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The Effect of a Clinical Pathway on Reducing the Rate of Healthcare-Onset *Clostridioides difficile*

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ABSTRACT

Introduction. Stool assays used to diagnose *Clostridioides difficile* infection (CDI) do not differentiate acute CDI from asymptomatic carriers, which contributes to a falsely elevated rate of healthcare-facility onset (HO) CDI when CD stool assays are inappropriately ordered. The aim of this study was to investigate the rate of HO-CDI before and after implementing a mandatory clinical pathway prior to ordering stool tests when suspecting CDI.

Methods. A single-center retrospective observational study was conducted that spanned 12 months. All patients who developed diarrhea 48 hours after being admitted and whose primary physician requested a CD stool assay were included in the study. The intervention consisted of a mandatory sequence of questions that allowed providers to order a CD stool assay only if clinically indicated.

Results. Differences in HO-CDI rates pre- and post-intervention were analyzed. The HO-CDI rate during the pre-intervention and post-intervention periods were 24.1 and 0.0, respectively ($p = 0.023$).

Conclusion. A marked reduction of the rate of HO-CDI occurred after implementing a mandatory clinical pathway. Setting up a mandatory pre-testing questionnaire could decrease the misclassification of asymptomatic carriers as HO-CDI and the unnecessary prescription of antibiotics in situations where it is not indicated.

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INTRODUCTION

Clostridioides difficile (CD) is an anaerobic, spore-forming, gram positive bacillus.[1] It is a well-known colonizer of the human colon and is transmitted via the fecal-oral route. *Clostridioides difficile* infection (CDI) symptomology ranges from mild diarrhea to life-threatening toxic megacolon and is an important cause of infectious disease death in the U.S. In 2011, *C. difficile* was estimated to cause almost one-half million infections and nearly 30,000 deaths in the U.S., resulting in excess of $4 billion healthcare dollars.[2] Established risk factors for developing CDI include antibiotic therapy in previous 90 days, elderly patients, extended hospitalization, inflammatory bowel disease, cirrhosis, and chemotherapy.[3] Unfortunately, up to 50% of the antibiotics prescribed in the hospitals were unnecessary.[4] In addition, inappropriate prescribing practices placed patients at increased risk for *C. difficile* infections.[5]

Asymptomatic *C. difficile* carriers play a role in transmission and contribute to healthcare-facility onset CDI (HO-CDI) rate.[6] Several studies have embarked on various screening and isolation of asymptomatic carriers upon hospital admission. Longtin et al.[7] and others[8-10] highlighted that detecting and isolating *C. difficile* carriers upon admission may result in reduced incidence of HO-CDI. However, the updated Infectious Disease Society of America (IDSA) *C. difficile* practice guidelines did not make a recommendation in regard to screening and isolating asymptomatic carriers due to insufficient evidence.[11]

Current prevention of HO-CDI focuses on early and appropriate diagnostic detection. The IDSA and the American College of Gastroenterology (ACG) both recommended using a multi-step algorithm: glutamate dehydrogenase (GDH) and CD toxin assay, followed by nucleic acid amplification test (NAAT), or NAAT followed by a confirmatory test such as enzyme immunoassay (EIA) for toxin A/B.[12] However, approved stool enzyme immunoassay (EIA) toxin tests vary greatly in sensitivity.[13-15] NAAT can be used alone and is recommended by the IDSA in facilities that have agreement between clinicians and laboratory personnel to only test samples from patients meeting the CDI diarrhea definition. In addition, these samples should not be from patients receiving laxatives.[11]

In quarter 2 of FY2018, our healthcare-facility onset *C. difficile* rate spiked up to 24.10 from a historical baseline of 3.62. The hospital's Infection Control Team identified the cases for review by the Antimicrobial Stewardship Team. A deep dive analysis showed that the acquired cases met the definition of HO-CDI. The cases were not a result of poor cleaning practices, poor hand hygiene, or poor personal protective equipment use by the hospital staff. Rather, the majority of the cases never met the clinical justification for testing, symptoms were present on admission and not tested in an appropriate window, or had received laxatives. Consequently, this information prompted the Antimicrobial Stewardship Team to implement a mandatory clinical pathway prior to ordering the polymerase chain reaction (PCR) CD toxin assay that allows the physician to order the test only when appropriate. We hypothesized that this would decrease the number of CD carriers who developed diarrhea secondary to other causes that are misclassified as HO-CDI.

METHODS

Hospital Setting and Population. This single center study was conducted at the Robert J. Dole Veteran Affairs Medical Center (VAMC), a 41-bed, academic hospital with eight intensive care unit (ICU) beds. All rooms have alcohol-based hand sanitizer and are equipped with precaution signage, isolation gowns, and gloves. The microbiology department utilized the following molecular test: Cepheid® PCR, which detects the *tcdB gene* for toxin B, binary toxin (CDT) gene sequences, and a deletion in the *tcdC gene*. The study period started on January 1, 2018 and ended on December 31, 2018. The patients included in the study were all patients (male and female) above the age of 18 admitted to the VAMC that met the following criteria: the patient developed diarrhea 48 hours after being admitted whose primary physician had a high index of suspicion for HO-CDI and requested a CD stool study. The following patients

were excluded: patients that developed diarrhea less than 48 hours following admission and patients admitted from community living centers.

Study Design. This study was exempted by the Veterans Integrated Service Network 15 Institutional Review Board since it was a quality improvement project. A one-group pretest/post-test quasi-experimental study was conducted using a double post-test and non-equivalent dependent variable via a retrospective and non-randomized observational design. Quasi-experimental studies (QE) follow a hierarchy with the following notation: (O1a, O1b) X (O2a, O2b, O3a, O3b; Figure 1).[16] Contact precautions limited readily available options for a non-equivalent variable. Methicillin-resistant Staphylococcus aureus (MRSA) was selected as the control variable, as the pathogen required the same contact precautions and would not be impacted by the intervention.

Each observation period corresponded to a Veteran Affairs fiscal quarter. A VA fiscal year (FY) begins in October and ends in September. To adjust for seasonality and observation bias, a two post-intervention window was utilized. Maturation bias is limited by the nearly parallel occurrence of study implementation, and the beginning of the academic year with incoming first year medical residents. Rates of HO-CDI and hospital acquired MRSA (HA-MRSA) were determined for the pre-intervention period FY2018 Quarter 2 (2018: Jan., Feb., Mar.) and compared with the post-intervention periods. During the intervention period FY2018 Quarter 3 (2018: Apr., May, Jun.), immediate action included educating medical staff about appropriate testing; however, education only provided a short-term effect and should not be exclusively utilized.[11,17] The intervention consisted of a clinical pathway built with a logical sequence of questions. The clinical pathway was instigated on June 18, 2018, with a six month, post-intervention window via post-intervention period 1 (O2a, O2b) and post-intervention period 2 (O3a, O3b) corresponding to FY2018 Quarter 4 (2018: July, Aug., Sept.) and FY2019 Quarter 1 (2018: Oct., Nov., Dec.), respectively.

Figure 1. Quasi-experimental studies hierarchy. Quasi-experimental design abbreviations: | O1a, O1b | : pre-study period, variables a & b; | X | : intervention to variable a only; | O2a, O2b | : post-period # 1; | O3a, O3b | : post-period #2.

CDI Infection Control Measures and Rate Calculations. Patients with suspected CDI were placed under contact isolation precautions empirically awaiting the confirmation of the diagnosis.[11,18] In accordance with the VA standard of practice, all patients with MRSA identified on culture or nasal polymerase chain reaction (PCR) were placed in contact precautions empirically until the presence of the pathogen was confirmed. Contact isolation precautions remained for the duration of the patient's hospitalization. Active surveillance for MRSA and CD was performed by the infection preventionists and the multi-drug resistant organism coordinator by data collection in the VA Inpatient Evaluation Center.

Intervention. Prior to July 1, stool samples were collected by nursing staff and sent to the laboratory. The microbiology department utilized the following molecular test: Cepheid® PCR, which detects the *tcdB gene* for toxin B, binary toxin (CDT) gene sequences, and a deletion in the *tcdC gene*. Stool samples were tested as part of a one-step PCR assay targeting the *tcdB gene for toxin B*.[7,14] Starting July 1, 2018, providers, nurses, and laboratory staff were required to comply with a clinical pathway, which consisted of a series of questions that ensured that the stool test was not ordered inappropriately (Figure 2). Providers were allowed to order the test only when the following criteria were met: the patient had clinically significant diarrhea (more than three bowel movements within 24 hours); the patient was not on laxatives over the preceding 48 hours; the patient did not have a negative CD stool test within the last week; and the patient did not have a positive CD stool test within the last month (Figure 3).

The goal of this intervention was to decrease the number of identified asymptomatic CD carriers that were misclassified as HO-CDI. By correctly completing the clinical pathway, providers were able to order the CD toxin PCR. Nurses were required to print the completed clinical pathway order and send it with the specimen to the laboratory for processing. Laboratory staff were instructed not to process any specimen if not unformed and without the accompanying completed clinical pathway order.

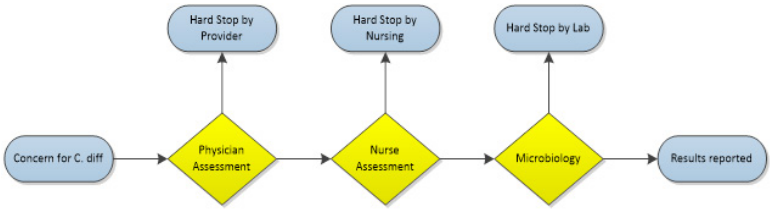

Figure 2. *C. difficile* clinical pathway utilized for this study.*
*Hard Stop by Provider: see Figure 3. Hard Stop by Nursing: cessation of pathway if patient with formed stool upon collection. Hard Stop by Lab: stool specimen received without completed physician decision-making algorithm order or receipt of formed stool.

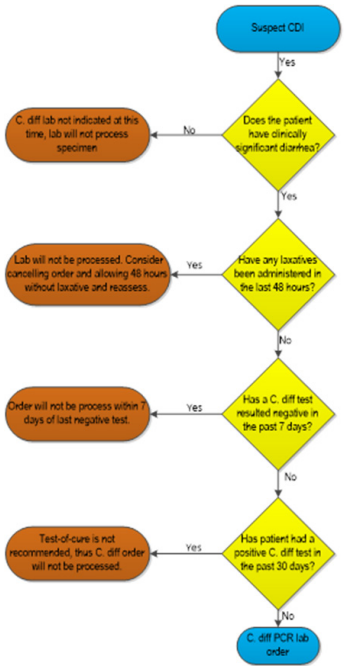

Figure 3. Physician decision-making algorithm prior to *C. difficile* PCR order.

Outcomes. Change in the HO-CDI incidence rate per 10,000 patient-days after implementation of the intervention at the Robert J. Dole VA Medical Center was selected as the main outcome. No change in the non-equivalent control variable would assist in determining if change in HO-CDI incidence rate is secondary to the intervention. The secondary outcomes that were monitored were provider and laboratory clinical pathway compliance.

Overall differences in HO-CDI and HA-MRSA rates in the pre- and post-intervention periods were analyzed using Poisson regression models by including only a pre/post predictor variable. Poisson mixed effects models were utilized with the outcome as the detection rate. Rates were reported per Centers for Disease Control National Health Safety Network criteria (CDC-NHSN) unless otherwise noted. Statistical analyses were performed using SAS V9.4 (Cary, NC) and SPSS V24 (Armonk, NY). P-values less than 0.05 were considered significant.

RESULTS

The incidence rates of HO-CDI by testing during the pre-intervention (O1a) and post-intervention periods 1 (O2a) per 10,000 patient-days were 24.1 and 0.0, respectively. This was statistically significant (p = 0.023). Statistically significant (p = 0.019) rates were noted while comparing the HO-CDI rates for O1a, 24.1, and O3a, 0.0, as well. MRSA comparator rates during the study periods were all 0.0 and showed no statistical significance difference (Table 1). Further case analysis revealed that of the six cases identified in the pre-intervention period, four of the patients likely were colonized (one had formed stool and three were on laxatives). Only two of these six cases were true HO-CDI. Adjusted calculations accounting for colonization vs. true HO-CDI in the above calculations still showed significance.

Provider and laboratory compliance showed greater than 90% compliance for study variables during the study periods. There was one month where the clinical pathway compliance dropped when the primary physician requested the testing to be completed for suspected fulminant CDI (in a patient with ileus and toxic megacolon) even though the criteria were not met (Figure 4). That was considered an appropriate deviation and an amendment was added to the clinical pathway post-study completion to allow testing of such cases.

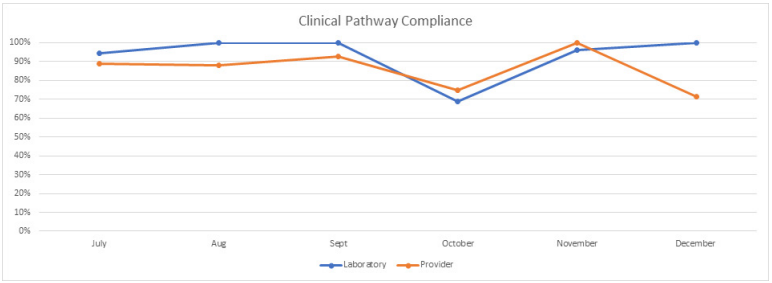

Figure 4. Laboratory and provider compliance with clinical pathway and algorithm.

DISCUSSION

HO-CDI makes up the majority of nosocomial infections in the United States. In 2013, the CDC classified CDI as an urgent threat associated with a substantial financial burden to the healthcare system.[2,19,20] Numerous efforts were set forth to decrease the rate of HO-CDI, such as instating facility antimicrobial stewardship programs, infection prevention, and reduction in unnecessary prescriptions of antibiotics and proton-pump inhibitors. Some progress was seen in a recent study highlighting an overall decrease in HO-CDI among the 170 VAMCs (10.87 to 6.41 per 10,000 patient-days) over a 10-year time period (2006 to 2016).[21] Despite compliance with preventative measures, the incidence of HO-CDI remains high.

Given the elevated prevalence and morbidity associated with CDI and wide availability of CD stool assays, clinicians are more likely to test for CD in any patient that develops diarrhea during the hospitalization. The increased incidence of CDI over the past decade correlated with increased use of molecular-based testing methods.[21,22] Between 2010 and 2015, the number of patients tested with PCR-based tests among the VAMCs increased from 33% in 2010 to over 80% in 2015.[23]

Table 1. Incidence rates of HO-CDI* and MRSA in the pre/post intervention period(s).**

	Pre-Intervention Period (a)	Post-Intervention Period 1 (b)	Post-Intervention Period 2 (c)	Change between (a) and (b)		Change between (a) and (c)	
				Rate (95% CI)	p-value	Rate (95% CI)	p-value
HO-CDI	24.1	0	0	24.1 (3.34 - 44.86)	0.023	24.1 (4.01 - 44.18)	0.019
MRSA	0	0	0	0	0.92	0	0.95
Patient-days	2,490	2,148	2,295				
PCR orders	28	8	12				

Abbreviations: HO-CDI: healthcare-facility onset *Clostridioides difficile* infection; MRSA: methicillin resistant Staphylococcus aureus. Incident rate ratio obtained in an adjusted multivariate Poisson regression.
*HO-CDI incident rates are expressed as CDIs per 10,000 patient days.
**MRSA incident rates are expressed as MRSA infection per 1,000 patient days

Physicians often overlook alternative reasons that cause acute self-limited diarrhea such as being on antibiotics, bed rest during hospitalization, tube feeds, change in dietary habits, nutritional supplements, daily stool softeners, medication side effects, and irritable bowel syndrome.[11] Subsequently, when the stool test indicates the presence of CD, patients are labeled with HO-CDI and are treated accordingly. These tests, however, do not differentiate between patients with an acute CDI and CD carriers.[21,24] Another concerning situation is when testing for a symptomatic patient results in a positive PCR test and a negative toxin assay. Patients are more likely to be treated for CDI since they are symptomatic.

To address this dilemma, creating a clinical pathway based on the physician's judgment prior to ordering the CD stool molecular testing should limit the amount of misclassification of asymptomatic carriers. This could be an alternative to testing every patient presenting to the hospital to ascertain their CD colonization status.[7] Decreasing the number of asymptomatic CD carriers misclassified as HO-CDI would reflect a more accurate rate of HO-CDI and would decrease the number of patients inappropriately treated for CDI.

In our study, implementing a mandatory clinical pathway that takes into account the physician's judgment prior to ordering the CD stool test has decreased the number of tests that were ordered significantly. This, in turn, decreased the rate of HO-CDI from 24.1 per 10,000 patient-days pre-intervention to 0.0 per 10,000 patient-days post-intervention maintained over a six month period. The clinical pathway used in our study inquired about the clinical significance of diarrhea, the use of laxatives in the last 48 hours, and whether CD test has resulted positive within the last 30 days and negative within the last seven days. Loo et al.[10] demonstrated that most CDIs are due to the North American pulsed-field gel electrophoresis type 1 strain, whereas asymptomatic patients were colonized by different strains. Identifying patients that were asymptomatic carriers could be unnecessary as well since the colonization strain is generally not the toxicogenic CD strain that is most associated with the development of CDI.

Limitations. This study has several limitations with one being the retrospective study design. It was limited to a single center in which the intervention was performed. Community acquired CDI, affiliated community liver center CDI, and HO-CDI outside the study period were excluded. External validity may be limited by our facility's veteran population consisting predominately of elderly Caucasian males; thereby, extrapolating the study findings to a more diverse population may be hindered. During the study, a limitation was noted in that patients presenting without diarrhea and fulminant CDI could result in a missed case of CDI. Currently, no molecular diagnostic test has been approved to differentiate between asymptomatic carriers and acutely infected patients. Different molecular detection tests are commercially available and if utilizing a multi-plex PCR that detects the *tcdA gene* for toxin A, in addition to testing for the *tcdB gene*, it is possible that different results would be obtained. The difference in molecular testing sensitivity and specificity was outside the scope of this study. Regardless, all molecular detection tests should be interpreted in a symptomatic patient presenting with associated risk factors.[24]

The study has numerous strengths and was designed to account for prototypical bias inherent in quasi-experimental studies. To adjust for seasonality and observation bias, a two post-intervention window was utilized. Maturation bias also was a limiting factor: the time period during which the intervention was implemented occurred in parallel with the beginning of the medical residents' academic year and incoming first year residents. Regression to the mean was minimized by taking repeated measurements with two post-test study periods. The selected control variable was as prevalent as CD in the study population, it was not affected by intervention and required the same standard of care as our variable of interest.

CONCLUSION

Implementing a mandatory clinical pathway prior to ordering a stool assay for detecting *C. difficile* in hospitalized patients with new-onset diarrhea could decrease the misidentification and misclassification of asymptomatic carriers as HO-CDI. This in turn would help to identify the true rate of HO-CDI and avoid unnecessary prescription of antibiotics in situations where it is not indicated otherwise. Executing this clinical pathway occurs at no additional cost to patients and healthcare facilities and offers more benefit than harm to patients. It would be very beneficial to trial it in larger hospitals to see if the results are reproducible and if the incidence of HO-CDI is as elevated as it is currently reported.

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