**Probiotics for Antibiotic Associated Diarrhea**

By: Taiba Shah, Katya Garashchenko, Erik Oatman, Lucas Cavalier,

**Clinical Question:** Moshe, a 4 year old patient with strep throat will need to be treated with antibiotics. Last time he was on antibiotics he developed diarrhea. His mother wonders whether taking probiotics will lessen the chance of diarrhea developing. What can you tell her?

**PICO Question:** Do probiotics safely and effectively prevent AAD in pediatric patients?

**P =** Antibiotics Associated Diarrhea

**I =** probiotics, prophylactic probiotics

**C =** no intervention, placebo

**O =** prevent antibiotic associated Diarrhea, decrease incidence of antibiotic associated diarrhea, reduce severity of antibiotic associated diarrhea

**Search Strategy:**

Searched for “probiotics pediatric antibiotics diarrhea” and “probiotics prevention AAD pediatric patients”

• **Pub Med**

• **Cochrane**

• **TRIP Database**

**Articles Chosen for Inclusion:**

**Katya**

**1)** **[Probiotics for the prevention of pediatric antibiotic‐associated diarrhea](https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD004827.pub4/full)**

Joshua Z Goldenberg, Lyubov Lytvyn, Justin Steurich, Patricia Parkin, Sanjay Mahant

**Abstract**

**BACKGROUND:**

Antibiotics are frequently prescribed in children. They alter the microbial balance within the gastrointestinal tract, commonly resulting in antibiotic-associated diarrhea (AAD). Probiotics may prevent AAD via restoration of the gut microflora.

**OBJECTIVES:**

The primary objectives were to assess the efficacy and safety of probiotics (any specified strain or dose) used for the prevention of AAD in children.

**SEARCH METHODS:**

MEDLINE, EMBASE, CENTRAL, CINAHL, AMED, and the Web of Science (inception to November 2014) were searched along with specialized registers including the Cochrane IBD/FBD review group, CISCOM (Centralized Information Service for Complementary Medicine), NHS Evidence, the International Bibliographic Information on Dietary Supplements as well as trial registries. Letters were sent to authors of included trials, nutraceutical and pharmaceutical companies, and experts in the field requesting additional information on ongoing or unpublished trials. Conference proceedings, dissertation abstracts, and reference lists from included and relevant articles were also searched.

**SELECTION CRITERIA:**

Randomized, parallel, controlled trials in children (0 to 18 years) receiving antibiotics, that compare probiotics to placebo, active alternative prophylaxis, or no treatment and measure the incidence of diarrhea secondary to antibiotic use were considered for inclusion.

**DATA COLLECTION AND ANALYSIS:**

Study selection, data extraction as well as methodological quality assessment using the risk of bias instrument was conducted independently and in duplicate by two authors. Dichotomous data (incidence of diarrhea, adverse events) were combined using a pooled risk ratio (RR) or risk difference (RD), and continuous data (mean duration of diarrhea, mean daily stool frequency) as mean difference (MD), along with their corresponding 95% confidence interval (95% CI). For overall pooled results on the incidence of diarrhea, sensitivity analyses included available case versus extreme-plausible analyses and random- versus fixed-effect models. To explore possible explanations for heterogeneity, a priori subgroup analysis were conducted on probiotic strain, dose, definition of antibiotic-associated diarrhea, as well as risk of bias. We also conducted post hoc subgroup analyses by patient diagnosis, single versus multi-strain, industry sponsorship, and inpatient status. The overall quality of the evidence supporting the outcomes was evaluated using the GRADE criteria.

**MAIN RESULTS:**

Twenty-three studies (3938 participants) met the inclusion criteria. Trials included treatment with either Bacillus spp., Bifidobacterium spp., Clostridium butyricum, Lactobacilli spp., Lactococcus spp., Leuconostoc cremoris, Saccharomyces spp., or Streptococcus spp., alone or in combination. Eleven studies used a single strain probiotic, four combined two probiotic strains, three combined three probiotic strains, one combined four probiotic strains, two combined seven probiotic strains, one included ten probiotic strains, and one study included two probiotic arms that used three and two strains respectively. The risk of bias was determined to be high or unclear in 13 studies and low in 10 studies. Available case (patients who did not complete the studies were not included in the analysis) results from 22/23 trials reporting on the incidence of diarrhea show a precise benefit from probiotics compared to active, placebo or no treatment control. The incidence of AAD in the probiotic group was 8% (163/1992) compared to 19% (364/1906) in the control group (RR 0.46, 95% CI 0.35 to 0.61; I(2) = 55%, 3898 participants). A GRADE analysis indicated that the overall quality of the evidence for this outcome was moderate. This benefit remained statistically significant in an extreme plausible (60% of children loss to follow-up in probiotic group and 20% loss to follow-up in the control group had diarrhea) sensitivity analysis, where the incidence of AAD in the probiotic group was 14% (330/2294) compared to 19% (426/2235) in the control group (RR 0.69; 95% CI 0.54 to 0.89; I(2) = 63%, 4529 participants). None of the 16 trials (n = 2455) that reported on adverse events documented any serious adverse events attributable to probiotics. Meta-analysis excluded all but an extremely small non-significant difference in adverse events between treatment and control (RD 0.00; 95% CI -0.01 to 0.01). The majority of adverse events were in placebo, standard care or no treatment group. Adverse events reported in the studies include rash, nausea, gas, flatulence, abdominal bloating, abdominal pain, vomiting, increased phlegm, chest pain, constipation, taste disturbance, and low appetite.

**AUTHORS' CONCLUSIONS:**

Moderate quality evidence suggests a protective effect of probiotics in preventing AAD. Our pooled estimate suggests a precise (RR 0.46; 95% CI 0.35 to 0.61) probiotic effect with a NNT of 10. Among the various probiotics evaluated, Lactobacillus rhamnosus or Saccharomyces boulardii at 5 to 40 billion colony forming units/day may be appropriate given the modest NNT and the likelihood that adverse events are very rare. It is premature to draw conclusions about the efficacy and safety of other probiotic agents for pediatric AAD. Although no serious adverse events were observed among otherwise healthy children, serious adverse events have been observed in severely debilitated or immuno-compromised children with underlying risk factors including central venous catheter use and disorders associated with bacterial/fungal translocation. Until further research has been conducted, probiotic use should be avoided in pediatric populations at risk for adverse events. Future trials would benefit from a standard and valid outcomes to measure AAD.

**Erik**

**2)** [**Probiotics for the prevention and treatment of antibiotic-associated diarrhea: a systematic review and meta-analysis.**](https://www.ncbi.nlm.nih.gov/pubmed/22570464)Hempel S1, Newberry SJ, Maher AR, Wang Z, Miles JN, Shanman R, Johnsen B, Shekelle PG.

PMID: 22570464

### **Abstract**

#### **CONTEXT:**

Probiotics are live microorganisms intended to confer a health benefit when consumed. One condition for which probiotics have been advocated is the diarrhea that is a common adverse effect of antibiotic use.

#### **OBJECTIVE:**

To evaluate the evidence for probiotic use in the prevention and treatment of antibiotic-associated diarrhea (AAD).

#### **DATA SOURCES:**

Twelve electronic databases were searched (DARE, Cochrane Library of Systematic Reviews, CENTRAL, PubMed, EMBASE, CINAHL, AMED, MANTIS, TOXLINE, ToxFILE, NTIS, and AGRICOLA) and references of included studies and reviews were screened from database inception to February 2012, without language restriction.

#### **STUDY SELECTION:**

Two independent reviewers identified parallel randomized controlled trials (RCTs) of probiotics (Lactobacillus, Bifidobacterium, Saccharomyces, Streptococcus, Enterococcus, and/or Bacillus) for the prevention or treatment of AAD.

#### **DATA EXTRACTION:**

Two independent reviewers extracted the data and assessed trial quality.

#### **RESULTS:**

A total of 82 RCTs met inclusion criteria. The majority used Lactobacillus-based interventions alone or in combination with other genera; strains were poorly documented. The pooled relative risk in a DerSimonian-Laird random-effects meta-analysis of 63 RCTs, which included 11 811 participants, indicated a statistically significant association of probiotic administration with reduction in AAD (relative risk, 0.58; 95% CI, 0.50 to 0.68; P < .001; I(2), 54%; [risk difference, -0.07; 95% CI, -0.10 to -0.05], [number needed to treat, 13; 95% CI, 10.3 to 19.1]) in trials reporting on the number of patients with AAD. This result was relatively insensitive to numerous subgroup analyses. However, there exists significant heterogeneity in pooled results and the evidence is insufficient to determine whether this association varies systematically by population, antibiotic characteristic, or probiotic preparation.

#### **CONCLUSIONS:**

The pooled evidence suggests that probiotics are associated with a reduction in AAD. More research is needed to determine which probiotics are associated with the greatest efficacy and for which patients receiving which specific antibiotics.

**Taiba Shah**

**3)** [**Systematic review with meta-analysis: Saccharomyces boulardii in the prevention of antibiotic-associated diarrhoea.**](https://www.ncbi.nlm.nih.gov/pubmed/26216624)Szajewska H1, Kołodziej M1.

PMID 26216624

**Abstract**

#### **BACKGROUND:**

Antibiotic-associated diarrhoea is a common complication of antibiotic use, but it can be prevented with administration of probiotics.

#### **AIM:**

To update our 2005 meta-analysis on the effectiveness of Saccharomyces boulardii in preventing antibiotic-associated diarrhoea in children and adults.

#### **METHODS:**

The Cochrane Library, MEDLINE, and EMBASE databases were searched up until May 2015, with no language restrictions, for randomised controlled trials; additional references were obtained from reviewed articles. The quality of evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) guidelines.

#### **RESULTS:**

Twenty-one randomised controlled trials (4780 participants), among which 16 were new trials, met the inclusion criteria for this updated systematic review. Administration of S. boulardii compared with placebo or no treatment reduced the risk of antibiotic-associateddiarrhoea (as defined by the study investigators) in patients treated with antibiotics from 18.7% to 8.5% (risk ratio, RR: 0.47; 95% CI: 0.38-0.57, number needed to treat, NNT: 10; 95% CI: 9-13). In children, S. boulardii reduced the risk from 20.9% to 8.8% (6 randomised controlled trials, n=1653, RR: 0.43, 95% CI: 0.3-0.6); in adults, from 17.4% to 8.2% (15 randomised controlled trials, n=3114, RR: 0.49, 95% CI: 0.38-0.63). Moreover, S. boulardii reduced the risk of Clostridium difficile-associated diarrhoea; however, this reduction was significant only in children (2 randomised controlled trials, n = 579, RR: 0.25; 95% CI: 0.08-0.73) and not in adults (9 randomised controlled trials, n = 1441, RR: 0.8, 95% CI: 0.47-1.34).

#### **CONCLUSIONS:**

This meta-analysis confirms that S. boulardii is effective in reducing the risk of antibiotic-associated diarrhoea in children and adults.

**Lucas Cavalier**

**4)** [**Probiotics for the Prevention of Antibiotic-Associated Diarrhea in Children.**](https://www.ncbi.nlm.nih.gov/pubmed/26756877) **Szajewska H1, Canani RB, Guarino A, Hojsak I, Indrio F, Kolacek S, Orel R, Shamir R, Vandenplas Y, van Goudoever JB, Weizman Z;**

PMID: 26756877

### **Abstract**

This article provides recommendations, developed by the Working Group (WG) on Probiotics of the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition, for the use of probiotics for the prevention of antibiotic-associated diarrhea (AAD) in children based on a systematic review of previously completed systematic reviews and of randomized controlled trials published subsequently to these reviews. The use of probiotics for the treatment of AAD is not covered. The recommendations were formulated only if at least 2 randomized controlled trials that used a given probiotic (with strain specification) were available. The quality of evidence (QoE) was assessed using the Grading of Recommendations Assessment, Development, and Evaluation guidelines. If the use of probiotics for preventing AAD is considered because of the existence of risk factors such as class of antibiotic(s), duration of antibiotic treatment, age, need for hospitalization, comorbidities, or previous episodes of AAD diarrhea, the WG recommends using Lactobacillus rhamnosus GG (moderate QoE, strong recommendation) or Saccharomyces boulardii (moderate QoE, strong recommendation). If the use of probiotics for preventing Clostridium difficile-associated diarrhea is considered, the WG suggests using S boulardii (low QoE, conditional recommendation). Other strains or combinations of strains have been tested, but sufficient evidence is still lacking.

**Raghda**

# **5)** **[Probiotics for the prevention of Clostridium difficile-associated diarrhea in adults and children.](https://www.ncbi.nlm.nih.gov/pubmed/29257353)**

# **Goldenberg JZ1, Yap C, Lytvyn L, Lo CK, Beardsley J, Mertz D, Johnston BC.**

PMID: 29257353

### **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 probioticgroup 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.

**Summary of the Evidence**:

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Author (Date)** | **Level of Evidence** | **Sample/Setting**  **(# of subjects/ studies, cohort definition etc. )** | **Outcome(s) studied** | **Key Findings** | **Limitations and Biases** |
| Hempel, S., Newberry, S., Maher, A., et al (2012) | Level 1 Systematic Review and Meta-Analysis | 82 RCTs with 11,811 participants | Prevention and treatment of abx-associated diarrhea | Pooled evidence suggests probiotics associated with reduction in AAD | Significant heterogeneity in pooled results. Evidence is insufficient to determine whether this association varies systematically by population, antibiotic characteristic, or probiotic preparation |
| Szajewska H1, Canani RB, Guarino A, Hojsak I, Indrio F, Kolacek S, Orel R, Shamir R, Vandenplas Y, van Goudoever JB, Weizman Z | System-  atic Reviews | 82 RTCs with 3255 participants (Children) | Use of Probiotics prevents AAD in children | Pooled results of 21 RCTs showed that compared with placebo or no intervention, probiotics as a class reduced the risk of AAD by 52% | Affective probiotic is related to the type of antibiotic given to the pediatric patient |
| H. Szajewska M. Kołodziej  First published: 27 July 2015 | Level 1-  Systematic review Meta-Analysis | 21 RCTs (4780 participants) | Whether Administration of *S. boulardii* compared with placebo or no treatment reduced the risk of antibiotic‐associated diarrhea | *S. boulardii* is effective in reducing the risk of antibiotic‐associated diarrhea in children and adults. | One limitation was that the trials included varied in methodological quality. Only 2 of the articles chosen were at low risk of bias. There were also inconsistencies between the articles in the way they defined AAD/ diarrhea was defined. |
| Goldenberg JZ1, Yap C, Lytvyn L, Lo CK, Beardsley J, Mertz D, Johnston BC. | Level 1-  systematic review and meta-analysis | 31 RCTs (8672 patients) | Probiotics for the prevention of Clostridium difficile-associated diarrhea in adults and children | Probiotics are effective for preventing CDAD | 10 of 31 studies were rated as having a low risk of bias, while 21 were rated as having a high or unclear risk of bias. Test of interaction between low and high or unclear risk of bias studies was not statistically significant. |
| Joshua Z Goldenberg, Lyubov Lytvyn, Justin Steurich, Patricia Parkin, Sanjay Mahant | Level 1-Systemic Review and Meta Analysis | Twenty-three studies (3938 participants) | Probiotics to prevent AAD in children receiving antibiotic therapy and whether probiotics cause any harms (side effects) | Probiotics have a protective effect in regards to Antibiotic associated diarrhea. | -The risk of bias was determined to be high or unclear in 13 studies and low in 10 studies. But these studies were still used when determining a clinical conclusion, although this was mentioned and addressed.  -Some of the measurements to make conclusions were not easily quantified, leaving room for bias |

**Conclusion:**

Pooled evidence from systematic reviews/ meta-reviews suggests that probiotics have a protective effect against AAD in pediatric populations.

Use of probiotics is dependent on type of antibiotic medication as well as the probiotic used. These probiotics show better results with decreasing AAD if the probiotic is started before the antibiotic is prescribed. The benefits of probiotics outweigh the risks associated with taking said probiotic.

The level of evidence involved systematic review, meta analysis and randomized control trials.

Sample settings included multiple RCTs and involved 3,000 to 12,000 participants.

Outcomes studied included:

Prevention/treatment of AAD

* Probiotic use is dependent on type of antibiotic treatment
* Probiotics for the prevention of Clostridium difficile-associated diarrhea in adults and children
* There is evidence that probiotics are beneficial and outweigh the risks
* *S. boulardii* is effective in reducing the risk of antibiotic‐associated diarrhea in children and adults.

The systematic review and meta analyses that were included in in this appraisal stated that many trials included had high risk of bias, however the biases were not significant enough to invalidate the results.

**Clinical Bottom Line:**

The highest levels of evidence state that providing probiotics to children on antibiotics reduces the incidence of antibiotic-associated diarrhea.

We would recommend that parents administer probiotics (particularly supplements that include Lactobacillus rhamnosus and/or Saccharomyces boulardii) during antibiotic use in children up until the age of 18.