**Probiotic use in preventing antibiotic associated diarrhea (AAD) in children**

Clinical Scenario: 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?

Clinical Question: In pediatric patients being treated with antibiotics, will concomitant administration of probiotics prevent antibiotic associated diarrhea (AAD)?

PICO Question:

|  |  |  |  |
| --- | --- | --- | --- |
| P | I | C | O |
| children | probiotic + antibiotic | antibiotic only | diarrhea (present/absent) |
| pediatric | *Lactobacillus rhamnosus* GG | no probiotics | number of episodes of diarrhea |
| strep throat | *Saccharomyces boulardii*  |  |  |
| bacterial infection | *Lactobacillus acidophilus* |  |  |
|  |  |  |  |

Search Strategy:

**PubMed:**

“Probiotic Prevent Diarrhea” turns up 254 Results

When adding Filters: turns up 17 Results

* Review
* Publication Date within 10 years
* Humans
* Child (Birth-18 years)

“Probiotic Antibiotic Diarrhea” → 775 results

Filters activated: Review, published in the last 10 years, Humans, English, Child: birth-18 years. → 42

“children, strep throat, diarrhea” turns up 98 Results.

When adding Filters:

-Humans

-Full Text

-Sort By: Best Match

“Children, Strep Throat, Diarrhea” 67 results

**Pubmed:**

Probiotic, Antibiotic associated diarrhea, children

Filters: Review, most recent $\rightarrow $86

Filters: Review, most recent, pub date within 5 yrs$\rightarrow $35

**Cochrane Reviews:**

“Pediatric Probiotics Diarrhea” turns up **2** Cochrane Reviews

How We Selected the Final Articles to Base Our CAT On:

Our search was **specific for**:

* Pediatric Antibiotic-Associated Diarrhea (AAD)
* Probiotics
* Offered Measurable Outcomes like:
	+ Incidence of diarrhea secondary to antibiotics when using probiotics, alternative active treatment, placebo, or no treatment
	+ Mean duration of diarrhea, mean stool frequency, and number and type of adverse effects (rash, nausea, gas, flatulence, abdominal bloating, abdominal pain, vomiting, increased phlegm, chest pain, constipation, taste disturbance, and low appetite)
	+ Need to discontinue antibiotic treatment and need for hospitalization

These articles were chosen because they are all systematic reviews and/or meta-analyses and are of the **highest** level of evidence per the evidence pyramid utilized in Evidence Based Medicine.

Articles Chosen for Inclusion (please copy and paste the abstract with link):

[Probiotics for the prevention of pediatric antibiotic-associated diarrhea.](https://www.ncbi.nlm.nih.gov/pubmed/26695080)

Goldenberg JZ, Lytvyn L, Steurich J, Parkin P, Mahant S, Johnston BC.

Cochrane Database Syst Rev. 2015 Dec 22;(12):CD004827. doi: 10.1002/14651858.CD004827.pub4. Review.

PMID: 26695080

[Antibiotic associated diarrhea in children.](https://vpn.york.cuny.edu/pubmed/%2CDanaInfo%3Dwww.ncbi.nlm.nih.gov%2CSSL%2B19556659)

Alam S, Mushtaq M.

Indian Pediatr. 2009 Jun;46(6):491-6. Review.

PMID: 19556659

Abstract:

**Context**: Keeping in view the recent flooding of the Indian market with antibiotic and probiotic combinations, we decided to

look at the prevalence of antibiotic associated diarrhea (AAD) and Clostridium difficile infection (CDI) in children and

reviewed evidence available for use of probiotics in the prevention of AAD.

**Evidence acquisition**: We did a PubMed, Medline and Cochrane libary search for literature available in last 25 years.

**Results**: Prevalence of antibiotic associated diarrhea (AAD) is around 11%. Children younger than 2 years and type of

antibiotics are the two risk factors identified for AAD. For the pediatric population, CDI reportedly decreased in a tertiary

care hospital in India, though number of suspected samples tested increased. The incidence of community acquired CDI

is increasing in the pediatric population also. Detection of toxin A and B by enzyme linked immunosorbent assay (ELISA)

and detection of toxin B by tissue culture form the mainstay in the diagnosis of C. difficile. Most of the AAD would respond

to only discontinuation or change of the antibiotic. Oral metronidazole or oral vancomycin are drugs of choice for CDI.

Probiotics reduce the risk of AAD in children and for every 7-10 patients one less would develop AAD. Conclusion:

Prevalence of AAD is low and majority will respond to discontinuation of antibiotic. CDI is uncommon in children. Probiotics

will prevent AAD in only 1 in 7 children on antibiotics. We need cost effectiveness studies to decide the issue of needing a

probiotic antibiotic combination to prevent AAD.

**Keywords**: Antibiotic associated diarrhea, C. difficile associated diarrhea, Children, Pseudomembranous colitis.

[Probiotics in the prevention of antibiotic-associated diarrhea in children: a meta-analysis of randomized controlled trials](https://www.ncbi.nlm.nih.gov/pubmed/16939749)

Szajewska H, Ruszczyński M, Radzikowski A.

J Pediatr. 2006 Sep;149(3):367-372.

PMID: 16939749

Abstract:

**Objective** To systematically evaluate the effectiveness of probiotics in preventing antibiotic-associated diarrhea (AAD) in children.

**Study design** The following electronic databases up to December 2005, in any language, were searched for studies relevant to AAD and probiotics: MEDLINE, EMBASE, and The Cochrane Library. Only randomized controlled trials (RCT) were considered for study inclusion.

**Results** Six placebo-controlled, RCTs (766 children) were included. Treatment with probiotics compared with placebo reduced the risk of AAD from 28.5% to 11.9% (relative risk, RR, 0.44, 95% CI 0.25 to 0.77, random effect model). Preplanned subgroup analysis showed that reduction of the risk of AAD was associated with the use of Lactobacillus GG (2 RCTs, 307 participants, RR 0.3, 95% CI 0.15 to 0.6), S. boulardii (1 RCT, 246 participants, RR 0.2, 95% CI 0.07-0.6), or B. lactis & Str. thermophilus (1 RCT, 157 participants, RR 0.5, 95% CI 0.3 to 0.95).

**Conclusions** Probiotics reduce the risk of AAD in children. For every 7 patients that would develop diarrhea while being treated with antibiotics, one fewer will develop AAD if also receiving probiotics. (J Pediatr 2006;149:367-72)

[Probiotics for the Prevention of Antibiotic-Associated Diarrhea in Children.](https://www.ncbi.nlm.nih.gov/pubmed/26756877)

Szajewska H, Canani RB, Guarino A, Hojsak I, Indrio F, Kolacek S, Orel R, Shamir R, Vandenplas Y, van Goudoever JB, Weizman Z; ESPGHAN Working Group for ProbioticsPrebiotics.

J Pediatr Gastroenterol Nutr. 2016 Mar;62(3):495-506. doi: 10.1097/MPG.0000000000001081. Review.

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.

Summary of the Evidence:

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| --- | --- | --- | --- | --- | --- |
| **Author (Date)** | **Level of Evidence** | **Sample/Setting****(# of subjects/ studies, cohort definition etc. )** | **Outcome(s) studied** | **Key Findings** | **Limitations and Biases** |
| Goldenberg JZ, Lytvyn L, Steurich J, Parkin P, Mahant S, Johnston BC | Meta-analysis of randomized controlled trials | 23 studies (3938participants) met the inclusion criteria | incidence of diarrhea secondary to antibiotic comparing probiotics to placebo, active alternative prophylaxis (i.e. - formula and diosmectite), or no treatment | any probiotic use significantly reduces the occurrence of AAD with a relative risk of 0.46 and a 95% confidence interval of 0.35–0.61 when compared with an alternative activetreatment, placebo, or no treatment in the pediatric populationreview's findings suggest that efficacy may be more closely tied toprobiotic dosage, as opposed to thespecific probiotic species and number of strains. However, more safety data are needed to determine both safe dosing and safe types of microbes for probiotics | 1. moderate quality of evidence because there was substantial unexplainedvariability between individualstudies in the analysis (authors list this as an improvement compared to previous study2. high risk of bias in some studies -- risk of bias determined to be high or unclear in 13 studies and low in 10 studies3. Variable definitions of diarrhea with respect to the frequency,duration, and consistency of bowelmovements4. sparse studies on side effects to treatment with probioticsneed for definitions of diarrhea, relatedsymptoms, and negative outcomes to be standardized |
| Szajewska H, Canini RB, Guarino A, Hojsak I, Indrio F, Kolacek S, Orel R, Shamir R, Vandenplas Y, van Goudoever JB, Weizman Z | Systematic Review of Previously Completed Systematic Reviews and of Randomized Controlled Trials | N = 21 RCTs# of subjects = 3255 children# of References and Total # of Subjects for Recommendation on:* *Lactobacillus rhamnosus* GG: 5 References; N = 445 subjects
* *Saccharomyces boulardii*: 6 References; N = 1,653 subjects

Note: All remaining Probiotics (and combinations) studied had one reference, thus recommendations were not made for them | Primary Outcome Measures: Diarrhea/AAD and *C difficile*-associated diarrhea (as defined by the investigators) | **Pooled Results**:Probiotics reduced risk of AAD by 52% versus placebo or no intervention (9.1% versus 21.2%; RR 0.48, 95% CI 0.37-0.61). For this measure, 21 RCTs, N = 3255 were evaluated.Probiotics reduced risk of *C difficile*-associated diarrhea versus placebo (RR 0.34, 95% CI 0.15-0.76). For this measure, 4 RCTs, N = 938 were evaluated.*Lactobacillus rhamnosus GG (LGG)*:LGG reduced the risk of AAD from 23% to 9.6% (RR 0.48, 95% CI 0.26-0.89, NNT 8, 95% CI 6-40). For this measure, 5 RCTs, N = 445 were evaluated. Future studies should assess for optimal dose as this is unknown.**Recommendation**: The WG (Working Group on Probiotics of the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition) recommends using LGG for prophylactically for the prevention of AAD in children (Quality of Evidence: Moderate, Strength of Recommendation: Strong)*Saccharomyces boulardii*:*S. boulardii* reduced the risk of diarrhea from 20.9% to 8.8% (RR 0.43, 95% CI 0.30-0.60, NNT 9, 95% CI 7-12). For this measure, 6 RCTs, N = 1653 were evaluated. Future studies should assess for optimal dose as this is unknown.*S. boulardii* reduced the risk of *C difficile*- associated diarrhea (RR 0.25, 95% CI 0.08-0.73). For this measure, 2 RCTs, N = 579 were evaluated.**Recommendation**: WG recommends using *S. boulardii* prophylactically for the prevention of AAD in children.WG recommends using *S. boulardii* prophylactically for the prevention of *C difficile*-associated diarrhea in children.Remaining Probiotics: Insufficient evidence to make recommendations (see Abstract - **at least 2** RCTs to make a recommendation)**WG Acknowledgements**:* Using antibiotics selectively (judiciously) is the best way to prevent AAD
* Though safety was not evaluated here, WG advises that caution should be considered regarding the use of Probiotics in certain patients (e.g. immunosuppression, prematurity, critical illness, presence of structural heart disease, presence of a central venous catheter, and the potential for translocation of probiotics across the bowel wall)
 | Szajweska, H:* Received research support (in the form of study products only i.e. Probiotics) from Biogaia and Dicofarm
* Has participated as a speaker on probiotics/microbiota-related subjects for many companies including the two from which she obtained the “research support” described above

Guarino, A:* Received support from Biocodex, Dicofarm, and Mead Johnson Nutrition

Other Authors:* Though disclosures are clearly made, many authors have been associated (i.e. clinical investigator, speaker, advisory board member, consultant, etc.) with companies such as Arla, Biogaia, Biocodex, etc. These companies are actively involved in microbiota-research and the creation of products like Probiotics

Pooled Results (Probiotics Overall):* Inclusion of one **unpublished** study
* Methodological quality summary revealed variability among the 21 RCTs including risks of bias (e.g. selection, performance, detection, etc.)

LGG Studies:* Of the 5 RCTs evaluated, Intention-to-treat analysis was performed in **only one**

*S. boulardii* Studies:* Of the 6 RCTs evaluated, Intention-to-treat analysis was performed in **only two**
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| Alam S, Mushtaq M | Systematic Review | Search of **PubMed, Medline, and Cochrane Library** for literature available **in last 25 years**# of subjects=1438Used the following search terms:* Antibiotic Associated Diarrhea (Diarrhoea)
* *Clostridium difficile*
* Psuedomembranous Colitis
* Probiotics

The following limitations were placed on the search:* Age: 0-12y
 | Antibiotic Associated Diarrhea (AAD), defined as **unexplained diarrhea occurring between 2h and 2mo. after starting antibiotics, where diarrhea is defined as more than 2 unformed stools for 2 or more days*** Prevalence of AAD
* Onset of AAD (How many days after starting antibiotic?)
* Antibiotics associated with the development of AAD
* *Clostridium difficile* associated AAD
* Incidence of AAD with administration of probiotics
 | **Prevalence of AAD**Thailand Study:* 6.2% of 225 children developed AAD
* Higher incidence (though **STATISTICALLY INSIGNIFICANT**) of AAD in children prescribed amoxicillin/clavulanate (16.7%) compared to amoxicillin (6.9%) and erythromycin (11.1%)
* **NO ASSOCIATION** between **younger age** or **high dosage** of antibiotics used and development of AAD

USA Study:* 11% (or 71 children) of 650 children on **various antibiotics** developed AAD
* >⅔ of those who developed AAD saw its onset **during therapy**
* 15% of those who developed AAD saw its onset the week **following stopping antibiotic**
* 17% experienced AAD **during antibiotic treatment that continued after discontinuing antibiotic therapy**
* AAD begins **5.3**±**3.5** **days** after starting antibiotic
* Mean duration of AAD = **4**±**3 days**
* Highest Incidence of AAD: **2mo. to 2 years** age group (18%)
* **Statistically significant** difference between onset of AAD associated with **amoxicillin/clavulanate** compared with **all other antibiotics combined** (P=0.003): amoxicillin/clavulanate (23%), Pen G and V (3%), Pen A and M (11%), Cephalosporins (9%), Macrolides (8%), trimethoprim-sulphamethoxazole (6%), and Erythromycin (16%)
* **No difference** between incidence of AAD between **entero-hepatic** administration and **oral** antibiotics
* Relative Risk for onset of AAD in child receiving Amoxicillin/Clavulanate = 2.43 and 3.5 when **child was <2y**

Possible Causes of AAD:* Osmotic Diarrhea (secondary to disruption of normal enteric flora, functional disturbances of intestinal carbohydrates and bile acids metabolism)
* Drugs may affect intestinal mucosa and motility (e.g. erythromycin - accelerates rate of gastric emptying and amoxicillin-clavunate - stimulates small bowel motility

***Clostridium difficile* associated AAD*** CDI responsible for **10-20% of cases of AAD**

Incidence of community acquired CDI* **increasing** in pediatric population
* Study from Children’s Medical Center in USA (2001-2006): 513 patients with CDI. Incidence of CDI increased in outpatient setting (e.g. ED) from 1.18 cases versus 2.47 cases per 1,000 visits, P = 0.02. On the other hand, incidence of CDI decreased in inpatients (1.024 cases versus 0.680 cases per 1,000 patient-days, P = 0.004).

**Treatment*** **Most AAD would respond to ONLY discontinuation/change of antibiotic**

**Prevention*** A Cochrane Review suggests that Probiotics are effective in preventing AAD in children (RR 0.49; 95% CI 0.32 to 0.74)
* Though, intention to treat analysis showed non-significant overall results (RR 0.90; 95% CI 0.50 to 1.63)
* NNT to prevent one case of AAD = 10 (NNT 10; 95% CI 7 to 18)
* A meta-analysis (the one listed below Szajewska H, Ruszcynski M, and Radzikowski A) showed that treatment with probiotics compared with placebo effectively reduced risk of AAD from 28.5% to 11.9% (RR, 0.44, 95% CI 0.25 to 0.77). NNT 7.
* Another meta-analysis reported reduction of AAD in children with the use of probiotics over placebo (RR 0.43, 95% CI 0.25-0.75), though when intention-to-treat analysis was performed, the results were insignificant (RR 1.01, 95% CI 0.64-1.61)
* Another study (a subgroup analysis specific to *Lactobacillus* GG, *L. sporogens* or *Saccharomyces boulardii*) reported RR 0.36, 95% CI 0.25-0.53, favoring the use of probiotics in preventing AAD.

**Areas of Future Research*** Must include cost-effective analysis of Probiotic use
* Must concentrate on specific probiotics (to avoid ineffective probiotics from diluting results of specific probiotics. I.e. to prevent what would be otherwise significant results from becoming insignificant.
 | * A limitation of this systematic review is the **scarcity of studies on AAD prevalence**
* Additionally, **varying definitions of AAD** (more stringent versus a standard definition of AAD) influence results
* Studies evaluating Probiotics **as a whole** may be diluting the effects of **truly effective** organisms
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| Szajewska H, Ruszczyński M, Radzikowski A. (2006) | Meta-analysis of RCTs | N=16 RCTs# of Subjects=766Clinical Setting: Both in-patient and out-patient | **Primary Measures:** Incidence of diarrhea or AAD and incidence of *c. difficile diarrhea***Secondary Measures:** mean duration of diarrhea, the need for discontinuation of the antibiotic treatment, hospitalization to manage and the diarrhea (in outpatients) or intravenous rehydration in any of the study groups and adverse events.     | **Overall Results:** **Incidence of diarrhea/AAD and of *c. difficile* associated diarrhea**Probiotics were effective in preventing incidence AAD in children with antibiotics for any reason but especially for respiratory tract infections. In patients treated daily with antibiotics, 1 less child out of 7 would develop diarrhea (NNT 7, 95% CI 5-10). **Risk Reduction: AAD and *c. difficile*** The reduction of the risk of AAD was associated with the use of *Lactobacillus* GG (2 RCT, 307 participants, RR 0.3, 95% CI 0.15 to 0.6, NNT 6, 95% CI: 4–13), *Saccharomyces boulardii* (1 RCT, 246 partic- ipants, RR 0.2, 95% CI 0.07-0.6, NNT 8, 95% CI 5-15), or *B. lactis & Streptococcus thermophilus* (1 RCT, 157 participants, RR 0.5, 95% CI 0.3 to 0.95, NNT 7, 95% CI 4-62). In contrast, the use of either *L. acidophilus/Bifidobacterium in-fantis* (1 RCT, 18 participants, RR 0.5, 95% CI 0.2 to 1.2) or *L. acidophilus/L. bulgaricus* (1 RCT, 38 participants, RR 0.96, 95% CI 0.6 to 1.5) was not associated with a significant reduction of the risk of AAD. 2 RCTs suggested a relationship between probiotic use and lower rick of *c.difficile* diarrhea in the probiotic vs control group ((RR 0.38, 95% CI 0.12 to1.18, fixed effect model).  discontinuation of the antibiotic treatment, hospitalization to manage and the diarrhea (in outpatients) or intravenous rehydration in any of the study groups and adverse events risks were not shown to be associated with probiotic use. **mean duration of diarrhea**  Mean duration results were inconclusive.**Future Recommendations:** 1. Which populations with high risk of AAD benefit from probiotics. 2. Determine efficacy of various probiotic strains. 3. Probiotic strain and efficacy to best prevent AAD caused by *C. difficle* or antibiotics which can cause diarrhea. 4. Effective doses and schedule 5. Weigh additional risks/benefits of probiotics preventing ADD in pediatric populations | Publishing bias: unpublished articles/trials were not included.Reporting bias: only one study measured the need for discontinuation of the antibiotic treatment, hospitalization to manage and the diarrhea (in outpatients) or intravenous rehydration in any of the study groups and adverse events. Though many RCTs were blinded, most did not state if it was the researchers, participants, or both whom were blinded.Limited Population:Sample sizes were limited to children and to relatively small number of participants in limited geography. Demographics of participants were not listed.No intention-to-treatanalysisPotentially outdated research (2006). Validity Parameters for diarrhea differed between RCTs, which could skew validity of data.       |

Conclusion(s):

Based on our literature review, the use of probiotics with antibiotics helped prevent Antibiotic-Associated Diarrhea (AAD) in the pediatric population. Available data focused on two specific, extensively studied, strains (*Lactobacillus rhamnosus* and *S. boulardii*). These specific strains were effective in reduction of Antibiotic-Associated Diarrhea and thus far, these are the only two Probiotics for which clinical recommendations have been made. Additionally, further research should focus both on dosage of probiotics, as well as use and safety in specific populations including immunocompromised, critical illness, disability, etc. More safety data on other strains need to be collected before being able to make recommendations on those.

Clinical Bottom Line:

Based on the research, clinicians should recommend *Lactobacillus rhamnosus* and *S. boulardii* in the prevention of AAD in infants and children. If the patient is at risk of developing *C difficile* associated diarrhea, *S. boulardii* is the preferred strain. However, specific information regarding dosage was not confirmed in the articles.