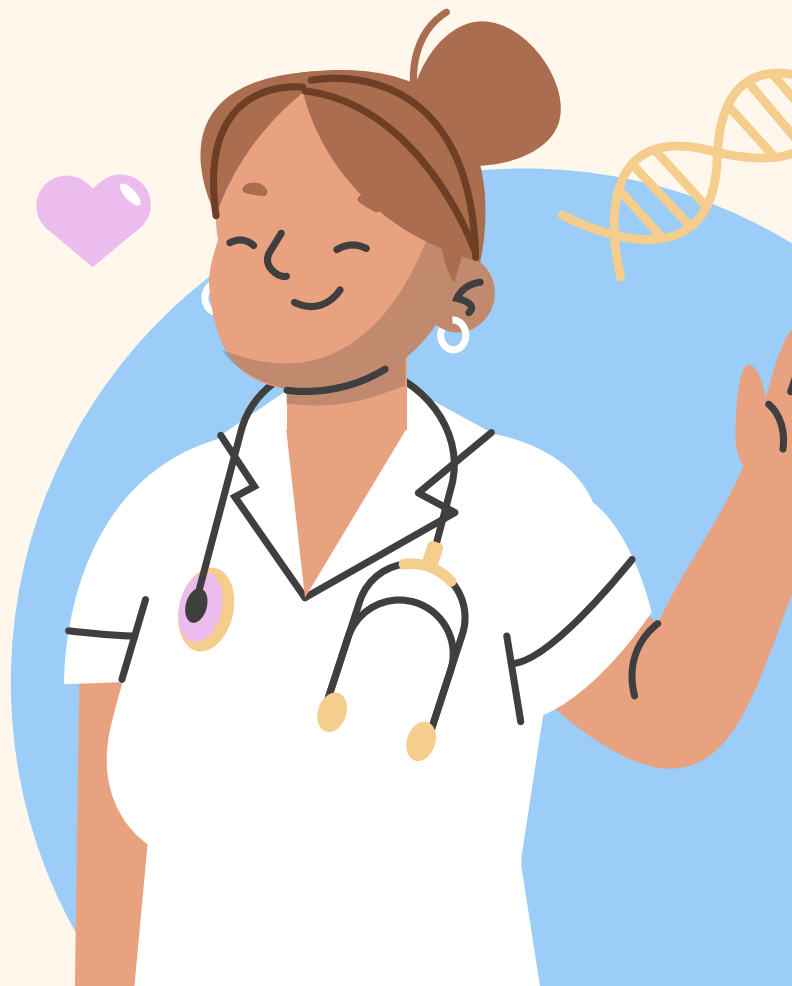


Mini-Cat Presentation

**Patrick Locoteta, Nayalise Montilla,
Michael Tan, Melissa Richard, Yamely
Hernandez Diaz**



Clinical Scenario

Moshe, a 4-year-old presenting with strep throat, has a history of antibiotic associated diarrhea. His mother asks if probiotics will help prevent diarrhea this time.






Clinical Question



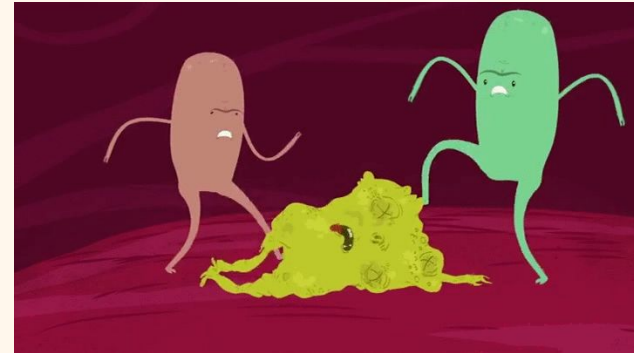
Does co-administration of probiotics reduce the incidence of antibiotic-associated diarrhea in children receiving antibiotic therapy?



If you take Probiotics
and antibiotics



do they cancel
each other out?



PICO Search Terms

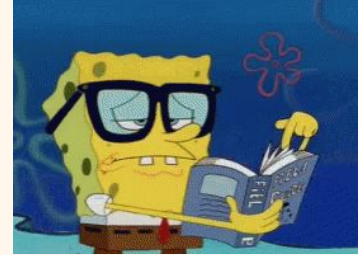


P	I	C	O
Pediatric Patients	Probiotics	No Probiotics	Antibiotic-Associated Diarrhea
Children on Antibiotics	Lactobacillus	Placebo	Incidence of Diarrhea
4 Years Old	Microbial supplement	Standard Therapy	GI Symptoms

Search Strategy Summary

Terms Used:

- Probiotics **AND** Antibiotic-Associated Diarrhea (AAD)
- Probiotics **AND** Children
- Lactobacillus **OR** Saccharomyces **AND** AAD



Databases Searched:

- **PubMed** - 23 relevant results
- **Cochrane library** - 1 relevant result
- **Trip Database** - 22 results



Articles used:

- The five articles were selected based on the strength of evidence, focusing on **recent systematic reviews** and large randomized controlled trials.
 - PubMed - 3
 - Cochrane - 1
 - Trip Database - 1

Appraised Articles



1. Probiotics for the Prevention and Treatment of Antibiotic-Associated Diarrhea: A Systematic Review and Meta-analysis (Hempel et al. (2012))
2. Probiotics for the Prevention of Clostridium difficile-Associated Diarrhea in Adults and Children (Goldenberg (2017))
3. Probiotics for the Prevention of Pediatric Antibiotic-Associated Diarrhea (Guo Q et al. (2019))
4. Perspectives from the Society for Pediatric Research: Probiotic use in Urinary tract infections, Atopic dermatitis, and Antibiotic-associated diarrhea: An Overview
5. Systematic review: Clinical Evidence of Probiotics in the Prevention of Antibiotic-Associated Diarrhea (Stengel, Andreas and Storr, Martin (2021))

Probiotics for the prevention of pediatric antibiotic-associated diarrhea

Aim: To examine the efficacy and safety of probiotics (any specified strains or dose) on prevention of antibiotic-associated diarrhea in children

Criteria: Children ages 0-18 y/o, male or female, being administered antibiotics for any indications

Methods: Systemic review and meta-analysis of 33 randomized controlled trials

- Probiotic agent vs. placebo/active/no treatment control
- MEDLINE, Embase, CENTRAL, CINAHL, Web of Sciences
 - Inception to May, 2018
 - No limits on language/publication
- What was measured?
 - AAD Incidence
 - # and type of adverse events
 - Duration of AAD
 - Microbiome characteristics



Probiotics for the prevention of pediatric antibiotic-associated diarrhea



Results: Probiotics prophylaxis demonstrated significant reduction of AAD in children.

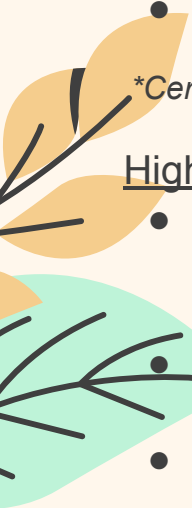
- Incidence of AAD
 - Probiotic - 8%
 - Control - 19%
- Relative risk - 0.45
 - Probiotic use reduces risk of AAD by 55% compared to control
- NNT - 9

**Certain strains of probiotics showed higher reduction rate - Lactobacillus rhamnosus GG or Saccharomyces boulardii*

High-dose probiotics

- Incidence of AAD
 - Probiotic - 8%
 - Control - 23%
- Relative risk - 0.37
 - Probiotic use reduces risk of AAD by 63% compared to control
- NNT - 6

** Low-moderate dose showed no significant reduction in AAD*



Probiotics for the prevention of pediatric antibiotic-associated diarrhea

Safety: Probiotic prophylaxis was generally safe in healthy children, and did **NOT** increase the risk of serious adverse events compared to control

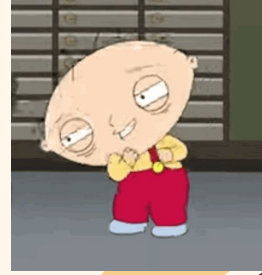
- 25/33 studies (N = 4,415) reported and monitored adverse events
 - 13 studies reported no adverse events
 - 12 studies reported mild side effects: gas, bloating, irritability
- Serious adverse events - rare
- 4% (probiotics) vs. (6%) control
 - Risk difference - ~ 0.00

Limitation:

- Attrition bias
 - High loss to follow up rates ($> 20\%$) in 6 out of 33 RCTs.
- Performance bias
 - 6 studies/trials were unblinded. Participants and researchers knew which interventions were given to them
- Poor reporting and monitoring of adverse effects



Probiotics for the prevention of pediatric antibiotic-associated diarrhea



Conclusion:

- Probiotics **reduce the risk of AAD** in children, especially at higher doses (≥ 5 billion CFU/day), and using strains like *Lactobacillus rhamnosus GG* or *Saccharomyces boulardii*
- Probiotics use is **safe** in children and has demonstrated **NO** increase in the risk of serious adverse events
- Adverse events were **uncommon** and comparable to control groups
- Probiotics can be a **beneficial adjunct** during antibiotic therapy for children



Probiotics for the Prevention and Treatment of Antibiotic-Associated Diarrhea: A Systematic Review and Meta-analysis


Aim: To determine the effectiveness of probiotics in preventing or treating antibiotic-associated diarrhea (AAD) in patients of any age group

Method: Systematic review and meta-analysis of 82 randomized controlled trials, with 63 trials (11,811 participants) included in the pooled analysis

Results: Probiotics reduced the risk of AAD by 42%

- Diarrhea occurred in 18% of control patients versus 11% of patients receiving probiotics
- Effect observed in both children and adults, and across multiple probiotic formulations





Probiotics for the Prevention and Treatment of Antibiotic-Associated Diarrhea: A Systematic Review and Meta-analysis

Safety: No serious probiotic-related adverse events were reported. However, most trials did not report or monitor safety outcomes.

Limitations:

- Significant variation in probiotic strains, doses, and treatment duration.
- Many studies did not fully report methods (randomization, allocation concealment, or strain identity)
- Limited data in older adults and high-risk populations

Conclusion: Probiotics are associated with a reduced risk of AAD. More research is needed to determine which probiotics provide the greatest efficacy and for which patients receiving which specific antibiotics.



Perspectives from the Society for Pediatric Research: Probiotic use in urinary tract infections, atopic dermatitis, and antibiotic-associated diarrhea: an overview

Aim:

- ★ To **identify peer-reviewed RCTs** researching probiotic use in children against AAD, UTI and atopic dermatitis
- ★ To use look at the **incidence and severity of AAD in probiotics vs no probiotics**
- ★ To draw pertinent conclusions and areas for future research

Methods:

- ★ Collected, reviewed, and summarized **13 studies** published between **1994 and 2020 using PubMed and Scopus**
- ★ Study sample sizes ranged from **70 to 600** children
 - Children as young as **3 months** to as old as **16 years**
- ★ Various probiotic strains included (saccharomyces, lactobacilli, streptococci, etc)
 - Excluded studies without clear strain breakdown (e.g. yogurt)

Perspectives from the Society for Pediatric Research: Probiotic use in urinary tract infections, atopic dermatitis, and antibiotic-associated diarrhea: an overview

Results:

- ★ Several RCTs showed **benefit of certain probiotic strains** (e.g. *Saccharomyces boulardii*, *Lactobacillus rhamnosus*)
 - One trial (Kotowska et al., 2005), found lower rates of AAD in probiotics vs. placebo (**3.4% vs. 17.3%**)
 - Another (Jindal et al., 2017) found lower rates of AAD in probiotics vs. antibiotics alone (**5.3% vs. 24%**)
 - Another (Fox et al., 2015) found a difference of **3% vs. 75%**
- ★ Others show **minimal-no difference** in rate of diarrhea between groups (**2% in both groups**)(e.g. Georgieva et al., 2015)
- ★ **5–40 billion CFUs/day** may be an effective dose
 - **NNT of 10 for *S. boulardii* and 9 for LGG** (Guo et al., 2019)

Limitations:

- ★ **Small sample sizes**
- ★ **Heterogeneous variables**
 - E.g. Probiotic strains, doses, durations of admin, and outcome definitions

Safety:

- ★ Generally considered safe
 - However, safety reporting limited



Perspectives from the Society for Pediatric Research: Probiotic use in urinary tract infections, atopic dermatitis, and antibiotic-associated diarrhea: an overview

Conclusion:

- ★ Probiotics may help prevent AAD in children
- ★ When deciding on probiotics, consider the
 - **Strain(s)**
 - **Dose**
 - **Duration**
 - **Financial aspect**
 - **Source**
 - **Patient compliance**

- ★ For Moshe, probiotics are a reasonable consideration
 - More suggestive than definitive



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

Aim: To evaluate whether probiotics given alongside antibiotics reduce the risk of Clostridium difficile-associated diarrhea (CDAD) in children & adults.

Methods: Systematic review & meta-analysis of 39 randomized controlled trials (pediatric studies), with a total of ~9,955 participants; up to March 2017

Results: Probiotics were associated with a **60% reduction** in CDAD.

- CDAD incidence: **1.5%** with probiotics vs **4.0%** in controls.
- In settings where the risk of CDAD was > 5%, risk reduction was greater compared to lower-risk settings.
- Probiotics were associated with a reduction in antibiotic-associated diarrhea (RR=0.58). **In children, the reduction was even greater.**(RR=0.38)

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



- **Safety:** Short-term use of probiotics appeared **safe** in immunocompetent patients; and no serious adverse events from probiotics were reported in the included trials.
- **Limitations:** Some trials had high/unclear risk of bias; effect in low baseline-risk populations less clear; heterogeneity, the study mainly focused on CDAD (which is more serious) rather than just general antibiotic-associated diarrhea (AAD)
- **Conclusion:** this study **supports** the idea that **probiotics** can significantly **reduce** the risk of **C. difficile-associated diarrhea and antibiotic-associated diarrhea** when given with antibiotics, especially in children and people who are at higher risk.

Systematic Review: Clinical Evidence of Probiotics in the Prevention of Antibiotic Associated Diarrhea

Level of Evidence: Systematic Review of Clinical Trials

Sample and Setting:

- 37 Clinical Trial
 - 33 of which are double-blind RCTs
- **N = 7,216**
 - **Children= 2,546** Adults= 4,670
 - The studies on children were all RCTs
- Outpt and Inpt settings were studied

Outcome Studied: “Does taking a probiotic during Abx tx reduce the rate of AAD and **which probiotics have the most robust effect?**”

- Secondary outcomes of interest
 - Outpt vs. Inpt effect

Systematic Review: Clinical Evidence of Probiotics in the Prevention of Antibiotic Associated Diarrhea

Key Findings: Only *S. boulardii* CNCM I-745 and *L. rhamnosus* GG should have an evidence-based recommendation for AAD prevention

- *S. boulardii* and LGG had similar benefits **regardless of which abx** caused the AAD
 - *S. boulardii*: **RR.43 -> 57% risk reduction**
 - LGG: **RR.48 -> 52% risk reduction**
- *S. boulardii* and LGG were equally effective at treating **in and outpt children w/ AAD**, but more a robust benefit was seen **outpt** (likely due to the comorbidities of hospitalized pts)
- **Broad-spectrum PCNs and Clinda** were more likely to cause AAD therefore have increased benefit from probiotic administration

Systematic Review: Clinical Evidence of Probiotics in the Prevention of Antibiotic Associated Diarrhea

Limitations: Some limitations apply to the Stengle review as a whole, but do not apply to our studies of interest. **All studies focusing on LGG and S. boulardii were double-blind RCTs.**

- Both adults and pediatrics were studied, but the authors **clearly differentiate** which population is being studied at any given time.
- There is **variability in the selected abx and doses** being studied
- There are studies other than RCTs included (**mainly on hospitalized adults**)

Biases:

- **Publication:** only studies published in **MEDLINE** and **EMBASE** were reviewed
- **Confounding:** Not controlling for the abx being administered
- **Selection Bias:** Some studies had **small sample sizes** (N=23 for L. reuteri study in **hospitalized adults**) but this was not our population of interest.

Summary of Mini-Cat Grid



**S. Boulardii and LGG
are preferred in
children**

Stengle, 2021

**Serious AE are very
rare, indicating high
safety**

Gou, 2019

**Probiotics reduce
the risk of AAD by
40-60%**

Hempel, 2012

**Probiotic use
reduced C.dif
diarrhea by 60%**

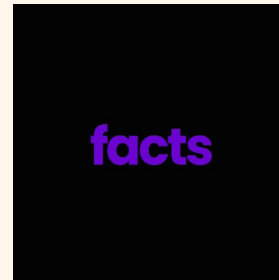
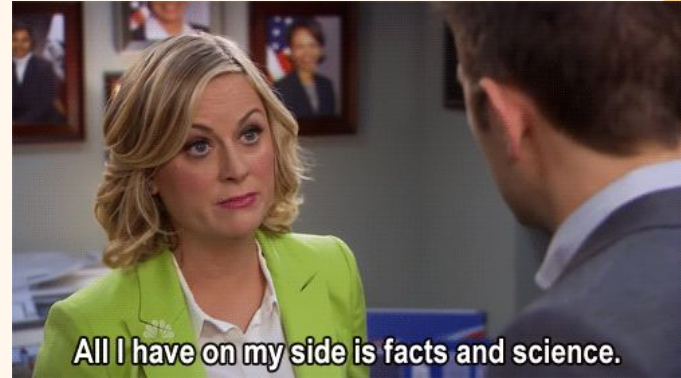
Goldenberg, 2017

**Dose 2 hrs before or
after abx, using
5-40 billion CFUs
per day**

Stengle, 2021

Clinical Bottom Line

- For Moshe, the use of probiotics is **highly recommended** due to his hx of AAD
- There is a strong landscape of **level 1 evidence**, suggesting a causal relationship between probiotics and a reduction in AAD for select pediatric pts
- Moshe's mother should consult with her clinician to select a proper probiotic product, dosage, and scheduling: the 2 most studied and effective are **LGG and S. boulardii**
- The probiotic should be administered **2 hours before or after** the abx dosage to ensure that the abx does not kill the probiotic





Next Steps: an Ideal Study for Moshe

Double-blind RCT with a large sample size.

Inclusion Criteria: Non-hospitalized, immunocompetent pts between 3-12 being treated w/ an abx and a hx of **AAD** receiving **LGG** at a **high fixed dose vs. placebo**. AAD defined as ≥ 3 unformed/watery stools per day for ≥ 2 consecutive days and a study length of **4-8 weeks**



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