Exploratory Study of Impact of Oral Metronidazole, Vancomycin and Fidaxomicin on the Extent and Quantity of Host Carriage and Environmental Contamination with C. difficile

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Purpose of the Study

We aim to perform an exploratory analysis on the impact of different oral antibiotic therapy on microbiologic kinetics in patients with C. difficile diarrhea, such as: shedding, colonization and environmental contamination. We believe data from this study can inform whether drug therapies may be used to interrupt disease transmission and to improve the infection control of C. difficile.

Background & Significance

C. difficile has emerged as one of the most important pathogens that threaten the health and quality of life for many populations. Data from different studies clearly indicate that shedding of viable spores and subsequent contamination of environmental surfaces play an important role in the transmission of C. difficile. We aim to perform an exploratory analysis on the impact of different oral antibiotic therapy on microbiologic kinetics in patients with C. difficile diarrhea, such as: shedding, colonization and environmental contamination. We believe data from this study can inform whether drug therapies may be used to interrupt disease transmission and to improve the infection control of C. difficile.

Clinical and in vitro data suggest fidaxomicin may be useful in reducing shedding, carriage and environmental contamination of C. difficile. These features include:

• Fidaxomicin has 8-fold higher bactericidal activity against C. difficile compared to vancomycin in in vitro studies.

• Fidaxomicin is associated with lower post-treatment spore counts as compared to vancomycin.

• Fidaxomicin is associated with less disturbance of non-Clostridial GI flora

• Fidaxomicin has prolonged post-antibiotic effect compared to vancomycin.

• Fidaxomicin therapy, compared with vancomycin, was associated with slightly shorter time to resolution of diarrhea.

Design & Procedures

General. Duke University Health System is uniquely positioned to study the impact of fidaxomicin on the microbiologic kinetics of C. difficile, including bacterial shedding, colonization and environmental contamination. In 2011, the Duke Program for Infection Prevention and collaborators from University of North Carolina, Chapel Hill were jointly awarded a five-year Preventions Epicenter grant by the Centers for Disease Control and Prevention (CDC). The keystone project funded by the Epicenters grant will study the efficacy of ultraviolet light and novel cleaning strategies in reducing environmental

contamination and disease incidence due to 4 main pathogens: MRSA, VRE, Acinetobacter and C. difficile. In Phase III of the Epicenter study, we will study bacterial shedding, level of bacterial colonization and level of environmental contamination starting from the time a patient is admitted into a freshly cleaned room. Microbiologic cultures will be obtained from enrolled patients and the designated surfaces of their rooms.

We propose an exploratory study that will describe and compare the impact of 3 oral antibiotic therapies on the microbiologic kinetics of C. difficile shedding, colonization and environmental contamination among patients with laboratory confirmed CDAD. The proposed study will take advantage of much of the infrastructure, study coordination and enrollment strategies already created for phase III of the CDC Epicenter study, resulting in high cost-effectiveness.

We will undertake a prospective, randomized controlled trial (RCT) to evaluate the impact of antibiotic treatment choice on environmental shedding and contamination with C. difficile spores. The proposed research will be a parallel study to the CDC Phase II (Duke IRB #Pro00032718 and Phase III studies (Duke IRB #Pro00036470).

Specific Aims. The specific aims of this study are to:

1) characterize the baseline and the temporal variation in the profile of C. difficile isolated from targeted surfaces in a hospital room;

2) determine the impact of oral fidaxomicin, oral metronidazole and oral vancomycin on the above relationships over time and specifically establish:

a. Extent and quantity of C. difficile shedding, colonization and environmental contamination in patients who received oral fidaxomicin vs. oral metronidazole or vancomycin.

b. Duration of diarrhea that were positive for CDAD.

This is a RCT of patients with documented CDAD, defined as any patients with a positive polymerase chain reaction (PCR) test for C. difficile in a patient with more than 3 loose stools within 24 hours. Eligible patients will be identified by microbiology-driven alerts or by orders for contact isolation for C. difficile. Study team will be alerted to approach the patient to provide information about the study and to obtain informed consent.

Outcomes. The primary outcome will be median total colony forming units (CFU) of C. difficile identified in the hospital room environment for each antibiotic. More specifically, the median environmental contamination in patients who receive fidaxomicin will be compared to the median environmental contamination in patients who receive vancomycin and to the median environmental contamination in patients who receive metronidazole. Secondary outcomes will include molecular relatedness of C. difficile isolates, changes in environmental contamination over time, and duration of diarrhea.

Inclusion criteria

Adult patients (> 18 years)with microbiology-proven CDAD, who are able to provide informed consent and are eligible to receive oral antibiotic therapy.

Exclusion criteria

Prisoners, pregnant women and children <18 years will be excluded (see Protection of Human Subjects and Inclusion of Children),

Patients requiring intravenous therapy for treatment of CDAD,

Patients who do not consent and those who withdraw consent, etc.

Patient Participation

This study will obtain microbiologic cultures from 2 sources: 1) environmental surfaces in the room and 2) stool or perianal swabs from the patient at predefined intervals starting the day of enrollment. The environmental cultures as well as the stool and perianal swabs will be labeled with a unique study number. Cultures will be obtained on Day 1 (day of enrollment), Day 3 and Day 7 following admission to the room, at the end of each subsequent week (Day 14, Day 21, etc.), and on the day of discharge from the hospital room. Microbiologic cultures will be obtained, including perianal swabs and stool specimens. Microbiologic cultures will be obtained from 5 high-touch environmental surfaces

A total of 30 patients are anticipated in this study; 10 patients will be included in each of the three study arms. Patients will always receive anti-C. difficile therapy for CDAD; the exact drug will be assigned based on block-randomization of fidaxomicin, metronidazole or vancomycin. Thus, the study will enroll 10 patients receiving metronidazole therapy, 10 patients receiving oral vancomycin therapy and 10 patients receiving oral fidaxomicin therapy. Patients will receive 10 days of therapy.

Subjects will be asked to return 7 days after discharge from hospital for an outpatient visit. Subjects will also be asked for a stool sample if possible. If not, a perianal swab will be obtained.

We will adhere to all Good Clinical Practice (GCP) guidelines. The protocol, clinical record form, and consent form will be submitted to the Institutional Review Boards for approval.

Onsite study coordinators will obtain informed consent. Study coordinators or a trained designee will collect specimens from patients using standard methodology. Results of study specimens will not be analyzed in real-time and will not be fed back to clinicians. Declination of participation in the study will not affect the clinical care of the patient.

Specimens from different environmental sites obtained at different time-points will be tested to determine the presence of C. difficile. The count and proportion of specimens from patients that are positive for the bacteria will be calculated for each time point. Relatedness of bacteria will be determined using antibiotic susceptibility and molecular techniques, including PFGE, ribotyping, and MLST methods for C. difficile that are found from patient and from the environment of the patient room. Statistical analysis of the final data set will include adjustments for length of stay and the average number of cultures taken per patient and per patient room.

Microbiologic cultures from the environment will be sent to UNC Hospital Epidemiology Microbiology laboratory (headed by Dr William Rutala) and swab and stool samples from subjects will be sent to the Duke VA Medical Center Molecular Epidemiology Research Laboratory (headed by Dr Chris Woods) for

analysis. All samples sent to UNC and the Duke VA are de-identified and labeled with a unique study number.

Selection of Subjects

Inclusion criteria

Adult patients (> 18 years)with microbiology-proven CDAD, who are able to provide informed consent and are eligible to receive oral antibiotic therapy.

Exclusion criteria

Prisoners, pregnant women and children <18 years will be excluded (see Protection of Human Subjects and Inclusion of Children),

Patients requiring intravenous therapy for treatment of CDAD,

Patients who do not consent and those who withdraw consent, etc.

Subject Recruitment and Compensation

Describe recruitment procedures, including who will introduce the study to potential subjects. Describe how you will ensure that subject selection is equitable and all relevant demographic groups have access to study participation (per 45 CFR 46.111(a) (3)). Include information about approximately how many DUHS subjects will be recruited. If subjects are to be compensated, provide specific prorated amounts to be provided for expenses such as travel and/or lost wages, and/or for inducement to participate.

A Waiver or Alteration of Consent and HIPAA Authorization will be submitted to the IRB for approval. Subjects will be identified through review of hospital records including lab results for C. difficile.

As soon as the PI or study coordinator identifies a patient with a positive C. difficile result, the primary service team (PST) in hospital will be contacted to discuss the patient. If the PST agrees that the patient is eligible and agrees to the drug-allocation schema outlined above the PST will introduce the study and the study coordinator to the patient and the study coordinator will go over the informed consent with the patient. The patient will be enrolled as a study subject if all eligibility criteria are met and after the informed consent is signed and dated by the patient. C difficile therapy will be assigned by block randomization. If the patient is allocated to oral vancomycin or oral metronidazole, then the PST will prescribe the drug as per usual practice. If the patient is assigned fidaxomicin, the study investigators will prescribe the drug from the Investigational Drug Service (IDS). The study sponsor will supply fidaxomicin, but not metronidazole or vancomycin.

Subject's Capacity to Give Legally Effective Consent

If subjects who do not have the capacity to give legally effective consent are included, describe how diminished capacity will be assessed. Will a periodic reassessment occur? If so, when? Will the subject be consented if the decisional capacity improves?

Subjects will need to be able to give consent to participate in this study.

Risk/Benefit Assessment

The three treatment options included in this study are part of routine care for CDAD. Vancomycin and metronidazole are recommended for the treatment of CDAD in multi-society guidelines. Fidaxomicin is FDA-approved for the treatment of CDAD, but is not included in guidelines because of its cost. Nevertheless, all antibiotics can lead to adverse events. Thus, patients may experience adverse effects from the antibiotics that they consent to receive as part of usual clinical care for CDAD. Secondly, the microbiological samples that will be taken may cause some discomfort and minor bleeding which will be discussed with the patient during the consenting process. Declining to participate in the study will not affect the clinical care of the patient. Results of study specimens will not be analyzed in real-time and will not be sent back to clinicians.

The PI will review and sign off on all adverse events or problems as they occur. SAEs are not anticipated for this study. Any standard SAE events that may occur will be reported to the manufacturer and to the IRB.

There is no direct benefit to the patient in the study. The sponsor will supply Fidaxomicin free of charge if the patient is randomized to this drug. The data from this study may prompt future studies that examine the use of oral antibiotics to reduce the transmissibility of C. difficile.

Costs to the Subject

The sponsor will supply Fidaxomicin free of charge if the patient is randomized to this drug.

Data Analysis & Statistical Considerations

Describe endpoints and power calculations. Provide a detailed description of how study data will be analyzed, including statistical methods used, and how ineligible subjects will be handled and which subjects will be included for analysis. Include planned sample size justification. Provide estimated time to target accrual and accrual rate. Describe interim analysis including plans to stop accrual during monitoring. Phase I studies, include dose escalation schema and criteria for dose escalation with definition of MTD and DLT.

Outcomes. The primary outcome will be median total colony forming units (CFU) of C. difficile identified in the hospital room environment for each antibiotic. More specifically, the median environmental contamination in patients who receive fidaxomicin will be compared to the median environmental contamination in patients who receive vancomycin and to the median environmental contamination in patients who receive metronidazole. Secondary outcomes will include molecular relatedness of C. difficile isolates, changes in environmental contamination over time, and duration of diarrhea.

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Statistics – Descriptive statistics would be used to correlate culture results from the environment and the patient. Medians will be compared using standard statistical tests such as Wilcoxon rank sums.

Data & Safety Monitoring

Summarize safety concerns, and describe the methods to monitor research subjects and their data to ensure their safety, including who will monitor the data, and the frequency of such monitoring. If a data monitoring committee will be used, describe its operation, including stopping rules and frequency of review, and if it is independent of the sponsor (per 45 CFR 46.111(a) (6)).

Data

Data collected by the study will be entered into secure REDCap databases managed by the Duke Office of Clinical Research. All connections to the system, both external and internal, occur over encrypted channels. Access to components of the system is role-based and can only be granted by administrators of the system. All collected information is stored on a secure server hosted by Duke Medicine