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-analysis[3])

(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 thermophilus*[6]
  - *S boulardii*[8,9]
  - *L acidophilus* CL1285 and *L casei*[10]
  - *L rhamnosus* GG, *L acidophilus* La-5 and *Bifidobacterium* Bb-12[11]
  - *L acidophilus*[12]
  - *L plantarum* 299v[13]
- 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 Outcomes
- 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 x10^9 cells/caplet) po BID vs matching placebo

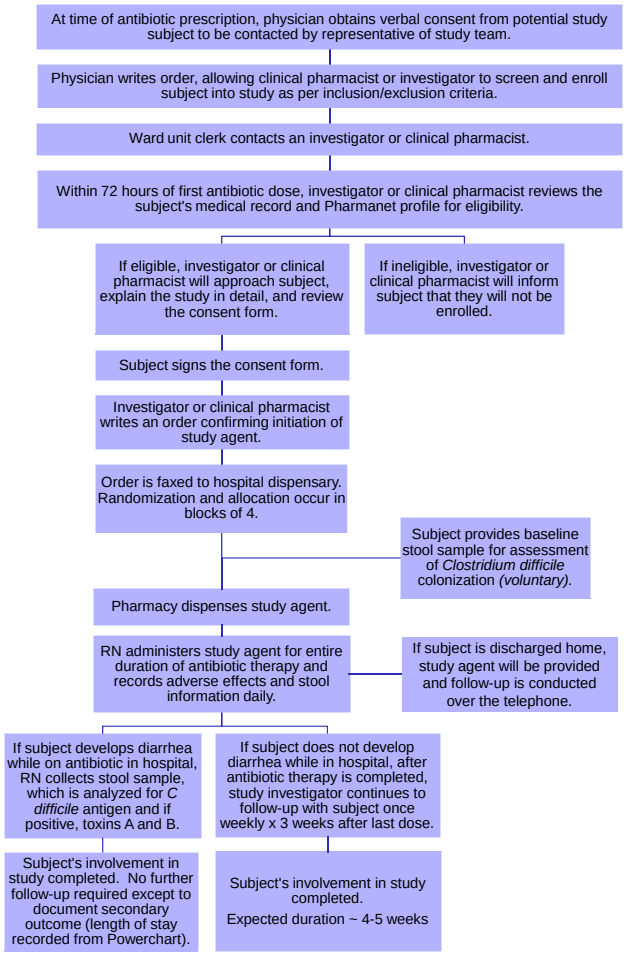
Inclusion Criteria
Inpatient on general medicine ward at Victoria General Hospital
Over the age of 60
Antibiotic(s) anticipated for more than 72 hours
Informed consent obtained

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)
Ileostomy 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

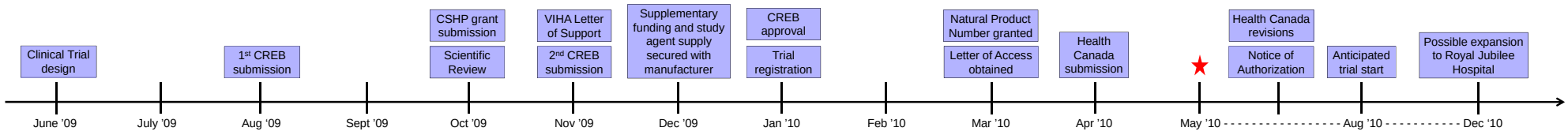
Sample Size
Estimated AAD incidence = 30% in placebo group vs 12% in probiotic group
Calculated sample size = 80 participants per group ($\alpha = 0.05$, 80% power)
Allowing for dropout rate of 20%, plan to enroll 100 patients per group

Projected Patient Flow

Figure. Sequence of Events from Recruitment to Study Completion



Project Timeline



References available on request