Lactobacillus GG for Primary Prevention of Clostridium Difficile Colitis A Randomized Prospective Placebo-Controlled Clinical Trial

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A. Study Purpose and Rationale

The purpose of the study is to determine whether C lostridium diffic] le colitis can be prevented in high-risk hospitalized patients receiving antibiotics with tile use ofthe probiotic agent, Lactobacillus GG. Clostridium difficile diarrhea is one of the most common nosocomial infections and a frequent cause of morbidity and mortality ıı older hospitalized adults. There are approximately three million new hospital cases per year. The less common and more severe form of the infection is colitis, which can progress to toxic megacolon and require surgical intervention. Infection Occurs when a person's normal protective intestinal microflora is altered by the administration of antibiotics, which leaves the host susceptible to colonization and subsequent infection by Clostridium difficile. The concept of a healthy gut microbial balance led to the idea of replenishing the resident gut flora by administering nonpathogenic bacteria to both prevent disease and treat Illness.

Probiotics are live microbial feed supplements that beneficially affect the host amnial by improving its intestinal microbial balance. Experimental and clinical research suggests a role for problotics in treating relapsing Clostridium difficile infection, antibiotic associated diarrhea, traveler ı s diarrhea, Inflammatory bowel disease and irritable bowel syndrome. Lactobacillus GG has been most extensively studied and found to be safe for human consumption. It is commercially available in capsule form and has been used in recent research for the prevention ofantiblotic associated diarrhea.

B. Study Design and Statistical Analysis

The study will consist of two groups of patients randomly assigned to either the treatment or placebo arms. Randomization will be stratified based on the number of antibiotics administered, either one or more than onc. The primary outcome will be the rate of colitis during the first 21 days after enrollment. Colitis will be diaonosed clinically by study Subjects' treating physicians (which will not be standardized) and confirmed by a standard cytotoxic assay, which has a sensitivity of 94-100% and a specficity of 99%.

The study was designed with a sample size of 1200 patients to provide 80% power to detect a difference of 8% vs 4% in the rate of occurrence of colitis between the two study groups. This calculation was based on a 2-sided χ^2 test with a type I error level of 5%. A randomization schedule will be computer-generated by the Department of Biomathematics and Biostatistics. The research pharmacy will dispense active and placebo capsules according to the randomization schedule, while both patients and investigators will be blinded to the treatment. There will be no crossover between the two study arms. Results will be analyzed using a Chi-squre test and a multiple logistic regression to account for the stratified randomization.

C. Study Procedure

Institutionalized and./or elderly hospitalized patients who are to be treated with antibiotics will be randomized to receive either Lactobacillus GG or placebo for two weeks. No other change to the patient's clinical management will be made for the purposes of this study. No additional procedures or examinations outside of routine hospital care will need to be performed. It is deemed unlikely that the

patient will experience pain or discomfort from participating in the study. A minor inconvenience of needing to take an additional medication thrice daily for two weeks will be incurred. It is estimated that the study will be performed for one year.

D. Study Drug

Lactobacillus GG is a food supplement riot under FDA regulation. Lactobacillus GCT capsules (CAG Functional Foods, Omaha, Neb) contain 10 x 10^9 CFU of live Lactobacillus GG and. inulin as filler. It needs to be stored refrigerated to ensure vlability. Placebo capsules will be identical to the drug and contain only the Inulin filler. The drug or placebo will be taken orally every 8 hours for two weeks. There are no known side effects and the drug has been well-tolerated in clinical trials.

E. Study Subjects

Study subjects will be drawn from patients admitted to the general medical service al NYPH and its affiliates who are treated with either intravenous or oral beta-lactam antiblotic(s) for any duration. Only patients being treated with ampicillin, arnoxicillin, cephalosporins, clindamyciti, penicillins, sulfonamides, erythromycin, trimethoprin, or quinolones will be eligible for inclusion. Inclusion criteria will further consist of age greater than or equal to 65 or an institutionalized patient (primary residence is a long-term care facility) of any age. Exclusion criteria will include treatment with antibiotic within 2 weeks prior to enrollment or for greater than 24 hours until time of enrollment, age younger than 65, immunocompromised state including HIV, pregnancy, diagnosis of Clostridium difficile colitis within the previous 3 months, Current inflammatory bowel disease, or inability to give informed consent. Older adults and institutionalized individuals are those at greatest risk of' acquiring Clostridium difficile colitis.

F. Recruitment Of Subjects

Hospital physicians will be informed of study's existence and asked to participate in enrolling their patients. Potential study subjects will be approached by their primary medical doctor responsible for their inpatient medical management. Only those patients who are willing to discuss the study will then be approached by the research team.

G. Confidentiality of Study Data

Each study subject will be assigned a unique identification number. All study data will be stored in a centralized secure location accessible only to the investigators.

H. Potential Risks

The study drug consists of colonies of live nonpathogenic bacteria, which when ingested, survives degradation by stomach acid and intestinal bile, and call be identified in stool specimens up to one week later. As a common normal constituent of the healthy intestinal microflora, there are no known adverse effects to consuming the drug. However, it is possible that patients' may experience unforeseen adverse effects. The product is classified as a nonregulated dietary supplement which is not under the regulations of the Food and Drug Administration.

I. Compensation and Costs to Subjects

Patients will not receive monetary compensation for their participation and will not incur any additional costs as a result of participating in the study.