Probiotics for the prevention and treatment of antibiotic-associated diarrhea: a systematic review and meta-analysis

CRD summary
The authors concluded that using probiotics as adjunct therapy reduced the risk of antibiotics-associated diarrhoea. The conclusions of this well-conducted review are likely to be reliable, although gaps in the reporting of the studies and differences between the included studies should be considered when interpreting the results.

Authors' objectives
To assess the evidence on probiotics and synbiotic interventions for prevention and treatment of antibiotic-associated diarrhoea.

Searching
The authors reported that they searched 12 databases (included DARE, The Cochrane Library, PubMed and EMBASE) up to February 2012 without language restrictions. References of included studies and reviews, trial registers and a specialist journal were searched. Search terms were reported.

Study selection
Randomised controlled trials (RCTs) that evaluated use of probiotics in addition to antibiotic treatment to prevent or treat antibiotic-associated diarrhoea were eligible. Eligible comparators were placebo, no treatment and a different probiotic or probiotic dose. Interventions based on the genera Lactobacillus, Saccharomyces, Bifidobacterium, Streptococcus, Enterococcus and/or Bacillus alone or in combination that used live (active or lyophilised) microorganisms in probiotic or synbiotic preparations were eligible for inclusion. Studies that included probiotics alongside antibiotics aimed at enhancing treatment effects rather than to prevent adverse effect of antibiotics were eligible if the outcome of diarrhoea was reported. All reports of diarrhoea were considered, including as an adverse effect or reason for drop-out. The definition of diarrhoea ranged from uncomplicated to severe with complications and included outcomes such as watery stool, stool consistency, physician-defined and self-reported diarrhoea.

Where reported, most patients were adults. The most common indication for antibiotics treatment was Helicobacter pylori eradication. Treatment types and dosages varied widely. Probiotics were most often Lactobacillus based, alone or combined with other genera such as Bifidobacterium. Probiotics were most often used to prevent antibiotic-associated diarrhoea.

Two reviewers independently selected studies for inclusion. Discrepancies were resolved through discussion with additional reviewers.

Assessment of study quality
Trial quality was assessed using the Cochrane risk of bias tool to appraise eight potential sources of bias that included random sequence generation, allocation concealment, blinding, selective reporting and incomplete outcome data. The reporting and ascertainment of included probiotic strains, statistical power, funding and potential for conflict of interest were addressed.

Two reviewers independently assessed study quality.

Data extraction
The number of participants with diarrhoea (primary outcome), severity of diarrhoea, measures of stool consistency were extracted to calculate risk ratios (RRs) and risk differences (RDs). Probiotics-related adverse events were extracted.

Two reviewers independently extracted the data. Discrepancies were resolved via discussion.
Methods of synthesis
A random-effects meta-analysis was used to calculate pooled risk ratios, risk differences and 95% confidence intervals (CIs). Number needed to treat (NNT) was calculated. Other results (adverse events) were synthesised narratively. Statistical heterogeneity was assessed using the $I^2$ statistic and potential sources of heterogeneity were explored. Subgroup analyses investigated the effect of probiotic genus, participant age, clinical condition and setting. Meta-regressions were used to assess the significance of any observed differences between subgroups. Sensitivity analyses were conducted to assess the robustness of the findings. Publication bias was assessed using Egger's and Begg's test.

Results of the review
Eighty-two RCTs were included in the review. Sixty-three studies (11,811 patients) that reported on the number of participants with antibiotic-associated diarrhoea were included in the meta-analysis; 45 of these studies were placebo-controlled. The quality of trial reporting was low. Fifty-nine studies reported insufficient information to assess the overall risk of bias. Many trials (64 out of 82) did not report allocation concealment, intention-to-treat analysis (31 trials) or a power calculation (39 trials). Fifty-three trials reported blinding both participants and outcome assessors.

The risk of developing antibiotics-associated diarrhoea was significantly lower for patients using probiotics (RR 0.58, 95% CI 0.50 to 0.68; $I^2$=54%). The pooled risk difference of developing antibiotics-associated diarrhoea was statistically significant (RD -0.07, 95% CI -0.10 to -0.05). Approximately 13 patients needed to be treated to prevent one additional case of antibiotics-associated diarrhoea (NNT 13, 95% CI 10.3 to 19.1).

Subgroup analyses did not significantly alter the overall results.

There was no evidence of publication bias.

Authors' conclusions
Use of probiotics as adjunct therapy was associated with a reduction in the risk of antibiotics-associated diarrhoea.

CRD commentary
The review questions and inclusion criteria for the review were clearly defined. An extensive search was performed and formal assessment found no evidence of publication bias. Appropriate attempts were made to reduce reviewer error and bias during study selection, data extraction and quality assessment. Relevant study details were reported but the authors found the interventions were insufficiently documented and this made the generalisability of the findings unclear.

Study quality was assessed and used in interpreting the results of the meta-analyses. There were significant gaps in the reporting of the study designs, which made the quality of the evidence unclear. Appropriate methods were used to pool data, assess and address statistical heterogeneity. Despite this, the sources of heterogeneity remained unclear. The analysis included a large number of RCTs and results were consistent across numerous subgroup analyses, which strengthened the reliability of the results.

The conclusions of this well-conducted review reflected the evidence presented and are likely to be reliable, although gaps in the reporting of the studies and the presence of heterogeneity should be born in mind when interpreting the results.

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

Research: The authors stated that larger (for example, multi-site) and adequately powered trials were needed to evaluate the effect of the intervention on the risk of antibiotics-associated diarrhoea, particularly in the elderly population. Direct head-to-head comparisons to assess the optimal dose of probiotic preparation and the comparative effectiveness of different probiotic interventions were needed. Future research should further assess heterogeneity in effectiveness among various types of patients, antibiotics and probiotic strains or blends and evaluate the risk of adverse events associated with probiotic use to prevent antibiotics-associated diarrhoea more explicitly.

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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.