Meta-analysis of probiotics for the prevention of antibiotic associated diarrhea and the treatment of Clostridium difficile disease

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CRD summary
This review, which evaluated the efficacy and safety of probiotics for the prevention of antibiotic-associated diarrhoea (AAD) and the treatment of Clostridium difficile disease (CDD), concluded that probiotics can significantly reduce the incidence of AAD and are an effective treatment for CDD. Considering the potential for bias in this review and important differences between the studies, these broad conclusions might not be entirely reliable.

Authors' objectives
To assess the efficacy and safety of probiotics for the prevention of antibiotic-associated diarrhoea (AAD) and the treatment of Clostridium difficile disease (CDD).

Searching
PubMed, MEDLINE and Google Scholar were searched from 1977 to 2005. There were no language restrictions and non-English articles were translated. The Cochrane CENTRAL Register, meta Register of Controlled Trials and ClinicalTrials.gov were also searched. Searches of reference lists, authors, reviews, commentaries, associated diseases, books and meeting abstracts were also performed. The search terms were reported in the paper.

Study selection
Study designs of evaluations included in the review
Blinded randomised controlled trials (RCTs) were included in this review.

Specific interventions included in the review
Studies in which specific probiotics were given to either prevent or treat AAD/CDD were eligible for inclusion. Trials of unspecified probiotics, or of prebiotics, were excluded.

The included studies of AAD compared a control with single strains of probiotic, with mixtures of two types of probiotic and with a synbiotic (a probiotic combined with a prebiotic substance). The probiotics investigated were Saccharomyces boulardii, Lactobacillus rhamnosus, GG, Bacillus clausii, Bifidobacterium longum, Clostridium butyricum miyairir, Lactobacillus acidophilus and Enterococcus faecium SF68. Daily doses of probiotics ranged from 1E7 to 1E11. The duration of the studies ranged from 1 to 8 weeks and follow-up ranged from 0 days to 12 weeks. The included studies of CDD compared control with the probiotics Saccharomyces boulardii, Lactobacillus rhamnosus GG, Lactobacillus plantarum 299v, Lactobacillus acidophilus and Bifidobacterium bifidum, alone or in combination with vancomycin and/or metronidazole. Daily doses of probiotic ranged from 2E10 to 6E11, while the dose of antibiotic varied. The duration of the studies ranged from 20 to 38 days and follow-up was either 0 days or 4 weeks.

Participants included in the review
The author did not state any inclusion criteria relating specifically to the participants, but it appeared that studies of participants with CDD or at risk of ADD were eligible for inclusion.

Outcomes assessed in the review
The author did not state any inclusion criteria relating to the outcomes. The primary outcome for studies of AAD was defined as diarrhoea (at least three loose stools/day for at least 2 days, or at least five loose stools/48 hours) within 2 months of antibiotic exposure. The primary outcome for studies of CDD was defined as a new episode of diarrhoea associated with a positive culture or toxin (A or B) assay within 1 month of exposure to antibiotics. The outcome for prevention of CDD was a new episode of Clostridium difficile-positive diarrhoea within 1 month of a previous CDD episode. The presence of diarrhoea was based on clinical assessment and self-report of symptoms by daily symptom diaries. Adverse events were also reported.
How were decisions on the relevance of primary studies made?
One reviewer identified studies for inclusion in the review.

Assessment of study quality
Methodological quality was assessed using a scale reported by the U.S. Preventive Services Task Force. This was based on randomisation, study design, sample size, generalisability, study biases and outcome assessment. The number of reviewers involved was not reported.

Data extraction
One reviewer extracted data on the key study characteristics.

Methods of synthesis
How were the studies combined?
Relative risks (RRs) with 95% confidence intervals (CIs) were used as summary statistics. Heterogeneous study results were pooled in a random-effects meta-analysis using the DerSimonian and Laird method. Homogeneous results were combined in a fixed-effect meta-analysis using the Mantel-Haenszel method. The studies were weighted by sample size. Publication bias was assessed using a funnel plot and the Begg rank correlation test.

How were differences between studies investigated?
Statistical heterogeneity was assessed using a chi-squared test.

Results of the review
Thirty-one RCTs (n=3,164) were included: 25 trials of AAD (n=2,810) and 6 trials of CDD (n=354).

AAD.
The results of the funnel plot indicated publication bias, but the Begg rank correlation test did not (z = -1.05, p=0.29).
The use of probiotics compared with a control was associated with a statistically significant protective effect for AAD (pooled RR 0.43, 95% CI: 0.31, 0.58, p<0.001). The studies were highly statistically heterogeneous (p<0.001).
Subgroup analyses were conducted for each strain of probiotic. The probiotic strains that showed significant efficacy were Saccharomyces boulardii (RR 0.37, 95% CI: 2.26, 0.52, p<0.0001), Lactobacillus rhamnosus (RR 0.31, 95% CI: 0.13, 0.72, p=0.006) and mixtures of two probiotics (RR 0.51, 95% CI: 0.38, 0.68, p=0.0001).

CDD.
The funnel plot analysis and the Begg rank correlation test did not indicate publication bias.
The pooled RR indicated that probiotics had a statistically significant protective effect for CDD (RR 0.59, 95% CI: 0.41, 0.85, p=0.005). The studies were statistically homogeneous (p=0.5). The author reported that only Saccharomyces boulardii showed a significant reduction in CDD, but no further information was given.

For both AAD and CDD, 26 trials presented data on adverse events. In 24 trials no adverse reactions were reported. No further details were given.

Authors' conclusions
The present meta-analysis suggests that probiotics can significantly reduce the incidence of AAD and are an effective treatment for CDD. In particular, Saccharomyces boulardii, Lactobacillus rhamnosus GG and probiotic mixtures help prevent antibiotic-associated diarrhoea. Only Saccharomyces boulardii appears useful for CDD.
CRD commentary
The review question was well defined and the inclusion criteria were clear with regards to the study design, intervention and the conditions being studied. However, the inclusion criteria did not address patient characteristics, which might have resulted in subjective decisions regarding inclusion. The search was extensive, including non-English articles and secondary and handsearches. However, only one author extracted the data, which might have introduced reviewer bias. The funnel plot for ADD indicated that publication bias may have been present. The quality of the individual studies was assessed and heterogeneity investigated. Significant statistical heterogeneity was found in the studies of ADD, so combining these studies in a meta-analysis might not have produced reliable results. There were also significant clinical differences between the studies combined, as they included a wide range of ages and varieties and doses of antibiotics and probiotics. However, this heterogeneity was investigated to some extent through the use of a priori subgroup analyses. Considering the potential for bias in this review, the author's conclusions might not be reliable.

Implications of the review for practice and research
Practice: The author did not state any implications for practice.
Research: The author stated that future studies should expand the types of probiotics tested and pay careful attention to proper study design and sample size considerations.

Bibliographic details

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16635227

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Other publications of related interest
This additional published commentary may also be of interest. Ellison RT. Review: probiotics are effective for prevention of antibiotic-associated diarrhea and treatment of Clostridium difficile disease. ACP J Club 2006;145:46.

Indexing Status
Subject indexing assigned by NLM

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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.