Use of Lactobacillus acidophilus/rhamnosus complex for the prevention of antibiotic-associated diarrhea in elderly hospitalized patients



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Background

- Antibiotic-associated diarrhea (AAD) is a common adverse drug reaction, occurring in 5-35% of patients.¹
- AAD rates depend on the type of antibiotic used, length of antibiotic treatment, pathogen exposure, and host factors such as age and health status.¹⁻³
- Potentially serious/significant consequences include longer hospital stays, higher medical costs, and other co-morbidities.⁴
- Severity can range from uncomplicated diarrhea to life-threatening pseudomembranous colitis (PMC).1
- Nearly all cases of PMC are due to Clostridium difficile infection (CDI), which accounts for approximately 15-25% of AAD cases.^{5,6}
- AAD, in particular CDI, is a significant cause of morbidity and mortality in hospitalized geriatric patients.⁷
- · Probiotics have been suggested as a preventative measure for AAD and CDI.

Overview of Literature

Data up to 2006 (as per McFarland's meta-analysis3)

- (1) Prevention of AAD: 7/16 RCTs conducted in adults reported a significant reduction in AAD incidence in the probiotic group compared with placebo.
- Saccharomyces boulardii, Lactobacillus rhamnosus GG, and 'mixtures of 2 probiotic strains' demonstrated significant efficacy.
- Relative risk for developing AAD = 0.43 (95% CI = 0.31 to 0.58, p < 0.001).
- Significant heterogeneity across the studies ($\chi^2 = 82.5$; p < 0.001).
- (2) Treatment of CDI: 1/6 RCTs reported significant reduction in CDI recurrence.
- Only the S boulardii showed this benefit.

Data 2006 and Later

- · Seven RCTs studying the following probiotics:
- L casei imunatass, L bulgaricus, Streptococcus thermophilus6
- S boulardii^{8,9}
- Lacidophilus CL1285 and L casei10
- L rhamnosus GG, L acidophilus La-5 and Bifidobacterium Bb-1211
- L acidophilus¹²
- L plantarum 299v13
- $\bullet\,$ 5/7 studies showed a reduction in AAD incidence using probiotic compared to placebo or no treatment.
- NNT range = 5 to 14.

Summary: Data available to date do suggest a benefit with probiotics in the prevention of AAD without additional adverse effects. However, these data come from clinical studies that have several important limitations, including:

- · Clinical and Methodological heterogeneity
- Lack of external validity
 - No consensus in regards to optimal agent, dose, and duration
- Lack of availability/regulation of products in Canada
- · Not all trials were placebo-controlled or analyzed by intention-to-treat principle
- Small sample size

Objective and Study Endpoints

To determine whether a probiotic combination of Lactobacillus species is safe and effective for preventing antibiotic-associated diarrhea in elderly hospitalized patients.

Primary Outcome

• Incidence of AAD (defined as 3 or more loose stools in a 24 hour period)

Secondary Outcome

- . Incidence of CDI as detected by a stool assay (detection of toxins A or B)
- · Duration of hospital stay
- Incidence of adverse effects

Methods

Design

Prospective, randomized, double-blind, placebo-controlled clinical trial

Intervention/Comparator

Lactobacillus acidophilus/rhamnosus 3 caplets (1 x10⁹ cells/caplet) po BID vs matching placebo

Inclusion Criteria

Inpatient on general medicine ward at Victoria General Hospital

Over the age of 60

Antibiotic(s) anticipated for more than 72 hours

Informed consent obtained

Exclusion Criteria

Received antibiotic(s) in past 2 weeks

Active diarrhea at enrollment

CDI diagnosis within the previous 3 months

Underlying chronic GI tract disease (IBD, IBS)

lleostomy or colostomy

Regularly take probiotics

Severely immunocompromised

Severe life-threatening illness

Lactose intolerant

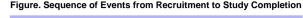
NPO or have a tubefeed

On prescribed antibiotic for more than 72 hours

Sample Size

Estimated AAD incidence = 30% in placebo group vs 12% in probiotic group Calculated sample size = 80 participants per group (α = 0.05, 80% power) Allowing for dropout rate of 20%, plan to enroll 100 patients per group

Projected Patient Flow



At time of antibiotic prescription, physician obtains verbal consent from potential study subject to be contacted by representative of study team.

| Physician writes order, allowing clinical pharmacist or investigator to screen and enroll subject into study as per inclusion/exclusion criteria.

Ward unit clerk contacts an investigator or clinical pharmacist.

Within 72 hours of first antibiotic dose, investigator or clinical pharmacist reviews the subject's medical record and Pharmanet profile for eligibility.

If eligible, investigator or clinical pharmacist will approach subject, explain the study in detail, and review the consent form.

If ineligible, investigator or clinical pharmacist will inform subject that they will not be enrolled.

Subject signs the consent form.

Investigator or clinical pharmacist writes an order confirming initiation of study agent.

Order is faxed to hospital dispensary. Randomization and allocation occur in blocks of 4.

Pharmacy dispenses study agent.

RN administers study agent for entire duration of antibiotic therapy and records adverse effects and stool information daily.

If subject is discharged home, study agent will be provided and follow-up is conducted over the telephone.

Subject provides baseline

tool sample for assessment

of Clostridium difficile

colonization (voluntary).

If subject develops diarrhea while on antibiotic in hospital, RN collects stool sample, which is analyzed for *C difficile* antigen and if positive, toxins A and B.

Subject's involvement in study completed. No further follow-up required except to document secondary outcome (length of stay

ecorded from Powerchart)

If subject does not develop diarrhea while in hospital, after antibiotic therapy is completed, study investigator continues to follow-up with subject once veekly x 3 weeks after last dose

Subject's involvement in study completed.

Expected duration ~ 4-5 weeks

Project Timeline

