Probiotics for prevention of antibiotic-associated diarrhea and Clostridium difficile-associated disease in hospitalized adults: a meta-analysis

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CRD summary
The review found that probiotics were effective for preventing antibiotic-associated diarrhoea and *Clostridium difficile*-associated disease in hospitalised adults. The review was generally well conducted but the authors’ conclusions require caution in interpretation because the evidence base was small in volume, diverse in character and of uncertain quality.

Authors’ objectives
To evaluate the effectiveness and safety of probiotics for preventing antibiotic-associated diarrhoea and *Clostridium difficile*-associated disease in hospitalised adults.

Searching
The following databases were searched for trials conducted after 1990: PubMed, CINHAL, HealthStar, Science Direct and The Cochrane Library. Search terms included key words, index terms, author names and words from the title and abstract of trials retrieved. Websites of the Joanna Briggs Institute Library of Systematic Reviews, Trip, SUMSearch, Agency for Healthcare Research and Quality, Google, Google Scholar, www.uptodate.com and the Complementary and Alternative Medicine site of the National Institutes of Health were screened. The reference lists of articles retrieved were checked for further trials. Eligible articles were in English and available in full-text.

Study selection
Eligible randomised controlled trials (RCTs) compared probiotics with placebo, active control or no treatment control in hospitalised adults (aged 18 to 80 years) taking antibiotics. The review outcomes were incidence of antibiotic-associated diarrhoea, *Clostridium difficile*-associated disease (primary outcomes) and adverse events. Trials of participants with pre-existing bowel disease or compromised immune status were excluded.

The included trials were set in hospitals in the USA, UK, Turkey and Sweden. Participants in half of the trials were older adults (mean age over 70 years, where stated). Other trials included younger adults (aged 25 to 50) or did not state participant age. Participants differed in their baseline severity of illness. Several different types of probiotic were used, administered as a drink, capsule or yoghurt (where stated). All controls received placebo. Diarrhoea was defined in the included trials as more than two liquid stools daily for three or more days in excess of normal. *Clostridium difficile*-associated disease was defined as a positive stool test. Adverse events were not reported in the review.

Two reviewers independently selected the trials.

Assessment of study quality
Trial quality was assessed with the Joanna Briggs Institute tool to evaluate randomisation, double-blindning, withdrawals and drop-outs.

Two reviewers independently conducted the assessment with disagreements resolved by discussion.

Data extraction
Risk ratios (RRs) with 95% confidence intervals (CIs) and relative risk reductions (RRRs) were calculated. It was not reported how many reviewers undertook data extraction.

Methods of synthesis
Pooled risk ratios with 95% confidence intervals were calculated with a Mantel Haenszel random-effects model for antibiotic-associated diarrhoea and a fixed-effect model for *Clostridium difficile*-associated disease. Pooled relative risk reductions were calculated. Statistical heterogeneity was assessed using $X^2$. No formal method was used to assess for...
Results of the review
Eight RCTs were included (1,246 participants, range 69 to 267). The authors stated that methodological limitations included lack of clear allocation concealment and lack of intention-to-treat analysis.

Compared with placebo, probiotics were associated with a significantly lower risk of antibiotic-associated diarrhoea (RR 0.56, 95% CI 0.44 to 0.71; RRR 44%; eight RCTs) or Clostridium difficile-associated disease (RR 0.29, 95% CI 0.18 to 0.46; RRR 71%; four RCTs). There was statistically significant heterogeneity for both analyses (X²=29, p<0.1).

Authors’ conclusions
Probiotics were effective for preventing antibiotic-associated diarrhoea and Clostridium difficile-associated disease in hospitalised adults.

CRD commentary
The objectives and inclusion criteria of the review were clear. Relevant sources were searched for trials. The restriction to English-language trials meant that one trial was excluded. The restriction to full text articles may have created potential for bias. As the authors noted, the potential for publication bias was unclear. The final search date was not reported. Steps were taken to minimise the risk of reviewer bias and error in trial selection and validity assessment, but it was unclear whether this applied to data extraction.

Relevant aspects of quality were assessed but no details were provided about the quality of individual trials (such as follow-up rates), which made it difficult to determine the reliability of the review findings. Adverse events were not reported and it was not entirely clear whether any data were available for this outcome. Appropriate statistical techniques were used to combine the trials and assess heterogeneity. Substantial statistical heterogeneity was found, which the authors attributed to use of a subtherapeutic dose of probiotics in one trial, but it was difficult to evaluate this explanation as the review provided insufficient detail about trial characteristics. As the authors noted, there were few trials, sample sizes were small and there were differences between the trials.

The review was generally well conducted but the authors’ conclusions require caution in interpretation because the evidence base was small in volume, diverse in character and of uncertain quality.

Implications of the review for practice and research
Practice: The authors stated that probiotics should be used to reduce the incidence of antibiotic-associated diarrhoea and Clostridium difficile-associated disease in hospitalised adults taking antibiotics, especially as the incidence and severity of these disorders was increasing and the effectiveness of conventional therapies was diminishing.

Research: The authors stated that further RCTs should be conducted to investigate the use of probiotic prophylaxis for antibiotic-associated diarrhoea and Clostridium difficile-associated disease in view of the small amount of evidence that was available.

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