Each of the studies was given a weighting but it is unclear what criteria were used to generate the weighting. While details of the individual studies were presented, the tabulated data could have been more comprehensive.

The authors’ conclusions appear to reflect the presented results. However, the findings are not considered in view of the quality of the pooled trials.

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

Practice: The authors did not state any implications for practice.

Research: The authors state that a further large trial in which probiotics are used as preventive agents should look at the
costs of, and need for, routine use of these agents.

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**Record Status**
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.