Mini-CAT EBM Final Project

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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

Do probiotics decrease the likelihood of antibiotic associated diarrhea in pediatric patients?

PICO Search Terms

Population	Intervention	Comparison	Outcome
Pediatric patients taking antibiotics	Probiotics	No probiotics	Lower incidence of antibiotic associated diarrhea
Pediatric patients		Placebo	Decreased antibiotic associated diarrhea

Summary of Search Strategy

Terms searched:

- Antibiotic associated diarrhea
- Probiotic usage in prevention antibiotic associated diarrhea
- Pediatric antibiotic associated diarrhea
- Probiotics to prevent pediatric antibiotic associated diarrhea

Databases used:

- PubMed
- Google Scholar
- Cochrane Library

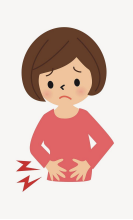
#articles retrieved:

- 223 (PubMed)
- 19,300 (Google Scholar)
- 3 (Cochrane)

List of the 4-5 articles chosen to appraise

- **Probiotics for the prevention of pediatric antibiotic-associated diarrhea: A systematic review**
  - Qin Guo, Joshua Z Goldenberg, Claire Humphrey, Regina El Dib, Bradley C Johnston
- **Can probiotic yogurt prevent diarrhea in children on antibiotics? A double-blind, randomized, placebo-controlled study**
  - Michael J Fox, Kiran D K Ahuja, Iain K Robertson, Madeleine J Ball, Rajaraman D Eri
- **Probiotics for the Prevention of Antibiotic-Associated Diarrhea in Outpatients—A Systematic Review and Meta-Analysis**
  - Sara Blaabjerg, Daniel Maribo Artzi, and Rune Aabenhus
- **Probiotics for the Prevention and Treatment of Antibiotic-Associated Diarrhea**
  - Susanne Hempel, Sydne J Newberry, Alicia R Maher, Zhen Wang, Jeremy N V Miles, Roberta Shanman, Breanne Johnsen, Paul G Shekelle

Probiotics for the prevention of pediatric antibiotic associated diarrhea: A systematic review



Criteria:

- 0-18 years old
- Compared **33** studies

Looked at:

- Randomized, parallel and controlled trials with children
  - Receiving antibiotic treatment **alone**
  - receiving antibiotics **with** probiotics
  - receiving antibiotics **with** placebo
  - Notable **side effects** were also studied of probiotics
- Studies were obtained from MEDLINE, Embase, CENTRAL, CINAHL and Web of Science
- The **incidence of AAD** in the **probiotic group** versus the **control groups** were studied across the 33 studies

Results

- Analyses showed statistically significant results that probiotics are **effective for preventing AAD.** The incidence overall in the probiotic group was **8%** compared to **19%** in the control group.
- A subgroup analysis found that a **high dose >5 billion CFUs per day** is more effective than a low probiotic dose → incidence of AAD in probiotic group was **8%** compared to **23%** in the control group.
- None of the 24 trials (4415 participants) that reported on adverse events reported **any serious adverse events** attributable to probiotics

Thoughts:

- Aggregate data meta-analysis does not allow the SR to fully explore participants (e.g. sex) and intervention level variables (# of abx prescribed)
- Greater duration of study could be useful

Comparison: Control (placebo or non-active control)

Outcomes	Anticipated absolute effects * (95% CI)			Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Baseline risk	Corresponding risk					
	Risk in Control	Risk with Probiotics	Risk Difference				
Incidence of AAD Follow-up: 5 days to 12 weeks	**190 per 1000**[1]	**86 per 1000** (68 to 106)	**104 fewer AAD cases per 1000** (84 fewer to 122 fewer)	**RR 0.45** (0.36 to 0.56)	6352 (33 studies)	⊕⊕⊕⊖ **Moderate**[2.3.4]	
Incidence of AAD: Probiotic dose (≥5 billion CFUs of probiotics/day) Follow-up: 5 days to 12 weeks	**190 per 1000**[1]	**70 per 1000** (57 to 87)	**120 fewer AAD cases per 1000** (103 fewer to 133 fewer)	**RR 0.37** (0.30 to 0.46)	4038 (20 studies)	⊕⊕⊕⊖ **Moderate**[5.6]	Based on our a priori subgroup analyses, high-dose probiotics (≥5 billion CFUs/day) are most effective Low dose probiotics (<5 billion CFUs of probiotics per day) were not as effective as high dose probiotics (RR 0.68, 95% CI 0.46 to 1.01; low certainty evidence)
Adverse events Follow-up: 5 days to 4 weeks	**55 per 1000**[7]	**39 per 1000** (25 to 61)	**16 fewer adverse events per 1000** (6 more to 30 fewer)	**RD -0.00** (-0.01 to 0.01)	4415 (24 studies)	⊕⊕⊖⊖ **Low**[8.9.10.11]	
Duration of diarrhea (days) Follow-up: 10 days to 12 weeks		**MD 0.91 fewer** (1.38 fewer to 0.44 fewer)			1263 (8 studies)	⊕⊕⊖⊖ **Low**[12.13]	

Can probiotic yogurt prevent diarrhea in children on antibiotics?

Criteria:

70 children (aged 1-12) randomly assigned to the placebo or probiotic group (36 placebo and 34 probiotic).

Methods:

This was a multisite, **randomized, double-blind, placebo-controlled clinical trial**.

Procedures:

Children were prescribed antibiotics and given **200 g/day** of either probiotic yogurt containing LGG, La-5 and Bb-12 or a placebo. The primary outcome was **stool frequency and consistency**, classified at different levels of diarrhea **severity.**

Key Findings

Findings:

In **all classifications of diarrhea**, there were significantly **fewer incidences** in children given a probiotic rich yogurt in comparison to children on a placebo yogurt.

A yogurt combination of **LGG, La-5 and Bb-12** is an effective method for reducing the incidence of antibiotic-associated diarrhea in children.

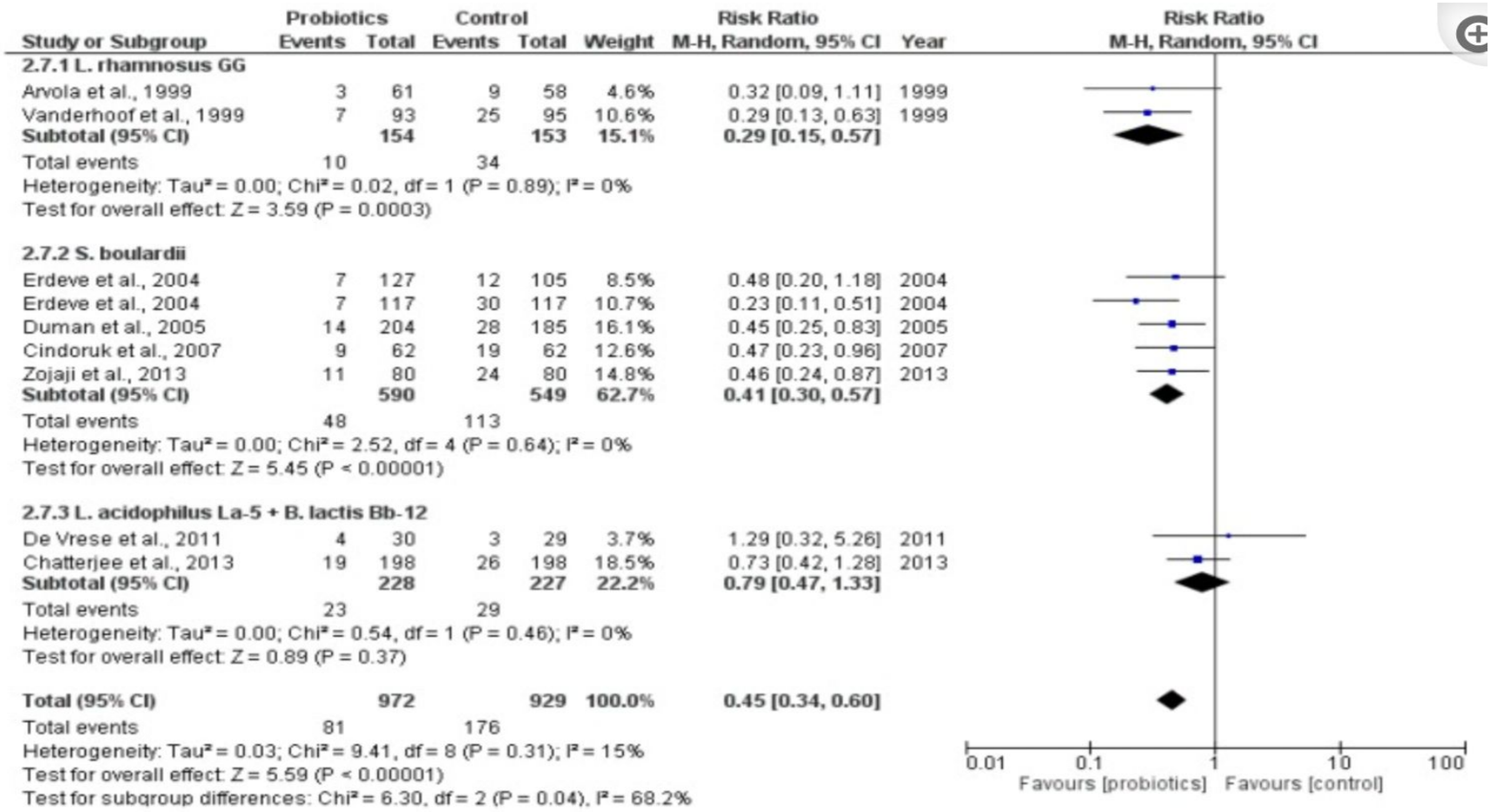
Limitations:

The study relied on **self reported data** by the parents or children – so children at school may have had less complete recording.

The effects on stool were only recorded for the **duration of the antibiotic treatment** + 1 week – so there may have been other incidences that were not recorded. This time frame was chosen because AAD usually begins in the **first 2 weeks** of beginning antibiotic treatment.

Probiotics for the Prevention of Antibiotic-Associated Diarrhea in Outpatients—A Systematic Review and Meta-Analysis

- This meta-analysis and systematic review used **PubMed** and included **17** Randomized control trials with **3631 participants.**
- Patient population consisted of all age and was restricted to **outpatient** taking oral antibiotics.
    - Seven of the trials targeted **children specifically.**
- All included studies were prospective, randomized, controlled trials with placebo, active, or no treatment control arms.


Probiotics
Control
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI Year
M-H, Random, 95% CI
2.7.1 L. rhamnosus GG
Arvola et al., 1999 3 61 9 58 4.6% 0.32 [0.09, 1.11] 1999
Vanderhoof et al., 1999 7 93 25 95 10.6% 0.29 [0.13, 0.63] 1999
Subtotal (95% CI) 154 153 15.1% 0.29 [0.15, 0.57]
Total events 10 34
Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.89); I² = 0%
Test for overall effect: Z = 3.59 (P = 0.0003)
2.7.2 S. boulardii
Erdeve et al., 2004 7 127 12 105 8.5% 0.48 [0.20, 1.18] 2004
Erdeve et al., 2004 7 117 30 117 10.7% 0.23 [0.11, 0.51] 2004
Duman et al., 2005 14 204 28 185 16.1% 0.45 [0.25, 0.83] 2005
Cindoruk et al., 2007 9 62 19 62 12.6% 0.47 [0.23, 0.96] 2007
Zojaji et al., 2013 11 80 24 80 14.8% 0.46 [0.24, 0.87] 2013
Subtotal (95% CI) 590 549 62.7% 0.41 [0.30, 0.57]
Total events 48 113
Heterogeneity: Tau² = 0.00; Chi² = 2.52, df = 4 (P = 0.64); I² = 0%
Test for overall effect: Z = 5.45 (P < 0.00001)
2.7.3 L. acidophilus La-5 + B. lactis Bb-12
De Vrese et al., 2011 4 30 3 29 3.7% 1.29 [0.32, 5.26] 2011
Chatterjee et al., 2013 19 198 26 198 18.5% 0.73 [0.42, 1.28] 2013
Subtotal (95% CI) 228 227 22.2% 0.79 [0.47, 1.33]
Total events 23 29
Heterogeneity: Tau² = 0.00; Chi² = 0.54, df = 1 (P = 0.46); I² = 0%
Test for overall effect: Z = 0.89 (P = 0.37)
Total (95% CI) 972 929 100.0% 0.45 [0.34, 0.60]
Total events 81 176
Heterogeneity: Tau² = 0.03; Chi² = 9.41, df = 8 (P = 0.31); I² = 15%
Test for overall effect: Z = 5.59 (P < 0.00001)
Test for subgroup differences: Chi² = 6.30, df = 2 (P = 0.04), I² = 68.2%
0.01
0.1
1
10
100
Favours [probiotics]
Favours [control]

Key findings:

Results: Use of probiotics produced a statistically significant reduction in the incidence of AAD.

- AAD was present in **8.0% of the probiotic groups compared to 17.7% in the control groups.**
- No significant risk of adverse events in the probiotic group.

Limitations:

- Overall quality of the included studies was **moderate**.
  - Only **18%** of the included studies had a **low risk of bias**, and these studies did not find a statistical significant reduction in the prevention of AAD.
- Half the studies did not provide placebo to the control group
- Definition of diarrhea varied among studies or unspecified

Probiotics for the Prevention and Treatment of Antibiotic-Associated Diarrhea

Criteria: Participants of **all ages** treated with antibiotics, **regardless of the indication** and the patients' underlying symptomatology.

Methods: **Meta-analysis** and **systematic review**; 63 RCTs, which included **11,811 participants**. Twelve electronic databases were searched (DARE, Cochrane Library of Systematic Reviews, CENTRAL, PubMed, EMBASE, CINAHL, AMED, MANTIS, TOXLINE, ToxFILE, NTIS, and AGRICOLA).

Outcomes studied:

- All reports of diarrhea were considered (adverse effects, dropouts).
- The primary outcome was the number of participants with diarrhea in each treatment group.

Key Findings

- Using probiotics as adjunct therapy reduces the risk of AAD. The result was consistent across a number of subgroup and sensitivity analyses.
- The **number of participants experiencing AAD was lower in the probiotics groups than in control groups**.

Limitations:

- Poor documentation of the **probiotic strains** (mostly *Lactobacillus*).
- Residual **unexplained heterogeneity** (difference in response to treatment among individuals/subgroups).
    - Evidence is insufficient to determine whether this association varies systematically by population, antibiotic characteristic, or probiotic preparation.

Clinical Bottom Line

After appraising each of the articles we found that:

- Probiotics are generally effective at **decreasing** the incidence of antibiotic associated diarrhea.
- Probiotics were generally not associated with **any major adverse effects** and demonstrated **protective effects** over other antibiotic associated side effects (abdominal pain, vomiting, headache).
- **LGG, La-5 and Bb-12** are three strains of probiotics that are effective in reducing the incidence of antibiotic-associated diarrhea in children.

However...

1. Further research needs to document which **specific strains** of probiotics help prevent antibiotic associated diarrhea.
2. Establish **one definition** of diarrhea among all studies.
3. Provide placebo probiotic to the control group.
4. Establish a post-antibiotic treatment time frame to study the incidence of diarrhea.

References:

Blaabjerg S, Artzi DM, Aabenhus R. Probiotics for the Prevention of Antibiotic-Associated Diarrhea in Outpatients-A Systematic Review and Meta-Analysis. Antibiotics (Basel). 2017;6(4):21. Published 2017 Oct 12. doi:10.3390/antibiotics6040021

Fox MJ, Ahuja KD, Robertson IK, Ball MJ, Eri RD. Can probiotic yogurt prevent diarrhea in children on antibiotics? A double-blind, randomized, placebo-controlled study. BMJ Open. 2015;5(1):e006474. Published 2015 Jan 14. doi:10.1136/bmjopen-2014-006474

Guo Q, Goldenberg JZ, Humphrey C, El Dib R, Johnston BC. Probiotics for the prevention of pediatric antibiotic-associated diarrhea. The Cochrane database of systematic reviews. April 30, 2019. Accessed November 19, 2023. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6490796/.

Hempel S. Probiotics for the Prevention and Treatment of Antibiotic-Associated Diarrhea: A Systematic Review and. JAMA. 2012;307(18):1959-1969. doi:10.1001/jama.2012.3507

Questions?