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Major article

Real-time polymerase chain reaction testing for *Clostridium difficile* reduces isolation time and improves patient management in a small community hospital

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Isolation reduction
Accurate testing
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Background: The impact of a switch from a toxin A/B enzyme immunoassay (EIA) to a polymerase chain reaction (PCR) method for detection of toxigenic *Clostridium difficile* was assessed for *C difficile* infection (CDI) rates, patient isolation-days, and CDI-related treatment.

Methods: A 6-month retrospective study was done on symptomatic patients tested by the toxin A/B EIA and PCR assays. Data on the number of *C difficile* tests ordered, patient isolation-days, and treatment with metronidazole or vancomycin were collected. CDI rates were reported as cases per 10,000 patient-days, and differences between both groups were compared by χ^2 and Z-test analysis.

Results: The CDI incidence was 11.2 and 12.7/10,000 patient-days in the EIA and PCR test periods, respectively ($P = .36$). Health care-associated CDI decreased from 4.4 per 10,000 patient-days during EIA testing to 0.9 per 10,000 patient-days during PCR testing ($P = .02$). A significant decrease in patient isolation-days ($P < .00001$), tests ordered ($P = .002$), and metronidazole treatment for patients with a negative *C difficile* test ($P = .02$) was observed with PCR testing.

Conclusion: PCR testing is a viable option for small community hospitals, providing accurate and timely results for patient management and infection control. This can potentially lead to improved outcomes, increased patient satisfaction, and significant hospital cost savings.

Clostridium difficile is an intestinal anaerobic bacterium found in 1% to 3% of healthy adults and is the leading cause of antibiotic-associated diarrhea in health care facilities.[1-3] A recent survey of US hospitals by the Association for Professionals in Infection Control and Epidemiology estimated that the incidence of *C difficile* infections (CDI) is 13 per 1000 in-patients and that approximately 109,000 patients die annually from CDI, which is higher than previously estimated.[4] In addition to increasing a patient's length of hospital stay, the cost of managing CDI is a nonreimbursable expense to many health care facilities. The recent guidelines by the Society for Healthcare Epidemiology of America and the Infectious Diseases Society of America address current practices for diagnosis and management of CDI patients, but many research gaps still exist.[5]

In the past 5 years, Pocono Medical Center observed an increase in CDI cases among patients admitted to the facility, as well as during their hospitalization. In February 2008, environmental cleaning routines were changed, and isolation signs directing health care workers and visitors on hand hygiene were installed.[6] When CDI rates spiked again in December 2008 despite educational and disinfection efforts, a new policy was initiated in which symptomatic patients were presumptively placed in isolation until toxigenic *C difficile* was ruled out by toxin A/B enzyme immunoassay (EIA), the test method used since 2002. However, after several incidents of hospital-onset CDI in roommates of toxin A/B EIA-negative patients, the requirement for removing a patient from isolation was changed from 1 to 3 negative toxin A/B EIA stools. Although this appeared to control CDI transmission for some time, concerns were raised that patients remained in isolation longer than necessary, contributing to excess work load for care providers, increased costs for additional personal protective equipment, and repeat patient testing. Furthermore, this approach did not necessarily change the physician's practice of treating symptomatic patients regardless of the test results, and patient satisfaction was poor as a result of prolonged isolation.

Polymerase chain reaction (PCR) assays have demonstrated higher sensitivity (93%-100%) than toxin A/B EIA (50%-73%) or cell culture cytotoxicity (58%-76%) methods[7-9] for detection of toxigenic *C difficile* in symptomatic patients. The objective of this study was to assess the impact of switching from toxin A/B EIA to a rapid

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PCR-based method for toxigenic *C difficile* detection on overall CDI rates; health care-onset, health care facility-associated (HO-HCFA) CDI; antibiotic therapy; and isolation-days associated with assessment and management of CDI.

METHODS

Patient setting

Pocono Medical Center is a 239-bed, nonprofit, community hospital in northeastern Pennsylvania, providing emergency and acute care services to the community as well as its transient population. Approximately 12,600 patients are admitted each year, and the Emergency Department is among the busiest in the state. An aging population (>65 years) comprises approximately 41% of patient admissions. In February 2010, the BD GeneOhm Cdiff assay (BD Diagnostics, Quebec, Canada) was implemented for detection of toxigenic *C difficile* to facilitate the diagnosis of CDI and symptomatic patients were pre-emptively placed in isolation until one PCR test came back negative. This was a change from the previous practice of requiring 3 negative stools by toxin A/B EIA for patient removal from isolation.

Study design

A retrospective study entailing chart review for in-patients tested for the presence of toxigenic *C difficile* during 2 time periods was undertaken. Group 1 comprised patients tested by the *C difficile* toxin A/B II EIA test (Techlab, Blacksburg, VA) for a 6-month period from August 2009 to January 2010. Group 2 patients were tested by the BD GeneOhm Cdiff assay (BD Diagnostics) between February 2010 and August 2010. This study constituted a quality improvement project and, therefore, was exempted by the Institutional Review Board.

Infection control practices

Patients with diarrhea in group 1 were pre-emptively placed in isolation until 3 stool samples were negative for the presence of toxigenic *C difficile* by the toxin A/B EIA method, the isolation practice since December 2008. Patients in group 2 were also placed in isolation but removed if a single negative PCR result for toxigenic *C difficile* was obtained. Contact precautions with gowns and gloves were used by staff on entry into the patient isolation rooms. Standard infection control practices, which were implemented in February 2008 and included enhanced environmental cleaning and hand hygiene, remained unchanged during both study periods.

Data collection and analysis

The following data for all patients tested for toxigenic *C difficile* by either toxin A/B EIA or PCR were collected for both study periods: primary diagnosis at admission, secondary diagnosis during hospital stay (if applicable), number of *C difficile* tests ordered, days to first *C difficile* test order, laboratory test results, length of patient isolation, and duration of antimicrobial treatment with metronidazole or oral vancomycin. Data collection and subsequent analysis were performed by 2 independent operators to minimize potential bias in the results. The incidence of CDI (overall and health care-associated) was measured as the number of CDI cases per 10,000 patient-days. Differences in CDI rates between the 2 study groups were determined using the Z-test of rates, and CDI rates were also established for the 12-month period after implementation of PCR. A χ^2 analysis was used to compare categorical variables (isolation-days, number of tests ordered, antibiotic therapy, and admission diagnosis) between the 2 study groups. A 1-sided P value of $<.05$ was considered statistically significant.

Definitions

Symptomatic patients were considered to have CDI if they had a positive *C difficile* toxin A/B EIA test (group 1) or a positive BD GeneOhm Cdiff assay result (group 2). Health care-associated infection surveillance was performed using standard Centers for Disease Control and Prevention (CDC) definitions for both phases of the study.[10] A case of HO-HCFA CDI was defined as a patient whose CDI symptoms occurred more than 48 hours after admission to the hospital. Patients in group 1 (toxin A/B EIA) who were symptomatic on admission but had a positive test greater than 72 hours (eg, first test negative, second or third test positive) were not considered HO-HCFA CDI and were counted as a single case.

RESULTS

Between August 2009 to January 2010, 5,603 patients were admitted to the hospital, and a total of 483 toxin A/B EIA tests was performed on 286 symptomatic patients (group 1; Table 1), of which 9.8% (28) were positive for toxigenic *C difficile*. A total of 5,925 patients was admitted during the PCR test period (February 2010 to August 2010), and 296 tests were performed on 250 patients suspected of CDI, with 11.6% (29) positive (group 2).

The overall incidence density of CDI in group 1 was 11.2/10,000 patient-days compared with 12.7/10,000 patient-days in group 2 ($P = .36$; Table 1). However, a significant decline in the HO-HCFA CDI rate was observed during the PCR period (0.9 vs 4.4/10,000 patient-days, respectively, $P = .02$; Table 1). In group 1 (toxin A/B EIA), HO-HCFA CDI comprised 52% of the total CDI cases, whereas, in group 2 (PCR), the contribution was only 16% (Table 1). In the 12-month period after implementation of PCR testing for toxigenic *C difficile*, the HO-HCFA CDI rates remained at < 3 per 10,000 patient-days (Fig 1) despite an increase in the overall CDI rate (Fig 1).

Group 1 patients accounted for a total of 1,022 patient isolation-days (Table 1). In contrast, patients in group 2 remained in isolation for a total of 364 patient isolation-days ($P < .00001$). The mean number of isolation-days per patient in the EIA and PCR test groups were 3.6 and 1.5, respectively. A statistically significant difference in the total number of tests ordered between the 2 study arms was observed; 483 EIA tests were performed compared with 296 PCR tests ($P < .002$; Table 1). The mean number of toxigenic *C difficile* tests ordered per patient was 1.7 in group 1 and 1.2 in group 2 (Table 1). The percentage of patients who had multiple tests performed was higher in group 1 (118/286, 41.3%) compared with group 2 (38/250, 15.2%; $P < .0001$; Table 1).

Of the patients tested by toxin A/B EIA, 138 were treated with metronidazole during their hospital stay, compared with 127 patients in the PCR group ($P = .43$; Table 1). Fewer patients with a negative PCR for toxigenic *C difficile* were continued on empiric therapy with metronidazole, compared with patients who were negative by the toxin A/B EIA test (Table 1; $P = .02$). Oral vancomycin therapy was given to 3 patients who were positive by toxin A/B EIA and 1 patient who was positive by PCR. Two of the 3 toxin A/B EIA-positive patients treated with oral vancomycin were only identified as positive for toxigenic *C difficile* after the second or third stool sample was tested (data not shown). In contrast, only 1 stool sample was submitted for the patient who was positive by PCR and treated with oral vancomycin.

The primary admission diagnosis of patients in the toxin A/B EIA and PCR study arms is shown in Table 2. Approximately 40% of the patients tested for toxigenic *C difficile* had gastrointestinal symptoms including diarrhea, abdominal pain, nausea and vomiting, and

Table 1
Characteristics of patients tested for toxigenic *C difficile* by toxin A/B EIA or PCR

	Toxin A/B EIA (Group 1)	*C difficile* PCR (Group 2)	*P* value
Hospital population			
Patients admitted	5,603	5,925	
Total length of stay (patient-days)	24,940	22,809	
Laboratory testing for toxigenic *C difficile*			
Symptomatic patients tested	286	250	
Total *C difficile* tests ordered	483	296	.002
Patients with >1 *C difficile* test	118	38	<.0001
Mean tests ordered per patient	1.7	1.2	
Patients positive for *C difficile*	28	29	.64
Prevalence of CDI			
Overall incidence density (per 10,000 pt days)	11.2	12.7	.36
HO-HCFA CDI (per 10,000 pt days)*	4.4	0.9	.02
Infection control practices			
Total patient isolation-days	1,022	364	<.00001
Mean patient isolation-days	3.6	1.5	.11
Antibiotic use			
Metronidazole	138	127	.43
Metronidazole with/negative *C difficile* test	38	16	.02
Oral vancomycin†	3	1	

CDI, *Clostridium difficile* infection; *EIA*, enzyme immunoassay; *HO-HCFA*, health care-onset, health care facility-associated; *PCR*, polymerase chain reaction; *pt*, patient.
*Health care-onset, health care facility-associated CDI: a patient whose symptoms developed >48 hours after admission to the hospital.
†Patients were confirmed as positive for toxigenic *C difficile* by EIA or PCR, respectively.

intestinal bleeding. Within each study group, only 1 patient was admitted with a prior history of CDI (Table 2), and these patients were promptly placed in isolation. Patients with respiratory conditions, notably pneumonia, comprised the second largest category of patients tested for CDI during their hospital stay (Table 2). Comparison of the study groups showed no significant difference in admission diagnosis particularly for gastrointestinal and respiratory symptoms ($P = .84$ and .35, respectively).

DISCUSSION

Accurate and early identification of CDI cases, along with appropriate treatment and infection control, are essential for reducing severe patient outcomes and preventing transmission. Although toxigenic culture is the most sensitive method for detecting toxigenic *C difficile*, it is technically difficult and has a long turnaround time. Rapid toxin A/B EIA tests are suboptimal in performance,[5] and glutamate dehydrogenase "common antigen" EIAs are less specific, requiring confirmation of positive results, adding to labor costs and turnaround time.[11-13] PCR testing appears to be a viable option in providing results as sensitive as toxigenic culture and with a rapid turnaround.

This study demonstrated the importance of rapid PCR testing for toxigenic *C difficile* in patient management and isolation practices in a small community hospital. A key finding was the impact of PCR testing on the overall and HO-HCFA CDI rates. Whereas there was a slight increase in the overall incidence of CDI after implementation of PCR, there were fewer HO-HCFA CDI cases (ie, patients who developed CDI during their hospital stay). Notably, the percentage of HO-HCFA cases contributing to the overall CDI rates declined from 52% in the pre-PCR period to 16% in the 6 months after PCR was implemented, and the trend continued for the another 6 months. A logical reason for the increase in the overall CDI rate is that more symptomatic patients were accurately identified as having CDI by the PCR method.

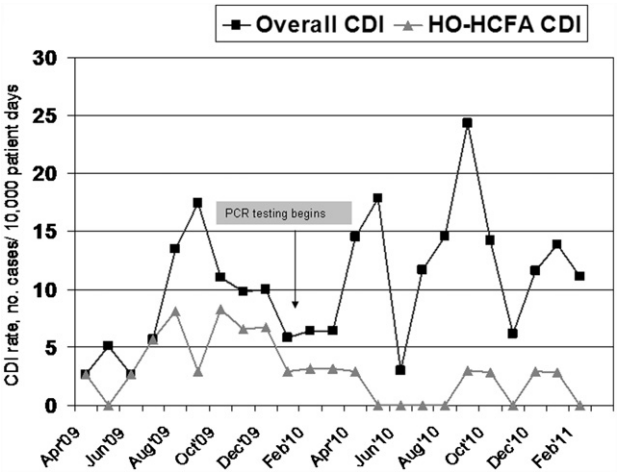

Fig 1. Distribution of health care-onset, health care facility-associated *C difficile* infection rates.

Table 2
Primary diagnosis of patients tested for toxigenic *C difficile* by toxin A/B EIA or PCR

Admission diagnosis	Toxin A/B EIA (n = 286)	*C difficile* PCR (n = 250)	*P* value
Gastrointestinal			
Diarrhea	25	21	
Abdominal pain	24	20	
Nausea/vomiting/dehydration	33	36	
Subtotal	82	77	.84
Hemorrhage	14	9	
CDI	1	1	
Ileus/intestinal/obstruction	3	3	
Intestinal perforation	0	1	
Colectomy/sigmoidectomy	1	1	
Other	5	14	
Total	106	106	.45
Nongastrointestinal			
Pneumonia	24	20	
Respiratory (other)	31	14	
Subtotal	55	34	.35
Cardiac/blood pressure	17	15	
Sepsis	11	10	
Renal failure/UTI	18	11	
Cancer/neoplastic disease	4	4	
Wounds	4	2	
Neurologic disorders	7	6	
Other	64	62	
Total	180	144	.58

CDI, *Clostridium difficile* infection; *UTI*, urinary tract infection.

Early identification of CDI patients, combined with sustained infection control practices such as environmental cleaning and hand hygiene, are essential components of a comprehensive CDI control program. Although it may be argued that standard infection control measures may have also contributed to the decrease in HO-HCFA CDI cases in this study, these practices were established for more than a year prior to the toxin A/B EIA study period, and no corresponding decline in HO-HCFA CDI rates was observed during that time. Although the PCR testing period may have increased the lag time to demonstrate effectiveness of the infection control measures, it is more likely that the decline in HO-HCFA CDI was directly due to the ability of the PCR assay to correctly identify (1) patients with CDI, who were appropriately kept in isolation, and (2) patients who did not have CDI and who could be removed from isolation, with a reduced risk of transmission to other patients.

The statistically significant reduction in isolation-days for patients suspected of CDI and the number of repeat tests ordered

during group 2 were expected, given the change in the infection control practices at the time the new test was implemented, ie, removal of patients from isolation after 1 negative PCR test result. It is important to note that, whereas these decreases were expected, the overall rate of CDI remains stable, indicating there were no negative consequences from the streamlined testing and de-escalation of isolation precautions. The new protocol with PCR testing is consistent with clinical practice guidelines that do not recommend repeat testing[5] and highlights the advantage of a more reliable test for accurate identification and management of CDI patients. Fewer days in isolation and fewer tests ordered can potentially translate into cost savings for the hospital, a decrease in staff workload, and an increase in patient satisfaction that is arguably harder to measure.

The choice of therapy for CDI is guided by disease severity, with metronidazole being used to treat mild to moderate disease and oral vancomycin therapy for severe infections.[5] In the study, the impact of PCR testing on patient treatment was difficult to assess because patients may have had metronidazole therapy for reasons other than CDI, including intra-abdominal infections and aspiration pneumonia. Because some patients had these conditions, the rationale for metronidazole therapy may be a potentially confounding factor in assessing the impact of PCR on CDI-related treatment. Nevertheless, the data showed a reduction in continued treatment with metronidazole when patients had a negative PCR assay compared with a negative toxin A/B EIA. This finding supports the idea that a rapid and reliable diagnostic test such as PCR increases clinician's trust in the results and can potentially influence the practice of empiric CDI therapy and decrease unnecessary antibiotic use, which represents a potential cost savings.

PCR testing for detection of toxigenic *C difficile* in symptomatic patients could minimize patient exposure to CDI while increasing staff compliance with isolation measures.[14] Because private rooms are provided for "presumed" CDI patients, reliable identification of patients who do not have the disease (ie, have negative stool results) optimizes bed utilization and only patients with persistent diarrhea who the physician suspects may be infectious in nature need remain in isolation. Overall, the shorter time a patient spends in isolation, the less negative impact on patient's mental well-being as well as less chance of adverse events.[15,16] Adoption of PCR testing allowed for compliance with recommended guidelines with the confidence that patients with CDI were correctly identified and placed in isolation appropriately. A further decrease in unnecessary treatment of patients with metronidazole or oral vancomycin is anticipated as physicians become more comfortable with the validity and reliability of PCR test results.

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