A comparison of fidaxomicin and oral vancomycin for the treatment of Clostridium difficile infection (CDI) in hospitalized patients receiving concomitant antibiotics for the treatment of concurrent infections

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Study Title: A comparison of fidaxomicin and oral vancomycin for the treatment of *Clostridium difficile* infection (CDI) in hospitalized patients receiving concomitant antibiotics for the treatment of concurrent infections

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1 STUDY RATIONALE/BACKGROUND

Administration of concomitant antibiotics (CA) is a known risk factor for treatment failure in the treatment of CDI, as well as for recurrence of CDI. Recent data suggested that among patients receiving CA, fidaxomicin 200 mg twice daily is superior to oral vancomycin 125 mg four times daily with clinical cure rates of 90.0% and 79.4%, respectively ($p= 0.04$)[1]. While these data are encouraging, many clinicians remain unclear on how to apply these data to patient care as a conservative definition for CA was used in this trial (any patient who received ≥ 1 dose of antibiotic was considered to have CA.) Additionally, patients were excluded from the trial if it was expected that they would require ≥ 7 days of CA[2].

Therefore, the clinical question still remains of how to apply these data to the real world patient who requires a long course of CA and develops CDI while on therapy. We therefore propose an open label, comparative and prospective study to compare fidaxomicin 200 mg twice daily vs oral vancomycin 125 mg four times daily for the treatment of CDI among patients who are receiving a long course of CA.

2 STUDY HYPOTHESIS

Fidaxomicin will be superior to vancomycin with respect to clinical cure for patients with CDI requiring a long course of broad spectrum CA for the treatment of concomitant systemic infections.

2.1 PRELIMINARY DATA

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The only preliminary data are the Mullane paper data, which are described above.

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 STUDY OBJECTIVES

3.1.1 PRIMARY OBJECTIVES:

To compare the clinical cure rate using fidaxomicin compared to oral vancomycin for the treatment of CDI in patients requiring CA.

3.1.2 SECONDARY OBJECTIVES:

To compare the impact of therapy (fidaxomicin versus vancomycin) on recurrence, length of stay, ICU length of stay (when applicable), time to resolution of diarrhea*, rates of colectomy, and 30 day mortality (both attributable and all cause) in patients with CDI requiring CA for concomitant systemic infections.

* Two definitions of time to resolution of diarrhea will be analyzed. The first, which will be a component of clinical cure, is consistent with published CDI literature and will be defined as ≤ 3 unformed stools for 2 consecutive days maintained until the end of therapy and for 2 days afterward. The second definition, which has important infection control implications, is complete resolution of diarrhea, which would facilitate removal of the patient from contact isolation.

3.2 STUDY ENDPOINTS

3.2.1 PRIMARY ENDPOINT:

Clinical cure

3.2.1.1 PRIMARY ENDPOINT DEFINITION:

Resolution of diarrhea (≤3 unformed stools for 2 consecutive days maintained until the end of therapy and for 2 days afterward). Clinical failure will be defined as persistent diarrhea and/or the need for additional treatment for CDI at the end of study therapy.

3.2.2 SECONDARY ENDPOINT(S):

Recurrence, length of stay (LOS), ICU LOS, time to resolution of diarrhea (total), rates of colectomy due to CDI, 30 day mortality, and 30 day readmission.

3.2.2.1 SECONDARY ENDPOINT DEFINITION(S):

Recurrence: defined as all three of the following within 4 weeks after successfully completing study treatment: reappearance of symptoms of CDI (>3 unformed stools in a 24 hour period), a positive stool test for *C. difficile* (**Figure 1**), and the need for retreatment with an agent active against *C. difficile.*

Length of Stay: defined as the length of stay from the time of study enrollment until discharge from the hospital.

ICU length of stay: pertinent to patients in the ICU at the time of study

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enrollment and patients admitted to the ICU within 48 hours after study enrollment/*C. difficile* onset. Defined as the length of stay from enrollment in the study until discharge from the ICU.

- Time from study enrollment to resolution of diarrhea (as defined earlier in 3.1.2)
- Rates of colectomy due to CDI
- 30 day mortality, both overall and attributable

Subgroup analysis: A subgroup analysis will be performed analyzing the above outcomes in patients with severe disease (defined as Scr ≥ 1.5 mg/dL or WBC ≥ 15,000 cells/mm3) and also for those with mild-moderate disease.

4 STUDY DESIGN

4.1 SITE

This study will be performed at The University of Michigan and at St. Joseph's Mercy Ann Arbor Hospital.

4.2 INCLUSION/EXCLUSION CRITERIA

4.2.1 INCLUSION CRITERIA

- Patients 18 years of age or older with >3 unformed stools/24 hours with positive stool test for *C. difficile*.
- Patients receiving ≥ 1 high or medium risk antibiotic for treatment of an infection other than CDI, for an anticipated duration of ≥ 5 days from the time of enrollment
  - High risk: carbapenems, 2nd-4th generation cephalosporins, fluoroquinolones, clindamycin, and beta-lactam/beta-lactamase inhibitor combinations
  - Medium risk: 1st generation cephalosporin, macrolides*, and aztreonam
    - *The macrolide would be considered to be low risk if patients are receiving intermittent macrolides for prophylaxis only and not for treatment of an acute infection

4.2.2 EXCLUSION CRITERIA

- Patients with severe-complicated disease that would compromise oral therapy (hypotension or shock, ileus or bowel obstruction, megacolon)
- Patients with an allergy to oral vancomycin or fidaxomicin

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- Patients anticipated to receive metronidazole after enrollment
- Patients who already received oral vancomycin or metronidazole (either oral or intravenous) for > 24 hours within the preceding 72 hours at the time of enrollment
- Patients anticipated to receive adjunctive *C. difficile* therapy (rifaxamin, nitazoxanide, tigecycline) after enrollment
- Patients who are on laxatives before they are enrolled into the study, such as lactulose, if:
  - Patients have had a recent dose adjustment;
  - Baseline number of bowel movement while on laxatives is unknown.
  - Number of bowel movements and/or consistency has not changed from baseline.
- Patients who have had colostomy or ileostomy
- Patients who will have colostomy or ileostomy after enrollment and before study ends
- Patients who are or will be on long-term (>12 weeks) medium or high-risk antibiotics prophylaxis after enrollment

4.3 SAMPLE SIZE

4.3.1 NUMBER OF CHARTS TO BE REVIEWED

Not applicable

4.3.2 NUMBER OF SUBJECTS TO BE ENROLLED

1500 patients will be expected over the study period (2.5 years) at the sites. During study assessment it was determined that ~ 41% of all patients at the sites would be eligible for the study (having CDI while on a high or medium risk CA for an expected duration of ≥ 5 days, and having not received 24 hours of pre-treatment of vancomycin or metronidazole) leaving 615 eligible patients over the study period. Given the open label nature of this study we anticipate being able to enroll 200 of these eligible patients, 100 to each treatment arm, based on the low drop-out rate (<2%) that we have seen thus far. This would allow us to have approximately 100 evaluable patients in each study arm.

4.3.3 SAMPLE SIZE DETERMINATION

We hypothesize that the clinical cure discrepancy should be greater than the discrepancy reported by Mullane and colleagues because more patients who are receiving long course of CA will fail to reach clinical cure on vancomycin. Therefore, our power calculations are based off an expected 90% cure rate with fidaxomicin and 75% with vancomycin, and a total sample number of 200. In order to have 80% power, with an alpha of 0.05, 100 patients will need to be randomized into each arm (total n = 200).

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4.4 SCREENING, RANDOMIZATION, BLINDING

4.4.1 SCREENING PROCEDURE

Patients will be screened for inclusion by real time surveillance of positive *C. difficile* results per the local standard of care *C. difficile* testing platform and assessed for eligibility using the Stool Testing Algorithm for *C. difficile* (Figure 1). Study personnel will receive all positive results in real time and will then screen the patient for inclusion and exclusion criteria. Screening will occur 7 days a week. If a patient meets inclusion criteria the study staff will approach the primary team and with their approval the patient for enrollment.

4.4.2 RANDOMIZATION

Patients will be stratified for randomization based on two criteria: severity of CDI, and CDI episode (stratified into first episode/first recurrence or > 1 recurrence).

Once a patient is enrolled in the study, study staff will randomize patients utilizing a randomization binder stored electronically by the coordinating center. The patient will be placed in an open label treatment arm as described below.

4.4.3 BLINDING

The study is open label so this is not applicable.

4.5 REGULATORY AND ETHICS

4.5.1 INFORMED CONSENT

Study staff will acquire informed consent at the time of patient enrollment either from the patient or their legally authorized representative (LAR).

4.5.2 INSTITUTIONAL REVIEW BOARD/ETHICS COMMITTEE

The coordinating center IRB, IRBMED at the University of Michigan, will review and approve the protocol followed by local IRBs at all performance sites.

4.5.3 INVESTIGATIONAL NEW DRUG (IND) FILING

Not applicable. Both agents are standard of care treatments for *C. difficile* infection and have an FDA indication for treatment of *C. difficile* infection.

5 STUDY PROCEDURES

5.1 TREATMENT

All patients with a positive stool test for *C. difficile* (Figure 1) at the study hospitals will be screened for inclusion. Patients will be eligible for inclusion if they are being treated with ≥ 1 concomitant high risk or medium risk antibiotic for treatment of another systemic infection and the anticipated duration of therapy with the CA per the physician of record is ≥ 5 days from the time of study enrollment (i.e. enrollment day.) Eligible patients will be randomized to receive open-label fidaxomicin 200 mg twice daily or vancomycin 125 mg orally four times daily for 10 days or until the end of the duration of CA exposure, whichever is longer. Patients will be allowed to have received up to 24 hours of *C. difficile*

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therapy prior to study enrollment.

Intervention: Fidaxomicin 200 mg PO BID vs. Vancomycin 125 mg PO QID

5.2 PROCEDURES

Schedule of Procedures / Study Events

Scheduled Assessment or Procedure	Study Day			
	-1 to 1 (Baseline)	Daily while in hospital	EOT	TOC
Physical Exam	X			
Standard of care lab results	X	X	X	X
Temperature	X	X	X	X
Number of unformed bowel movements/24 hours	X	X	X	X
Adverse Events	X	X	X	X

* Laboratory values will be recorded as ordered and evaluated by attending team caring for the patient outside of this study. The standard of care lab results that will be collected from subject medical records as a part of the study are your white blood cell count, platelets, ALT, AST, total bilirubin, albumin, prothrombin time, serum creatinine, lactic acid, and carbon dioxide. No laboratory values will be ordered by study personnel or charged to the study. If the patient has left the hospital before end of treatment (EOT) or Test of Cure (TOC), they will be instructed to monitor their symptoms daily and keep note of fevers and number of bowel movements. Follow up phone calls to assess cure and recurrence will be made at the EOT and TOC dates when necessary.

5.3 ADVERSE EVENT REPORTING

5.3.1 DEFINITIONS

A mild adverse event is one that is noticeable to the investigator, physicians caring for the patient and/or the patient, however does not interfere with routine clinical care and requires no specific intervention. An example of this would be mild nausea from study medication.

A moderate adverse event interferes with routine clinical care, however responds to symptomatic management. An example would be vomiting that responds to anti-emetic therapy.

A severe adverse event is one that limits the subject's ability to perform routine activities and does not respond to symptomatic treatment. An adverse event would also be considered severe if it worsens clinical prognosis, requires escalation in level of care (i.e. ICU admission), or negatively impacts outcome variables. An example of this would be anaphylactic shock secondary to the study medications.

5.3.2 RELATIONSHIP TO STUDY MEDICATION

The following criteria will be used to determine relatedness to the study medication:

Not Related: an AE with a temporal relationship to the drug administered that makes a causal relationship improbable, and/or for which other drugs or underlying or concurrent disease provide a plausible explanation.

Unlikely Related: an AE that has a plausible temporal relationship to the drug

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administered, but for which other causative factor(s) more likely account for the event and where dechallenge (withdrawal of drug treatment) or dose reduction was not felt clinically indicated or improvements on dechallenge or dose reduction have not been observed.

Possibly Related**:** an AE that has a plausible temporal relationship to the drug administered, but for which other causative factor(s) could account for the event and where improvements on dechallenge or dose reduction may or may not have been observed.

5.3.3 EXPECTEDNESS OF AE

An AE is considered unexpected if the specificity or severity is not consistent with the applicable product information for either fidaxomicin or vancomycin.

5.3.4 RECORDING AND REPORTING A SAE

5.3.4.1 STUDIES NOT PERFORMED UNDER AN IND

Adverse Events (AEs) will be recorded on the case report form in REDCap. Serious Adverse Events (SAEs) and non-serious AEs will be reported to the performance site IRBs in accordance with local guidelines. SAEs meeting the NIH definition of Unanticipated Problem will be reported to the FDA. Coordinating center staff will also work with Cubist/Merck as necessary to address any AE's related to study product.

5.3.4.2 STUDIES PERFORMED UNDER YOUR OWN IND

Not Applicable.

6 DATA COLLECTION AND ANALYSIS

6.1 DATA COLLECTION

Data collection will be completed by performance site using a standardized data collection form provided by the coordinating center through REDCap with all relevant patient-specific and treatment-related information.

6.2 DATA VALIDATION

Members of each performance site's study team who do not participate in data entry will validate clinical outcomes, as reported in the data collection form, in 10% of patient cases. If significant discrepancies are found in ≥ 10% of the analyzed cases, then full validation will occur for all patient cases.

6.3 DATA / STATISTICAL ANALYSIS

All statistical analyses will be performed by the coordinating center via SAS version 9.3. For objective 1, the clinical cure rates of the two treatment arms will be compared using Fisher's exact test. Other analyses relevant to objective 1 will be performed with Chi Square test, Student t test and Wilcoxon rank sum test. Multivariate models will be constructed using logistic regressions to identify individual factors associated with either cure or failure. Variables associated with cure or failure in the bivariate analyses with p values < 0.10 will be put into the multivariate models. Treatment arm will be forced into the model as appropriate and other variables that the investigators deem

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clinically relevant may be placed in the model as appropriate. For objective 2, analyses will be conducted using the same tests as above and multivariate modeling will also be performed. For the time to resolution of diarrhea, cox proportional hazard models will be performed to compare the two groups.

For patients who are lost to follow up, their endpoints that have not yet been assessed (recurrence, readmission, and potentially cure) will be considered indeterminate. Two analyses will be done, one where these patients are omitted (clinically evaluable population), and one where these patients are failures (intent to treat).

7 PUBLICATION

It is expected that this will be a high impact article and we will target Clinical Infectious Diseases for publication. Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), IDWeek, or European Congress of Clinical Microbiology and Infectious Diseases (ECCMID) are potential places for abstract submission depending on the time of year that results are finalized.

8 TIMELINE

IRB approval x 3 months
Study duration x 48 months
Manuscript preparation x 3 months

9 REFERENCES

Mullane KM et.al. Efficacy of Fidaxomicin Versus Vancomycin as Therapy for Clostridium Difficile Infection in Individuals Taking Concomitant Antibiotics for Other Concurrent Infections. Clin Infect Dis. 2011; 53(5): 440-7.

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Cohen SH, et al. Clinical practice guidelines for Clostridium difficile infection in adults: 2010 update by the society for healthcare epidemiology of America (SHEA) and the infectious diseases society of America (IDSA). Infect Control Hosp Epidemiol. 2010; 31(5):431-55.

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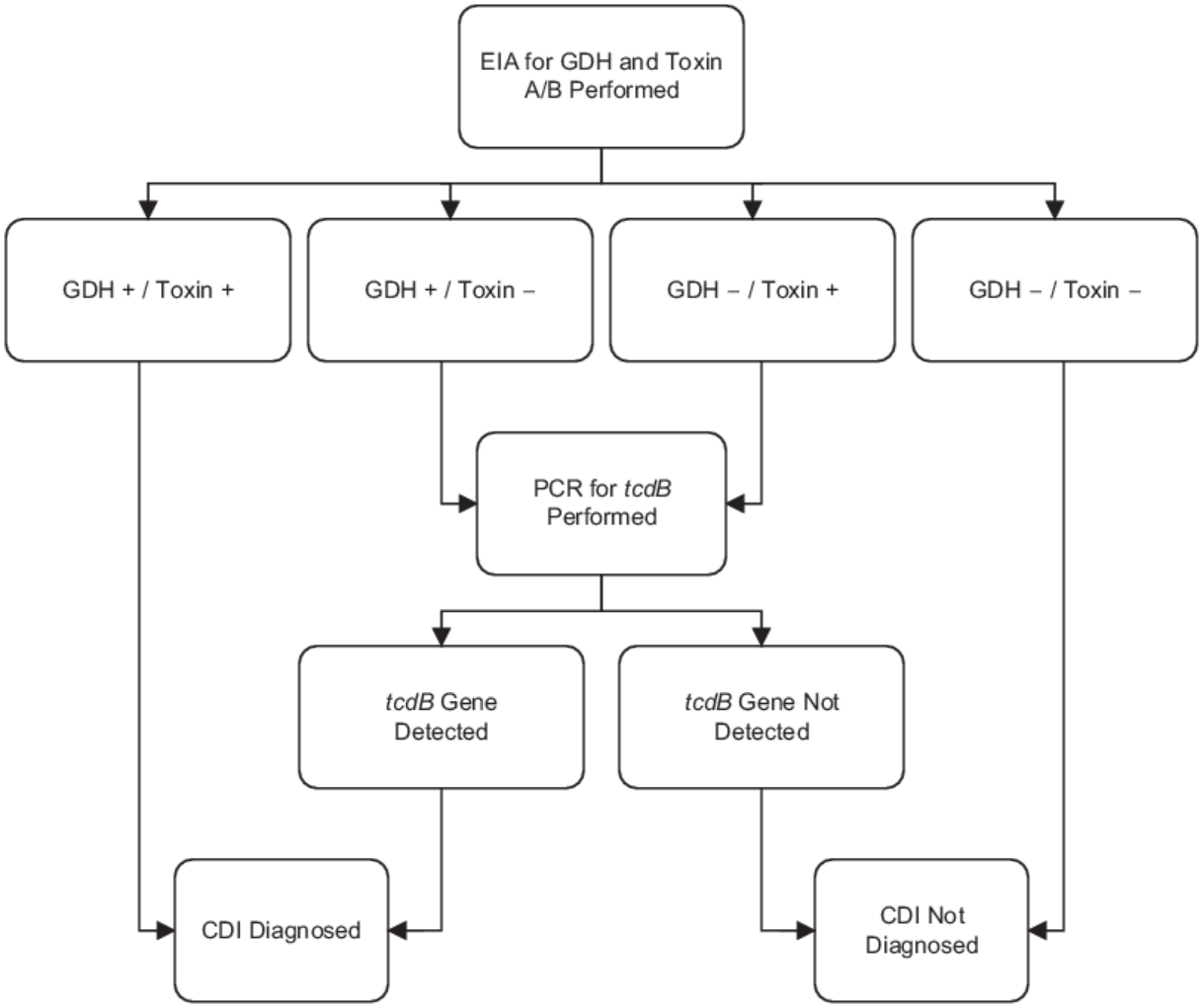
Figure 1. Performance site Stool Testing Algorithm for *C. difficile*,
Abbreviations: EIA, enzyme immunoassay; GDH, glutamate dehydrogenase.



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