Mini-CAT

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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: Will taking probiotics with antibiotic administration lessen the chance of diarrhea developing?

P → Children taking antibiotics

I → Probiotics

C → No probiotics

O → Decrease diarrhea development

P	**I**	**C**	**O**
Pediatrics on antibiotics	Probiotics	No probiotics	No diarrhea
Children taking antibiotics	Lactobacillus	No probiotic*	No diarrhoea
Child taking antibiotic*	Probiotic*		Diarrhea
	Yogurt		

Search Strategy: Outline the terms used, databases or other tools used, how many articles returned, and how you selected the final articles to base your CAT on

Terms Used: Probiotics, Antibiotics Associated Diarrhea, Children

Databases Searched:

- Cochrane → Search criteria gave 46 results which were not specifically applicable to our clinical question.
- PubMed → Search criteria gave 123 results, which were narrowed down to 112 after filters. We skimmed through the first 25 - 30 “Best Match” abstracts to find the ones we liked.
- Up to Date → 12 results showed up, but none were relevant to search questions.

Articles Used: Based on most recent research, sample size, type of study, we chose 5 PubMed articles

We searched: “Child* AND Antibiotic* AND Diarrhea AND Probiotic*” and obtained 293 results. After applying filters: “publication within 10 years,” “children ages” results were narrowed down to 94 results.

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

(1) Probiotics for pediatric antibiotic-associated diarrhea: a meta-analysis of randomized placebo-controlled trials Author: Bradley C Johnston, Alison L Supina, Sunita Vohra	**Link**	https://pubmed.ncbi.nlm.nih.gov/16908901/
	ABSTRACT	**Background:** Antibiotic treatment is known to disturb gastrointestinal microflora, which results in a range of clinical symptoms — most notably, diarrhea. This is especially important in children, for whom antibiotics are prescribed frequently. Although meta-analyses have been conducted to evaluate the ability of probiotics to prevent antibiotic-induced diarrhea in the general population, little is known about which probiotic strains and doses might be of most benefit to children. Our objective in this study was to assess the efficacy of probiotics (of any specified strain or dose) for the prevention of antibiotic-associated diarrhea in children and to assess adverse events associated with the use of probiotics when coadministered with antibiotics to children. **Methods:** A comprehensive search was performed of the major electronic databases (e.g., CENTRAL, MEDLINE, EMBASE, CINAHL, AMED) from their inception to January 2005. We also contacted experts and searched registries and meeting abstracts for additional relevant articles. Randomized controlled trials that compared probiotic treatment with placebo or no treatment, involving pediatric subjects less than 19 years of age were included. Two reviewers independently applied eligibility criteria and assessed the studies for methodological quality. Data were independently extracted by 2 reviewers and analyzed via the standard Cochrane methodology. **Results:** Six studies were included (total n = 707 patients). The combined results, analyzed with a per-protocol method that reported on the incidence of diarrhea during antibiotic treatment, showed significant benefit for the use of probiotics over placebo (relative risk [RR] 0.43, 95% confidence interval [CI] 0.25–0.75, I2 = 70.1%). In contrast, results from intention-to-treat analysis were nonsignificant overall (RR 1.01, 95% CI 0.64–1.61). Subgroup analysis on 4 studies that provided at least 5 billion single-strain colony-forming units (CFUs) daily (range 5.5–40 × 109 Lactobacillus GG, L. sporogens or Saccharomyces boulardii) showed strong evidence with narrow CIs for the preventative effects of probiotics for antibiotic-associated diarrhea (RR 0.36, 95% CI 0.25–0.53, I2 = 3.5%). No serious adverse events were reported. **Interpretation:** The potential protective effects of probiotics to prevent antibiotic-associated diarrhea in children do not withstand intention-to-treat analysis. Before routine use is recommended, further studies (with limited losses of subjects to follow-up) are merited. Trials should involve those probiotic strains and doses with the most promising evidence (i.e., Lactobacillus GG, L. sporogens or S. boulardii at 5–40 × 109 CFUs daily).
(2) Lactobacillus reuteri DSM 17938 in the prevention of antibiotic-associated diarrhoea in children: a randomized clinical trial Author: M. Kolodziej and H. Szajewska	**Link**	https://pubmed.ncbi.nlm.nih.gov/30149135/
	ABSTRACTt	**Objectives:** To assess the effectiveness of Lactobacillus reuteri DSM 17938 for the prevention of diarrhoea and antibiotic-associated diarrhoea (AAD) in children. **Methods:** Hospitalized children who received antibiotics were assigned by a computer-generated list to receive L. reuteri (at 2 × 108 CFU) or placebo, twice daily, for the duration of antibiotic treatment. Follow up was for 1 week after antibiotic cessation. The primary outcome measures were diarrhoea and AAD. Both were defined according to one of three definitions (i) three or more loose or watery stools per day for ≥48 h; (ii) three or more loose or watery stools per day for ≥24 h; or (iii) two or more loose or watery stools per day for ≥24 h. For AAD, it had to be diarrhoea caused by Clostridium difficile or otherwise unexplained diarrhoea. **Results:** A total of 250 children were randomized and 247 were analysed (L. reuteri n = 123, placebo n = 124; median age 4 months). The occurrences of diarrhoea and AAD were similar in both groups, regardless of the definition used. Using the strictest definition (i.e. definition (i)), the occurrence of diarrhoea in the L. reuteri group was 25 (20%) compared with 16 (13%) in the placebo group (absolute risk reduction -0.07 (-0.17 to 0.02). The occurrence of AAD was 14 (11.4%) in the L. reuteri group compared with 8 (6.5%) in the placebo group (absolute risk reduction -0.05 (-0.13 to 0.02)). The groups were similar with respect to all secondary outcome measures, including adverse events. **Conclusions:** Lactobacillus reuteri was not effective in the prevention of diarrhoea or AAD in children.

(3) Can probiotic yogurt prevent diarrhoea in children on antibiotics? A double-blind, randomised, placebo-controlled study Author: Michael J Fox, Kiran D K Ahuja , Iain K Robertson , Madeleine J Ball, Rajaraman D Eri	**Link**	**https://pubmed.ncbi.nlm.nih.gov/25588782/**
	ABSTRACT	**Objective**: To estimate the efficacy of a probiotic yogurt compared to a pasteurised yogurt for the prevention of antibiotic-associated diarrhoea in children. **Design and setting:** This was a multisite, randomised, double-blind, placebo-controlled clinical trial conducted between September 2009 and 2012. The study was conducted through general practices and pharmacies in Launceston, Tasmania, Australia. **Participants and interventions:** Children (aged 1-12 years) prescribed antibiotics, were randomised to receive 200 g/day of either yogurt (probiotic) containing Lactobacillus rhamnosus GG (LGG), Bifidobacterium lactis (Bb-12) and Lactobacillus acidophilus (La-5) or a pasteurised yogurt (placebo) for the same duration as their antibiotic treatment. **Outcomes:** Stool frequency and consistency were recorded for the duration of treatment plus 1 week. Primary outcome was stool frequency and consistency, classified at different levels of diarrhoea severity. Due to the small number of cases of diarrhoea, comparisons between groups were made using Fisher's exact analysis. **Results:** 72 children commenced and 70 children (36 placebo and 34 probiotic) completed the trial. There were no incidents of severe diarrhoea (stool consistency ≥6, ≥3 stools/day for ≥2 consecutive days) in the probiotic group and six in the placebo group (Fisher's exact p=0.025). There was also only one episode of minor diarrhoea (stool consistency ≥5, ≥2 stools/day for ≥2 days in the probiotic group compared to 21 in the placebo group (Fisher's exact p<0.001). The probiotic group reported fewer adverse events (1 had abdominal pain, 1 vomited and 1 had headache) than the placebo group (6 had abdominal pain, 4 had loss of appetite and 1 had nausea). **Conclusions:** A yogurt combination of LGG, La-5 and Bb-12 is an effective method for reducing the incidence of antibiotic-associated diarrhoea in children.
(4) A retrospective study of probiotics for the treatment of children with antibiotic-associated diarrhea Author: Xue Rui, Shu-Xia Ma	**Link**	**https://pubmed.ncbi.nlm.nih.gov/32502043/**
	ABSTRACT	This retrospective study aimed to explore the benefits and safety of probiotics (live combined Bacillus subtilis and Enterococcus faecium granules with multivitamines) for the treatment of children with antibiotic-associated diarrhea (AAD).A total of 72 children with AAD were analyzed in this study. Of these, 36 children received routine treatment plus probiotics, and were assigned to a treatment group. The other 36 children underwent routine treatment alone, and were assigned to a control group. Patients in both groups were treated for a total of 7 days. The efficacy and safety were evaluated by duration of diarrhea (days), number of dressings needed daily, abdominal pain intensity, stool consistency (as assessed by Bristol Stool Scale (BSS)), and any adverse events. After treatment, probiotics showed encouraging benefits in decreasing duration of diarrhea (days) ($P < .01$), number of dressings needed every day ($P < .01$), abdominal pain intensity ($P < .01$), and stool consistency (BSS (3-5), $P < .01$; BSS (6-7), $P < .01$). In addition, no adverse events were documented in this study.The findings of this study demonstrated that probiotics may provide promising benefit for children with AAD. Further studies are still needed to warrant theses findings.

(5) Probiotics for the prevention of pediatric antibiotic-associated diarrhea Author: Joshua Z Goldenberg, Lyubov Lytvyn, Justin Steurich, Patricia Parkin, Sanjay Mahant, Bradley C Johnston	**Link**	https://pubmed.ncbi.nlm.nih.gov/26695080/
	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., orStreptococcus 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.

Summary of the Evidence:

Author (Date)	Level of Evidence	Outcome(s) studied	Key Findings	Limitations and Biases
(1) Probiotics for pediatric antibiotic-associated diarrhea: a meta-analysis of randomized placebo-controlled trials Author: Bradley C Johnston, Alison L Supina, Sunita Vohra	Meta-analysis	-> 1 or more abnormally loose bowel movements per day throughout the study period -> at least 3 watery or loose stools per day for at least 2 consecutive days.	*Lactobacillus GG, L. sporogens* or *Saccharomyces boulardii*) showed strong evidence for the preventative effects of probiotics: Children with 5.5–40 × 10^9 bacteria or yeast cells per day showed evidence for the preventative effects of probiotics on diarrhea	Of the 6 studies, only 1 lists adverse events associated with probiotic use Difficulty standardizing 'diarrhea' in infants vs children vs adolescents (age range of studies ranged from 2 weeks - 15 years old)
(2) Lactobacillus reuteri DSM 17938 in the prevention of antibiotic-associated diarrhoea in children: a randomized clinical trial Author: M. Kolodziej and H. Szajewska	RCT	→ 3 or more loose/ watery stools per day (48 hours) → 3 or more loose or watery stools per day (24 hours) → 2 or more loose or watery stools per day (24 hours)	Patients taking L. Reutri were found to have more episodes of diarrhea vs placebo group. The results were not clinically significant.	Only one probiotic was tested. Patients below the age of 18 were enrolled, the majority of the patients were below 48 months. Only one dose was used. Patients were only followed up for 1 week.
(3) Can probiotic yogurt prevent diarrhoea in children on antibiotics? A double-blind, randomised, placebo-controlled study Author: Michael J Fox, Kiran D K Ahuja , Iain K Robertson , Madeleine J Ball, Rajaraman D Eri	RCT	→ stool consistency ≥6, ≥3 stools/day for ≥2 consecutive days → Stool consistency ≥5, ≥3 stools/day for ≥2 days → Stool Consistency ≥6, ≥2 stools/day for ≥2 days → Stool Consistency ≥6, ≥3 stools/day for ≥2 days → Any of the above	→ No incidents of severe diarrhoea in the probiotic group and six in the placebo group → One episode of minor diarrhoea in the probiotic group compared to 21 in the placebo group → Probiotic group reported fewer adverse events	→ Effects on stool were only recorded for the duration of antibiotic treatment plus 1 week; there may have been further incidents outside this time frame that have not been reported. → The time it took to recruit participants was almost 3 years which may have caused selection bias
(4) A retrospective study of probiotics for the treatment of children with antibiotic-associated diarrhea Author: Xue Rui, Shu-Xia Ma	Retro-spective - Cohort study	Primary outcomes studied: duration of diarrhea (days), and number of dressings needed every day. Secondary outcome: abdominal pain intensity (scale of 1 to 10), stool consistency (using Bristol	Patients in the treatment group who received probiotics achieved more benefit in duration of diarrhea, number of dressings needed every day, abdominal pain intensity, and stool consistency compared to control patients.	→ Study did not apply randomization procedure to assign patients to the treatment and control groups since it was retrospective. → All patient were collected from 1 center of First Affiliated Hospital of

		stool scale), and any adverse events		Jiamusi University, which may affect generalization to other hospitals → Study only evaluated the efficacy and safety of probiotics for the treatment of children with AAD within 7-day period, with no follow up. → Sample size was too small, may impact findings → Retrospective study with intrinsic limitations
(5) Probiotics for the prevention of pediatric antibiotic-associated diarrhea Author: Joshua Z Goldenberg, Lyubov Lytvyn, Justin Steurich, Patricia Parkin, Sanjay Mahant, Bradley C Johnston	Meta-Analysis	→ Dichotomous Date: incidence of diarrhea, adverse events 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. → Continuous Date: mean duration of diarrhea, mean daily stool frequency	→ Moderate quality evidence suggests a protective effect of probiotics in preventing antibiotic associated diarrhea. → Among the various probiotics evaluated, *Lactobacillus rhamnosus* or *Saccharomyces boulardi* were associated with less adverse events. → It is still premature however, to draw conclusions about efficacy and safety of other probiotic agents of pediatric antibiotic associated diarrhea	→ More refined trials are necessary since the study did not assess single or multiple strain specific probiotics among oral vs intravenous antibiotics and outpatients vs inpatient. → Trials included immune-competent children only, the safety of probiotics among immunocompromised and severely debilitated children remains unknown.

Conclusion(s):

→ There were variable results among the different studies finding that there was either benefit or mixed results of benefit versus no benefit. However, none of the studies found negative harms of giving probiotics.

Clinical Bottom Line: Please include an assessment of the worth to practice

→ Giving probiotics to children while taking a course of antibiotics may decrease the incidence of diarrhea and even if there is no benefit there is little risk of harm. Overall, most probiotic strains are safe to use and demonstrate some improvement in mitigating adverse effects associated with antibiotic use. So, although some results were inconclusive and premature, studies agree that giving probiotics to children while taking a course of antibiotics may decrease the incidence of diarrhea and even if there is no benefit there is little risk of harm.