Title: Probiotics and antibiotic associated diarrhea in pediatric complicated appendicitis: Prospective Controlled-Comparison Trial

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Purpose: To determine the effectiveness of the use of probiotics in patients with a diagnosis of complicated appendicitis on antibiotic associated diarrhea (AAD).

Background:
Appendicitis is the most common urgent surgical procedure performed on children. Approximately one third of the population end up having complicated appendicitis with evidence of peritoneal contamination and infection or abscess requiring the use of IV antibiotics and prolonged hospital stay. Antibiotic Associated Diarrhea (AAD) is a common complication seen in both outpatient and inpatient settings in approximately a third of all patients treated with antibiotics (Mantegazza, et al., 2018). In particular, pediatric patients experience ADD 11-62% of the time and can up upwards to 80% in hospitalized toddlers (Mantegazza, et al., 2018). Current literature defines AAD as three or more liquid stools per day. The causes of AAD are often related to the use of multiple antibiotics, prolonged hospital stay and gastrointestinal surgery. Antibiotics often disturb the normal enteric microbiome in the gut and allow for an increased growth of pathogens (Hojsak, 2017). AAD can occur as late as six to eight weeks after antibiotic exposure.

Probiotics are defined as live microbial organisms that when administered in sufficient amounts, can provide a protective benefit to the host (Hojsak, 2017). Use of probiotics in a pediatric population exposed to antibiotics and gastrointestinal surgery such as an appendectomy may provide a protective effect and prevent ADD (Alper, Zangwill, LaRue & Manheimer, 2017; Hayes & Vargas, 2016). In a meta-analysis of randomized controlled trials in pediatrics, literature found that treatment with *Lactobacillus rhamnosus GG* (LGG) reduced in risk of ADD from 23% to 9.6% (RR, 0.48; 95% CI, 0.26 to 0.89) (Szajewska & Kolodziej, 2015). Studies indicate it is suggested to administer LGG simultaneously with the initiation of antibiotic therapy, before the modification of gut microbiota and overgrowth of pathogens (Szajewska & Kolodziej, 2015).

Lactobacillus rhanmosus GG(LGG®)(Culturelle) is an over the counter dietary supplement that can help to restore the balance in the gut by promoting colonization to support better digestion and immune health. As such, this dietary supplement is not reviewed and approved by the FDA. This study does not intend to investigate route of administration, dose, patient population, or other factor that significantly increases the risk (or decreases the acceptability of the risk) associated with the use of the dietary supplement.

At Children's Medical Center, we see over 1000 cases of appendicitis a year with approximately 1/3 of those patients being complicated appendicitis. Our current treatment at Children's Medical Center for

complicated appendicitis follows two pathways: 1) drainage and deferred appendectomy approximately 6 to 8 weeks later or 2) immediate appendectomy. All children are typically admitted to the hospital for 3 to 5 days, receive a course of IV antibiotics while in hospital and are discharged with oral antibiotics to complete their treatment. There has been an increase in the number of patients receiving prescribed probiotics after surgery.

We propose to perform a randomized controlled trial where one group of patients receive probiotic therapy and another group of patients does not.

We hypothesize patients given probiotics after a diagnosis of complicated appendicitis with immediate appendectomy who receive antibiotic treatment during their inpatient stay will decrease the overall length of stay (LOS) by 25% vs the LOS in those patients who do not receive probiotics.

3. Concise Summary of Project:
Upon IRB approval, patients admitted to the pediatric surgery service with complicated appendicitis who undergo an immediate appendectomy will be approached about participation in the study. Once written consent has been obtained, patients will be randomized into one of two potential study groups. Those randomized to the treatment group will be given probiotic therapy until discharge, while those randomized to the placebo group will be given a placebo until discharge. Data will be collected from the Electronic Health Record (EHR) at Children's Medical Center will include MRN, standard demographics, length of stay, presence or absence of diarrhea, ambulation/activity level, abdominal pain, stool counts, surgical history, medications, emergency department visits and readmission rates. Data will be stored in a CMC/UTSW secured RedCap with access only granted to study team members.

4. Study Procedures:

Design. Prospective Randomized Controlled Trial

Sample.
Data will be obtained from the electronic health record (EHR) from a convenience sample of patients in a single-center pediatric inpatient surgery unit with a diagnosis of complicated appendicitis that undergoes an immediate appendectomy.

Patients will be randomized into two study groups using randomization and utilizing a sealed envelope randomization plan. 120 envelopes will be sealed with a standard sized document marked "probiotic treatment" and 120 envelopes will be sealed with a standard sized document marked "placebo". 240 envelopes will be thoroughly shuffled then labeled sequentially from 1-240 in pen. Envelopes will be placed in a plastic container in numerical order ready for use. One group of 120 patients will be given probiotic therapy until discharge and the other group of 120 patients will be given a placebo until discharge

Methods:
After the appendectomy, patients who meet the inclusion criteria and none of the exclusion criteria will be approached by the study team and offered participation for this study. Patients and families will be approached after their surgery on the inpatient floor. A member of the research team will provide families information about the study in their preferred language (English/Spanish). Aconsent will be signed and scanned into to the patient's medical record.

Those who are in agreeance will be consented for the study following all IRB procedures. Randomization will be used to allocate patients into treatment and control group. The treatment group includes 120 patients who have immediate appendectomy and will receive probiotics. The control group includes 120 patients who have an immediate appendectomy and will receive a placebo.

Patients in the treatment group will receive a standard dose of Lactobacillus rhamnosus GG capsule twice a day until discharge. The control group will receive a placebo until discharge. If the patient is unable to swallow the probiotic capsule or placebo, the capsule can be opened and sprinkled with food. Current antibiotic standard of care for complicated appendicitis patients includes: ceftriaxone RTA 50mg/kg dose every 24 hours x 7 days and metronidazole RTA 30mg/kg dose every 24 hours x7 days. In patients with a sensitivity to ceftriaxone, metronidazole RTA 30mg/kg dose every 24 hours x7 days and ciprofloxacin 10-15 mg/kg every 8 hours x 7 days will be administered.
Treating medical team and patients/family will be blinded to whether patient is on probiotic or placebo.

Data will be collected as stated in section titled, "Concise Summary of Project."

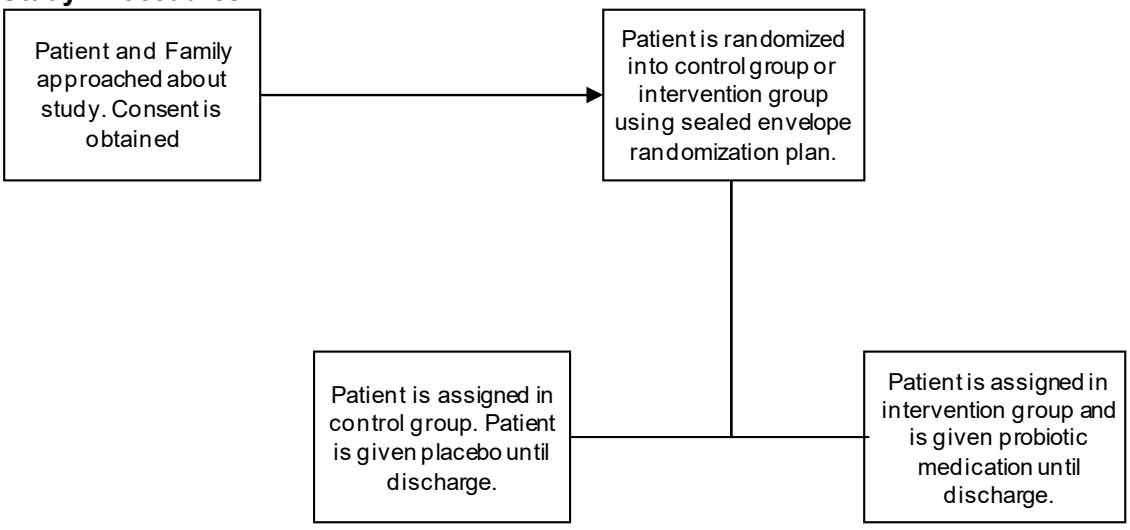
5. Criteria for Inclusion of Subjects:

- Patients with a post-operative diagnosis of complicated appendicitis who undergo an immediate appendectomy.
- Patients between the ages of 4 and 18 years of age.

6. Criteria for Exclusion of Subjects:

- Patients diagnosed with a complicated appendicitis with deferred appendectomy or non-perforated appendicitis
- Patients that have a history of being immunosuppressed, on immunosuppression therapy, or long-term steroid therapy within the last month.
- Patients that have central line access.
- Patients under 4 years of age.
- Patients that are developmentally delayed and cannot ambulate at baseline.
- Patients with significant past medical history.
- Patients that are in Child Protective Services custody.
- Patients that are incarcerated.
- Patients that are pregnant.
- Patients that speak languages other than English and Spanish.

Study Procedures



7. Sources of Research Material:

All participants will be patients under the care of the General Surgery Department. Information from the Children's Medical Center EHR will be reviewed. Data on outcomes such as length of stay, presence or absence of diarrhea, ambulation/activity level, abdominal pain, surgical history, medications, emergency department visits, readmission rates and stool counts will be extracted from medical records. Standard demographic data will also be obtained.

8. Recruitment Methods and Consenting Process:
After confirmed complicated appendicitis diagnosis, patients and families will be approached by the study team to participate in the study. If families agree to participate, written consent will be obtained, and the patient will be randomized to a study group.

9. Potential Risks:
Inadvertent disclosure of personal medical information. Special precautions are mentioned below in the paragraph *Procedures to Maintain Confidentiality*.

There are potential risks for patients taking probiotics. There have been reported accounts of sepsis in immunosuppressed patients receiving probiotics. Our study will exclude patients with a history of being immunosuppressed, on immunosuppression therapy, or long-term steroid therapy within the last month.

There is a potential risk of psychological stress. Some of the questions we will ask may make the patient/legal guardians feel uncomfortable.

10. Subject Safety and Data Monitoring:
All data will be stored on a password protected computer approved by UTSW and CMC. Access to study data will be restricted to authorized study personnel only.

All data will be stored on a password protected computer in a RedCap system approved by UTSW and CMC. Access to study data will be restricted to authorized study personnel only.

The Principal Investigators and faculty sponsor will review all patient outcomes on a monthly basis. All adverse events, expected and unexpected will be reviewed within 24 hours by the study team and reported to the DSMB and the IRB as per policy.

11. Procedures to Maintain Confidentiality:
All patient information and case report forms will be kept in a locked office with limited access. All computer files will be password protected, encrypted and stored on a secure server. Access will be limited to study team members only. Data will be collected and stored in a secured CMC server in RedCap. The case report includes a unique subject number. The data will be collected, analyzed, and archived following strict confidentiality guidelines. The Investigator will consider all information, results, discoveries, records accumulated, records acquired, or deductions in the course of the study as confidential; other than that information to be disclosed by law.

12. Potential Benefits:
There may be benefit to those patients who receive a probiotic during their course of treatment in a reduction of the incidence of AAD. Future patients may benefit if the protocol proven to be effective in decreasing the incidence of AAD.

13. Sample size calculation
Based on the patient population in Children's Medical Center Dallas, the mean and standard deviation of LOS is 114 and 75.6 hours, respectively. The LOS in the probiotic group is expected to be 75% of the control group. With 120 patients in each group, we have 83% of power to detect statistically significant difference in LOS between the probiotic group and control group.

14. Biostatistics

Descriptive analyses of the continuous and categorical data were performed using means, confidence intervals, proportions and frequencies. Wilcoxon Rank Sum test will be used to compare the LOS, as well as the number of diarrheas, between the treatment group and control group. To investigate which type of patients benefits the most from the treatment, regression analysis will be used to model log-transformed LOS. The independent variable will be treatment type and prognostic factors. The statistical analyses were performed with SAS 9.4.

References:

Agamennone, V., Krul, C. A. M., Rijkers, G., & Kort, R. (2018). A practical guide for probiotics applied to the case of antibiotic-associated diarrhea in The Netherlands. *BMC Gastroenterology, 18*(1):103. https://doi.org/10.1186/s12876-018-0831-x

Alper, B. S., Zangwill, M., LaRue, J., & Manheimer, E. W. (2017). Point of care application of: 'Probiotics for the prevention of pediatric antibiotic-associated diarrhea' (Cochrane review). *European Journal of Integrative Medicine, 12*: 129-130. https://doi.org/10.1016/j.eujim.2017.06.001

Hayes, S. R. & Vargas, A. J. (2016). Probiotics for the Prevention of Pediatric Antibiotic-Associated Diarrhea. *Explore NY, 12*(6): 463-466. doi: 10.1016/j.explore.2016.08.015

Hojsak, I. (2017) Probiotics in Children: What Is the Evidence?. *Pediatr Gastroenterol Hepatol Nutr.;20*(3):139-146. https://doi.org/10.5223/pghn.2017.20.3.139

Mantegazza, C., Molinari, P., D'Auria, E., Sonnino, M., Morelli, L., & Zuccotti, G. V. (2018). Probiotics and antibiotic-associated diarrhea in children: A review and new evidence on Lactobacillus rhamnosus GG during and after antibiotic treatment. Pharmacological Research, 128, 63–72. https://doi.org/10.1016/j.phrs.2017.08.001

Szajewska, H., & Kołodziej, M. (2015). Systematic review with meta-analysis: Lactobacillus rhamnosus GG in the prevention of antibiotic-associated diarrhoea in children and adults. *Alimentary Pharmacology & Therapeutics, 42(*10), 1149–1157. https://doi.org/10.1111/apt.13404

Wanke, M. & Szajewska, H. (2014). Probiotics for preventing healthcare-associated diarrhea in children: A meta-analysis of randomized controlled trials. *Pediatria Polska, 89*(1): 8-16. https://doi.org/10.1016/j.pepo.2013.12.003