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[Intervention Review]

# Probiotics for the prevention of *Clostridium difficile*-associated diarrhea in adults and children

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## ABSTRACT

### Background

Antibiotics can disturb gastrointestinal microbiota which may lead to reduced resistance to pathogens such as *Clostridium difficile* (*C. difficile*). Probiotics are live microbial preparations that, when administered in adequate amounts, may confer a health benefit to the host, and are a potential *C. difficile* prevention strategy. Recent clinical practice guidelines do not recommend probiotic prophylaxis, even though probiotics have the highest quality evidence among cited prophylactic therapies.

### Objectives

To assess the efficacy and safety of probiotics for preventing *C. difficile*-associated diarrhea (CDAD) in adults and children.

### Search methods

We searched PubMed, EMBASE, CENTRAL, and the Cochrane IBD Group Specialized Register from inception to 21 March 2017. Additionally, we conducted an extensive grey literature search.

### Selection criteria

Randomized controlled (placebo, alternative prophylaxis, or no treatment control) trials investigating probiotics (any strain, any dose) for prevention of CDAD, or *C. difficile* infection were considered for inclusion.

### Data collection and analysis

Two authors (independently and in duplicate) extracted data and assessed risk of bias. The primary outcome was the incidence of CDAD. Secondary outcomes included detection of *C. difficile* infection in stool, adverse events, antibiotic-associated diarrhea (AAD) and length of hospital stay. Dichotomous outcomes (e.g. incidence of CDAD) were pooled using a random-effects model to calculate the risk ratio (RR) and corresponding 95% confidence interval (95% CI). We calculated the number needed to treat for an additional beneficial outcome (NNTB) where appropriate. Continuous outcomes (e.g. length of hospital stay) were pooled using a random-effects model to calculate the mean difference and corresponding 95% CI. Sensitivity analyses were conducted to explore the impact of missing data on efficacy and safety outcomes. For the sensitivity analyses, we assumed that the event rate for those participants in the control group who had missing data was the same as the event rate for those participants in the control group who were successfully followed. For the probiotic group, we

calculated effects using the following assumed ratios of event rates in those with missing data in comparison to those successfully followed: 1.5:1, 2:1, 3:1, and 5:1. To explore possible explanations for heterogeneity, a priori subgroup analyses were conducted on probiotic species, dose, adult versus pediatric population, and risk of bias as well as a post hoc subgroup analysis on baseline risk of CDAD (low 0% to 2%; moderate 3% to 5%; high > 5%). The overall quality of the evidence supporting each outcome was independently assessed using the GRADE criteria.

## Main results

Thirty-nine studies (9955 participants) met the eligibility requirements for our review. Overall, 27 studies were rated as either high or unclear risk of bias. A complete case analysis (i.e. participants who completed the study) among trials investigating CDAD (31 trials, 8672 participants) suggests that probiotics reduce the risk of CDAD by 60%. The incidence of CDAD was 1.5% (70/4525) in the probiotic group compared to 4.0% (164/4147) in the placebo or no treatment control group (RR 0.40, 95% CI 0.30 to 0.52; GRADE = moderate). Twenty-two of 31 trials had missing CDAD data ranging from 2% to 45%. Our complete case CDAD results proved robust to sensitivity analyses of plausible and worst-plausible assumptions regarding missing outcome data and results were similar whether considering subgroups of trials in adults versus children, inpatients versus outpatients, different probiotic species, lower versus higher doses of probiotics, or studies at high versus low risk of bias. However, in a post hoc analysis, we did observe a subgroup effect with respect to baseline risk of developing CDAD. Trials with a baseline CDAD risk of 0% to 2% and 3% to 5% did not show any difference in risk but trials enrolling participants with a baseline risk of > 5% for developing CDAD demonstrated a large 70% risk reduction (interaction P value = 0.01). Among studies with a baseline risk > 5%, the incidence of CDAD in the probiotic group was 3.1% (43/1370) compared to 11.6% (126/1084) in the control group (13 trials, 2454 participants; RR 0.30, 95% CI 0.21 to 0.42; GRADE = moderate). With respect to detection of *C. difficile* in the stool pooled complete case results from 15 trials (1214 participants) did not show a reduction in infection rates. *C. difficile* infection was 15.5% (98/633) in the probiotics group compared to 17.0% (99/581) in the placebo or no treatment control group (RR 0.86, 95% CI 0.67 to 1.10; GRADE = moderate). Adverse events were assessed in 32 studies (8305 participants) and our pooled complete case analysis indicates probiotics reduce the risk of adverse events by 17% (RR 0.83, 95% CI 0.71 to 0.97; GRADE = very low). In both treatment and control groups the most common adverse events included abdominal cramping, nausea, fever, soft stools, flatulence, and taste disturbance.

## Authors' conclusions

Based on this systematic review and meta-analysis of 31 randomized controlled trials including 8672 patients, moderate certainty evidence suggests that probiotics are effective for preventing CDAD (NNTB = 42 patients, 95% CI 32 to 58). Our post hoc subgroup analyses to explore heterogeneity indicated that probiotics are effective among trials with a CDAD baseline risk >5% (NNTB = 12; moderate certainty evidence), but not among trials with a baseline risk ≤5% (low to moderate certainty evidence). Although adverse effects were reported among 32 included trials, there were more adverse events among patients in the control groups. The short-term use of probiotics appears to be safe and effective when used along with antibiotics in patients who are not immunocompromised or severely debilitated. Despite the need for further research, hospitalized patients, particularly those at high risk of CDAD, should be informed of the potential benefits and harms of probiotics.

## PLAIN LANGUAGE SUMMARY

### The use of probiotics to prevent *Clostridium difficile* diarrhea associated with antibiotic use

#### What is *Clostridium difficile*-associated diarrhea?

Antibiotics are among the most prescribed medications worldwide. Antibiotic treatment may disturb the balance of organisms that normally populate the gut. This can result in a range of symptoms, most notably, diarrhea. *Clostridium difficile* (*C. difficile*) is a particularly dangerous organism that may colonize the gut if the normal healthy balance has been disturbed. *Clostridium difficile*-related disease varies from asymptomatic infection, diarrhea, colitis, and pseudo-membranous colitis to toxic megacolon and death. The cost of treatment is expensive and the financial burden on the medical system is substantial.

#### What are probiotics?

Probiotics are live organisms (bacteria or yeast). thought to improve the balance of organisms that populate the gut, counteracting potential disturbances to the gut microbial balance that are associated with antibiotic use, and reducing the risk of colonization by pathogenic bacteria. Probiotics can be found in dietary supplements or yogurts and are becoming increasingly available as capsules sold in health food stores and supermarkets. As 'functional food' or 'good bacteria', probiotics have been suggested as a means of both preventing and treating *C. difficile*-associated diarrhea (CDAD).

#### What did the researchers investigate?

The researchers investigated whether probiotics prevent CDAD in adults and children receiving antibiotic therapy and whether probiotics causes any harms (side effects). The researchers searched the medical literature extensively up to 21 March 2017.

#### What did the researchers find?

This review includes 39 randomized trials with a total of 9955 participants. Thirty-one studies (8672 participants) assessed the effectiveness of probiotics for preventing CDAD among participants taking antibiotics. Our results suggest that when probiotics are given with antibiotics the risk of developing CDAD is reduced by 60% on average. Among trials enrolling participants at high risk of developing CDAD (> 5%), the potential benefit of probiotics is more pronounced with a 70% risk reduction on average. Side effects were assessed in 32 studies (8305 participants) and our results suggest that taking probiotics does not increase the risk of developing side effects. The most common side effects reported in these studies include abdominal cramping, nausea, fever, soft stools, flatulence, and taste disturbance. The short-term use of probiotics appears to be safe and effective when used along with antibiotics in patients who are not immunocompromised or severely debilitated. Despite the need for further research, hospitalized patients, particularly those at high risk of CDAD, should be informed of the potential benefits and harms of probiotics.