Original Article

Implementation of Polymerase Chain Reaction to Rule Out *Clostridium difficile* Infection Is Associated With Reduced Empiric Antibiotic Duration of Therapy

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Abstract

Purpose: The polymerase chain reaction (PCR) test has higher sensitivity and a faster turnaround time than the enzyme immunoassay (EIA) for identification of *Clostridium difficile*, although the clinical implications of these variables are not well described.

Methods: Inpatients with a negative EIA ($n = 79$) or PCR ($n = 87$) test were retrospectively evaluated. Patients were excluded if they had a positive EIA or PCR test during the same hospitalization or if they were currently receiving treatment for *C. difficile* infection (CDI) prior to admission. The primary outcome was empiric CDI antibiotic duration of therapy associated with each test method.

Results: Empiric CDI antibiotic duration of therapy was 2.31 (95% confidence interval [CI], 1.48–3.15) days for the EIA group and 0.88 (0.45–1.33) days for the PCR group ($P = .007$). Number of diagnostic laboratory tests performed per patient were 2.73 (2.64–2.83) and 1.16 (1.04–1.28) tests, respectively ($P < .001$).

Conclusion: Use of the PCR test to rule out CDI was associated with reduced duration of empiric CDI antibiotic therapy and fewer diagnostic laboratory tests performed per patient. When combined with fewer diagnostic laboratory tests performed per patient and shorter duration of contact isolation, the higher acquisition cost of the PCR test was offset, resulting in cost neutrality. These findings provide additional data to support the routine use of the PCR test.

Key Words—antibiotic, *Clostridium difficile*, enzyme immunoassay, polymerase chain reaction, stewardship

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Clostridium difficile infection (CDI) is one of the most important health-care associated infectious diseases in the United States. It is defined by the presence of diarrhea (the passage of 3 or more unformed stools in 24 or fewer consecutive hours) and either a stool test positive for toxigenic *C. difficile* or colonoscopic or histopathologic findings

revealing pseudomembranous colitis.¹ It is an increasingly common disease; the national rate of *C. difficile* hospitalizations per 1,000 adult discharges increased from 5.6 in 2001 to 11.5 in 2010.^{2,3} Additionally, CDI is also responsible for significant morbidity, which can range from mild gastrointestinal symptoms to severe complications, including pseudomembranous

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colitis, toxic megacolon, colonic perforation, and even death.^{4,5} The cost of CDI has been estimated to carry an economic burden of \$1.1 to \$3.2 billion per year in the United States.⁶⁻⁸ Timely, accurate diagnosis and appropriate treatment are essential to combat this disease effectively.

Several tests are available for the detection of *C. difficile*.¹ Because of its high sensitivity, toxigenic culture has traditionally been regarded as the gold standard for the diagnosis of CDI, but it is not clinically practical due to slow turnaround. The toxin A/B enzyme immunoassay (EIA) is largely limited by its lack of sensitivity, rendering it a suboptimal alternative approach for diagnosis, and therefore it is no longer recommended to be used alone.¹ In an attempt to improve diagnostic sensitivity, the EIA is often carried out in combination with glutamate dehydrogenase detection or performed daily for 3 consecutive tests, yielding final results in 3 days.^{1,9} The polymerase chain reaction (PCR) to detect toxin A/B genes is rapid, sensitive, and specific, yielding results in as little as 1 hour.¹ To date, most research has focused on epidemiology, utility, specificity, and sensitivity of the different tests; they have not been evaluated with regard to their impact on hospital resources, such as drug costs, isolation costs, and laboratory costs.

We hypothesized that a change from EIA to the PCR test would be associated with reduced empiric CDI antibiotic duration of therapy for patients with negative tests. Our primary outcome is empiric CDI antibiotic duration of therapy. Secondary outcomes include the number of CDI diagnostic laboratory tests (EIA or PCR) performed per patient, duration of contact isolation, and estimated total cost of treatment per patient as secondary outcomes.

MATERIALS AND METHODS

This study was approved by the institutional review board at a 500-bed academic medical center. Adult patients aged 18 to 85 years admitted to Froedtert Hospital who had a negative *C. difficile* test, either EIA or PCR, during their inpatient stay were eligible for inclusion. Patients were excluded if they had a positive EIA or PCR test during the same hospitalization as the negative test or if they were receiving treatment for CDI prior to admission.

Laboratory records were queried, selecting only those patients with negative *C. difficile* tests. Patients were included in 1 of 2 groups based on the method used to detect *C. difficile*: the EIA group (*C. DIFFICILE* TOX A/B II; TECHLAB, Inc, Blacksburg, VA) or the PCR group (Xpert *C. difficile* Assay; Ceh-

peid Innovation, Sunnyvale, CA). Independent of this study, the EIA was phased out in September 2009, at which point the PCR diagnostic test was implemented. This change in practice was not accompanied by an educational component beyond an e-mail to all clinical staff providing an overview of the new process. Other initiatives to aid with diagnosis and/or management of CDI, such as antimicrobial stewardship programs or changes in infection control policies, were not concurrently modified. One hundred consecutive patients in the EIA group were screened starting in August 2009, immediately preceding EIA discontinuation. Following a 6-month transition period, 100 consecutive patients in the PCR group were screened starting in March 2010.

Using the inpatient electronic medical record (EPIC, Verona, WI), the following information was collected for each patient: age, sex, admitting floor (dichotomous; ward vs intensive care unit), documented history of CDI prior to admission (either positive EIA or PCR), method for detecting the presence of *C. difficile* and subsequent test result, duration of contact isolation, and hospital length of stay. The electronic medication administration record was reviewed to collect the data pertaining to CDI treatment regimen: indication, drug, dosage, route of administration, frequency, duration, and total doses of antibiotic(s) prescribed for the empiric treatment of CDI.

The primary endpoint was empiric CDI antibiotic duration of therapy, defined as days of antimicrobial therapy empirically started for CDI until discontinuation based on EIA or PCR test results. Secondary outcomes included the number of CDI diagnostic laboratory tests (EIA or PCR) performed per patient, duration of contact isolation, and estimated total cost of treatment per patient. Contact isolation was initiated in all patients in whom CDI was suspected and was then discontinued once CDI was ruled out. Total cost per patient was defined as the sum of the diagnostic test cost, antibiotic therapy cost, and contact isolation cost for each patient. Diagnostic test cost per patient was calculated by multiplying the number of tests performed by test acquisition cost. Antibiotic therapy cost per patient was measured by multiplying the sum of all doses administered by the 2011 average wholesale price (AWP). Contact isolation cost per patient was calculated by multiplying the duration (days) of contact isolation by the acquisition cost of 25 isolation gowns. A mean of 25 gowns was used for each patient-day in contact isolation based on records from the materials management department.

The cost of gloves and hand hygiene was not factored into isolation cost, because their use is routine irrespective of contact precautions.

For duration of therapy, it was estimated that a sample size of 142 patients was needed to detect a difference of 1 day using a *t* test with a 2-tailed level of significance of .05 and 80% power. Comparison of continuous variables was performed using a *t* test, and dichotomous variables were compared using the chi-square test. All data were analyzed using Minitab 16 (Minitab Inc., State College, PA).

RESULTS

Of the 200 patient charts reviewed, 166 were included in the analysis (79 in the EIA group and 87 in the PCR group). Reasons for exclusion were the following: tests conducted while outpatient immediately prior to inpatient admission (*n* = 15), incomplete medical record (*n* = 10), age greater than 85 years (*n* = 8), and positive EIA or PCR test during the same hospitalization (*n* = 1). Baseline demographics were similar between the groups (Table 1).

The primary endpoint, empiric CDI antibiotic duration of therapy, was reduced from 2.31 days (95% confidence interval [95% CI], 1.48-3.15) for the EIA group to 0.88 days (95% CI, 0.45-1.33) for the PCR group (*P* = .007) (Table 2). This resulted in a reduction of 3.33 doses administered per patient (Table 3). Additionally, 81% of patients in the PCR group were not initiated on empiric antibiotic therapy while awaiting test results, compared to 61% in the EIA group. Diagnostic laboratory tests performed per patient were reduced by 42%, from 2.73 (95% CI, 2.64-2.83) for the EIA group to 1.16 (95% CI, 1.04-1.28) for the PCR group (*P* < .001) (Table 2). Duration of contact isolation was also reduced from 1.46 days (95% CI, 0.61-2.32) in the EIA group to 0.62 days (95% CI, 0.08-1.32) in the PCR group (*P* = .131). The diagnostic test cost per patient was lower in the EIA group, whereas therapy cost and contact isolation cost were less in the PCR group (Table 2). When these 3 costs were combined, the total treatment cost per patient did not differ between groups: \$69.54 (95% CI, 43.36-95.73) and \$65.97 (95% CI, 46.61-85.34) for EIA and PCR groups, respectively (*P* = .828).

Table 1. Baseline demographics and characteristics of study population

Demographics and characteristics	EIA (<i>n</i> = 79)	PCR (<i>n</i> = 87)	<i>P</i>
Age in years, mean (CI)	55.9 (52.54-59.30)	56.8 (53.22-60.46)	.713
History of <i>C. difficile</i> , <i>n</i> (%)	4 (5.06)	6 (6.89)	.794
Hospital LOS in days, mean (CI)	15.86 (11.61-20.12)	17.83 (12.69-22.97)	.558
Male, <i>n</i> (%)	42 (53.16)	38 (43.67)	.276
Test performed in ICU, <i>n</i> (%)	13 (16.45)	13 (14.94)	.883

Note: *C. difficile* = *Clostridium difficile*; CI = 95% confidence interval; EIA = enzyme immunoassay; ICU = intensive care unit; LOS = length of stay; PCR = polymerase chain reaction.

Table 2. Primary and secondary clinical and economic outcomes

Clinical and economic outcomes	EIA (<i>n</i> = 79)	PCR (<i>n</i> = 87)	<i>P</i>
Duration of antibiotic therapy in days, mean (CI)	2.31 (1.48-3.15)	0.88 (0.45-1.33)	.007
Diagnostic test performed per patient, mean (CI)	2.73 (2.64-2.83)	1.16 (1.04-1.28)	<.001
Duration of contact isolation in days, mean (CI)	1.46 (0.61-2.32)	0.62 (0.08-1.32)	.131
Total treatment cost per patient ^a (CI)	69.54 (43.36-95.73)	65.97 (46.61-85.34)	.828
Diagnostic test cost ^a (CI)	13.67 (13.08-14.26)	37.15 (32.51-41.79)	<.001
Antibiotic therapy cost ^a (CI)	36.95 (12.70-61.20)	20.64 (5.08-36.20)	.262
Contact isolation cost ^a (CI)	19.39 (8.07-30.71)	8.19 (1.14-17.52)	.131

Note: CI = 95% confidence interval; EIA = enzyme immunoassay; PCR = polymerase chain reaction.

^aCosts are reported in US dollars.

Table 3. Empiric antimicrobial prescribing for *Clostridium difficile*

Antimicrobial prescribing	EIA (<i>n</i> = 79)	PCR (<i>n</i> = 87)	<i>P</i>
Doses administered, mean (CI)	7.24 (4.71-9.77)	3.91 (1.71-6.13)	.051
No treatment, <i>n</i> (%)	54 (68.4)	71 (81.6)	.071
Metronidazole monotherapy, <i>n</i> (%)	16 (20.2)	11 (12.6)	.211
Vancomycin monotherapy, <i>n</i> (%)	7 (8.9)	3 (3.5)	.195
Combination therapy, <i>n</i> (%)	2 (2.5)	2 (2.3)	.999

Note: CI = 95% confidence interval; EIA = enzyme immunoassay; PCR = polymerase chain reaction.

DISCUSSION

In September 2009, our institution replaced the EIA with the PCR test as the sole method for detecting *C. difficile*. We describe the impact of this change on the use of hospital resources. The most clinically significant aspect of this study is the association between implementation of the PCR test and a reduction of empiric CDI antibiotic duration of therapy. This may be a result of prescribers' ability to more rapidly rule out CDI. Additionally, fewer patients in the PCR group were initiated on empiric antibiotic therapy while awaiting test results. We believe that prescriber anticipation of rapid test results contributed to this finding, demonstrating a change in culture. However, these patients were not stratified by risk of CDI or severity of symptoms upon presentation. These confounding variables may contribute to a selection bias and may have skewed the duration of therapy, although duration of therapy was still less in the PCR group even when these patients were not factored into our analysis. Regardless, the benefits of minimizing unnecessary antimicrobial therapy are numerous and of particular importance in a health care system that has seen a steady rise in antimicrobial resistance over the last several decades and a significant reduction in research and development of novel antimicrobial agents.^{10,11}

Isolation for infectious diseases, which has been associated with increased incidence of adverse events and decreased patient comfort and satisfaction, was reduced by nearly 1 full day.¹²⁻¹⁴ These findings are consistent with those of Catanzaro and Cirone,¹⁵ who demonstrated a reduction in duration of treatment and contact isolation following transition from EIA to the PCR test in a small community hospital. Our findings suggest that these results are also applicable at a large academic medical center.

The total treatment cost per patient in our study remained unchanged. This was made possible by reductions in antibiotic therapy cost and contact iso-

lation cost, which offset the increased diagnostic test cost. This is similar to that reported by Currie,¹⁶ who suggests that the PCR test is a cost-effective option compared to EIA when treatment and isolation costs are factored into total cost. The cost analysis was conservative as it did not factor in laboratory time and resources to perform the diagnostic tests; nursing time to verify and administer medication; pharmacy time to enter, verify, dispense, check, and deliver medication; or complications resulting from additional unnecessary antibiotic administration. Consideration of laboratory burden is of particular importance; the PCR test is easier to perform, involves fewer steps, is available in batch testing and on demand, and requires fewer laboratory personnel. This is especially true if EIA is either performed in triplicate or used in combination with glutamate dehydrogenase detection, which cannot differentiate toxigenic from non-toxigenic *C. difficile* and may require additional testing. However, efficiency and turnaround time may vary from institution to institution.

The patients in each arm of our study had similar baseline demographics, which allowed for appropriate comparison between groups. Additionally, external validity is maintained, owing to the study's limited exclusion criteria. The length of hospital stay was long, at just over 2 weeks for each group. This is likely associated with the acuity of the patient population; nearly one-third of all patients spent at least one day in the intensive care unit, and 18% of patients were immunocompromised and admitted to the bone marrow transplant service, oncology service, or solid organ transplant service. An additional limitation must be considered. The retrospective, nonrandomized nature of the study limits application of the results; only an association between variables may be made rather than a cause and effect relationship. One must also consider the limited scope of the study, as it only pertains to patients in whom CDI was ruled out; these data should not be applied to

other populations. In addition, our conclusions are based on the assumption that the EIA is routinely performed in triplicate. Some have challenged this practice, suggesting that little value is gained with repeat testing. Deshpande et al¹⁷ found that the first stool sample tested produced positive results for 90.7% of cases. When samples were consecutively tested for the second and third time, an additional 6.6% and 2% of patients had positive test results, respectively. Therefore our comparisons have less validity in an institution that utilizes a single EIA result to drive practice. This study does not purport to assess the impact of a change from EIA to the PCR test on the overall use of hospital resources related to all *C. difficile* testing, treatment, and isolation, given that the use of the PCR test may be counterbalanced with increases in costs due to the increased proportion of *C. difficile*-infected patients identified with the PCR test. This was observed at our institution during the study period; hospital-acquired CDI increased from 0.92 to 1.54 cases per 1,000 patient-days.

SUMMARY

The rapid reporting of PCR test results was associated with a reduced empiric CDI antibiotic duration of therapy. When combined with fewer diagnostic laboratory tests performed per patient, shorter length of empiric antibiotic therapy, and briefer duration of contact isolation, the higher acquisition cost of the PCR test was offset and resulted in cost neutrality. These findings provide additional data to support the routine use of the PCR test.

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