

Oral Vancomycin for Primary Clostridium Difficile Infection
Prophylaxis in Patients Receiving High-Risk Antibiotics

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Introduction

Clostridium difficile infection (CDI) occurred in over 500,000 patients in 2011, and was found to account for 14,000 deaths in the United States in 2007.¹ CDI provides a burden of approximately \$3.2 billion annually in the United States.² Transmission of *Clostridium difficile* from one patient to others can easily occur, and CDI outbreaks have been reported across the country. Additionally, once a patient has an initial episode, the rate of recurrence is approximately 20%.³ Rates of CDI have increased over the past couple decades across the country and St. Luke's Hospital has also seen a rise in CDI incidence.

A variety of risk factors have been identified for CDI: antibiotic use, number and duration of antibiotics, duration of hospitalization, age greater than 65 years, gastrointestinal (GI) acid suppression, GI surgery and tube feeds, and immunosuppression such as chemotherapy and HIV.³⁻⁵ The largest contributor to CDI risk is the use of antibiotics. Fluoroquinolones, clindamycin, and 3rd generation cephalosporins have been identified as carrying the highest risk.^{4,6} Additionally, broad-spectrum penicillins have been found to convey a higher risk of CDI.^{4,6} Hospitalized patients on antibiotics are particularly vulnerable because often additional risk factors are present such as simply being in the hospital and receipt of gastrointestinal (GI) acid suppression therapy with a proton-pump inhibitor (PPI) or histamine-2 receptor antagonist (H2RA).

As the CDI incidence has been on the rise, a variety of preventative measures have been utilized and are supported by guidelines from the Infectious Diseases Society of America/Society of Healthcare Epidemiology of America (IDSA/SHEA).³ These recommendations include use of gloves and gowns upon entry into patient rooms who have CDI, hand hygiene with soap and water, patient isolation, and antimicrobial use restrictions.³ Despite these implementations in hospitals throughout the country and at St. Luke's Hospital, CDI still remains an issue. Van Hise and colleagues found that prophylactic oral vancomycin in patients with a history of CDI and treated actively with antibiotics at the time of inclusion had a reduction in CDI recurrence up to 4 weeks following the discontinuation of antibiotics. This is one retrospective, single-center study and thus further studies are needed to uniformly adopt this practice, but it may be a promising lead in reducing CDI recurrence if results can be replicated.⁷

The study by Van Hise and colleagues reviewed secondary prophylaxis. St. Luke's Hospital and hospitals throughout the country have adopted preventive strategies recommended by the IDSA guidelines, and yet CDI incidence continues to increase. As a result, further preventative measures need to be explored to prevent the first episode of CDI. Currently there is no literature regarding the use of oral vancomycin for primary CDI prophylaxis in high-risk patients for infection. The purpose of the study is to evaluate the efficacy of primary oral vancomycin prophylaxis in patients deemed high risk for CDI.

Objectives

The primary outcome of this study is CDI occurrence 4 weeks following the completion of antibiotic therapy or hospital discharge, whichever occurs first.

Secondary outcomes include time to CDI occurrence and CDI severity which will be based on the IDSA/SHEA criteria for mild to moderate, defined as white-cell count less than 15,000 cells/ μ L or increase in serum creatinine (SCr) by <1.5 times the baseline; severe, defined as white-cell count greater than 15,000 cells/ μ L or increase in SCr by >1.5 times the baseline; and fulminant, defined as the criteria above for severe with shock, hypotension, ileus, or megacolon.

Methods

This will be a pre-post intervention cohort study of patients treated for infection with the below listed risk factors for CDI in addition to antibiotic therapy. This study will be limited to the infectious diseases physicians at St. Luke's Hospital. This will allow for expert review and decision-making regarding prophylaxis for each patient. The CDI prophylaxis intervention will be vancomycin 125 by mouth daily.

The intervention will be the identification of "high risk" patients and subsequent clinical decision to start prophylaxis based on collaboration with the consulted infectious disease physician on the case. Oral vancomycin 125 mg by mouth daily was selected for inclusion since oral vancomycin is known to concentrate in the colon with stool concentrations exceeding 800 mcg/g in patients receiving treatment doses (vancomycin 125 mg PO every 6 hours), and minimal inhibitory concentrations (MICs) for *Clostridium difficile* are typically 1 to 2 mcg/mL.⁸⁻¹⁰ Additionally, we hypothesize that vancomycin 125 mg daily may minimize disruption of normal flora and allow for increased vancomycin dose and interval if overt infection develops.¹¹

Infectious diseases providers will be notified through daily pager notification of potential patients on whom they are consulted that meet inclusion criteria and the decision is left to the infectious disease physician to start oral vancomycin or to withhold from prophylaxis. If therapy will be started, consent will be obtained. The discontinuation of oral vancomycin prophylaxis will be left to the discretion of the infectious disease provider.

Patients at high risk must be 65 years of age or older, on GI acid suppression with an H2RA or PPI, and receiving pre-specified antibiotics. Age and GI acid suppression have been identified

in the literature as risk factors for CDI in addition to antibiotic risk factors. Patients must receive a select group of antibiotics for greater than 24 hours. The antibiotics considered for inclusion are a fluoroquinolone (ciprofloxacin, levofloxacin), clindamycin, a 3rd or 4th generation cephalosporin, a broad-spectrum aminopenicillin (ampicillin-sulbactam, piperacillin-tazobactam), or a carbapenem. These antibiotics were chosen due to their association with a higher risk of CDI occurrence. Patients will be excluded if they do not meet all three requirements for "high risk" (age, acid suppression, and antibiotic) or if they have a vancomycin allergy that precludes its use. Additionally, patients who had active CDI prior to antibiotic initiation, who were on prophylactic vancomycin prior to antibiotic therapy, or who received medications that cover CDI as part of the primary antibiotic treatment will be excluded (metronidazole, rifaximin, fidaxomicin). Patients will be excluded if they are pregnant or breastfeeding.

CDI will be defined as documentation of loose stools or diarrhea with a positive *C. diff* toxin and glutamate dehydrogenase (GDH) or positive polymerase chain reaction (PCR). The diagnosis of CDI at St. Luke's Hospital begins with a toxin and GDH. If both are positive, then the patient is determined to have CDI, if both are negative, then the patient does not have CDI. If the results are discordant (i.e. one positive and one negative) then a PCR is run to determine the presence of CDI. Thus a patient can be diagnosed with CDI by either a positive toxin and GDH or by a positive PCR.

Baseline patient information will also be gathered including age, race, sex, antibiotic indication, antibiotics used, antibiotic duration, probiotic use, H2RA, or PPI use prior to or during hospitalization, oral vancomycin duration, severity of disease parameters (white blood cell count, SCr, hypotension, shock, ileus, megacolon).

Data collection will occur for patients admitted to St. Luke's Hospital from May 1, 2014 to May 1, 2017. The pre-intervention arm will be patients treated at St. Luke's Hospital between May 1, 2014 and August 1, 2016. Pre-intervention patients will be identified based upon a report that identifies patients older than 65 years of age and receiving the antibiotics outlined above. If patients meet all three "high risk" criteria, they will be matched according to antibiotic received with the post-intervention arm. The post-intervention arm will be included through April 1, 2016 and evaluated from November 1, 2016 through May 1, 2016. All patients meeting criteria and consenting to treatment will be included. The study will target a total of 100 patients in each arm.

Statistics

The difference in the primary outcome will be assessed using chi-square and Fisher's exact, as appropriate. CDI severity (mild-moderate, severe, fulminant) will be assessed using chi-square and time to CDI occurrence will be analyzed using a Kaplan-Meier curve.

Data Handling and Record Keeping

Data will be stored on a password-locked computer. The computer is located in the clinical pharmacy office which is locked and requires a key for access during off hours. Patient data will

be collected from electronic records that require a username and password for access. Patient identifiers will be removed when sharing information with others.

References

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