American Journal of Infection Control ■■ (2017) ■■-■■

Contents lists available at ScienceDirect

American Journal of Infection Control

journal homepage: www.ajicjournal.org

Major Article

Impact of real-time notification of *Clostridium difficile* test results and early initiation of effective antimicrobial therapy

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Key Words:
Clostridium difficile
infection prevention
antimicrobial stewardship program
early initiation
time to effective therapy

Background: *Clostridium difficile* is a prominent nosocomial pathogen and is the most common causative organism of health care–associated diarrhea. To our knowledge, no studies have investigated the impact of real-time notification of culture results with rapid antimicrobial stewardship program (ASP) intervention in the setting of *C difficile* infection (CDI). The purpose of this study was to assess the impact of real-time notification of detection of toxigenic *C difficile* by DNA amplification results in patients with confirmed CDI.

Methods: This is a single-center, retrospective cohort study at a 433-bed tertiary medical center in central Kentucky. The study consisted of 2 arms: patients treated for CDI prior to implementation of real-time provider notification and patients postimplementation. The primary outcome was time to initiation of effective antimicrobial therapy.

Results: The median time to initiation of effective antimicrobial therapy decreased from 5.75 hours in the preimplementation cohort to 2.05 hours in the postimplementation cohort ($P = .001$). ASP intervention also resulted in a shorter time from detection of CDI to order entry of effective antimicrobial therapy in the patient's electronic medical record (3.0 vs 0.6 hours; $P = .001$).

Conclusions: The implementation of a real-time notification system to alert a pharmacist-led ASP of toxigenic CDI resulted in statistically significant shorter times to order entry and subsequent initiation of effective antimicrobial therapy and contact precautions.

Clostridium difficile is an increasingly prominent nosocomial pathogen and is the most common causative organism of health care–associated diarrhea.[1] This gram-positive, spore-forming, anaerobic bacillus is transmitted through the fecal-oral route and exerts its pathogenicity on susceptible patients through colonization of the colon and subsequent release of exotoxins. Exotoxins TcdA and TcdB are the pathogenic exotoxins of interest in *C difficile* infection (CDI) and are responsible for the clinical manifestations of CDI, ranging from mild diarrhea to pseudomembranous colitis.[2] The most notable risk factor for CDI is the use of antibiotics, particularly clindamycin, ampicillin, amoxicillin, cephalosporins, and fluoroquinolones.

According to a Centers for Disease Control and Prevention report describing antibiotic resistance threats, approximately 250,000 cases of CDI are reported each year in the United States, and 14,000 deaths occur annually a result of infection.[3,4] In addition to mortality, CDIs also create a substantial economic impact on the health care system. In 2008 alone, CDIs had an estimated $4.8 billion cost for acute care facilities nationwide.[5] The consequences of *C difficile* on patients, and the health care system as a whole, have made the treatment and prevention of *C difficile* a top priority.[4,5]

Antimicrobial stewardship programs (ASPs) are used in many institutions to provide a variety of services. These programs have proven particularly useful in improving the inappropriate prescribing of antibiotics that are commonly associated with *C difficile*. Studies have demonstrated that decreasing the frequency of use of certain antibiotic therapies can help to reduce the incidence of CDIs.[6,7] In addition to improving antibiotic prescribing practices, ASPs can help to rapidly implement infection control measures and to initiate effective antimicrobial therapy when CDI is present. The capability of ASPs to impact clinical and economic outcomes in patients with CDI is caused in part by rapid diagnostic tools for CDI detection. Polymerase chain reaction–based tests and other rapid diagnostic systems are now being used in many institutions for the detection of *C difficile* in stool samples. Although toxigenic stool

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Conflicts of interest: Nothing to report.

0196-6553/
https://doi.org/10.1016/j.ajic.2017.11.010

cultures are still considered the gold standard against which other diagnostic systems are compared, polymerase chain reaction–based technology is becoming a preferred method for the identification of CDI because of rapid turnaround times and improved sensitivity and specificity compared with enzyme immunoassays.[8]

The 2010 clinical practice guidelines for CDI in adults emphasize the importance of infection control measures that are aimed at reducing rates and transmission of CDIs.[8] The use of contact precautions are of particular importance when a CDI has been confirmed. Numerous studies have shown that *C difficile* spores are transmittable from the hands and clothing of health care workers who are in close contact with infected patients.[8-10] Furthermore, decreasing the time to initiation of effective antimicrobial therapy has been shown to improve patient outcomes in a variety of settings. Previous studies have focused on decreasing the use of high-risk antibiotics and instituting hand hygiene and other infection control practices to reduce the incidence and risk for transmissibility of CDI.[6,7,10,11] Although there is ample evidence to suggest that early initiation of effective antimicrobial therapy is essential to improve outcomes in patients with other serious bacterial infections,[11-13] to our knowledge, no studies have investigated the impact of real-time notification of *C difficile* test results with rapid ASP intervention in the setting of CDI. The purpose of this study was to assess the impact of real-time notification of ASP team members regarding detection of toxigenic *C difficile* strains via DNA amplification on time to initiation of effective antimicrobial therapy in patients with confirmed CDI.

METHODS

Study design

This study was conducted at a 433-bed tertiary care medical center in Lexington, Kentucky. It was a retrospective, single-center, cohort study. The preimplementation cohort included patients who were treated for CDI prior to implementation of a real-time notification system, whereas the postimplementation cohort included patients who were treated for CDI after implementation of a real-time notification system. Adult patients (≥18 years of age) with microbiologic evidence of CDI were eligible for inclusion in the study. Patients were excluded if effective antimicrobial therapy was initiated prior to CDI detection or if CDI was detected outside of the normal ASP clinical work hours. The pharmacist-led ASP team was contacted via a secure listserv when toxigenic strains of *C difficile* were detected by DNA amplification. An alert was also created in TheraDoc (Premier, Inc., Charlotte, NC), an electronic clinical surveillance system, to notify the ASP team in real time when *C difficile* was identified in the microbiology laboratory. Once a CDI was detected, the ASP team notified the patient's health care provider to ensure that effective antimicrobial therapy was initiated and that contact enteric precautions were implemented.

The study groups were further stratified based on disease severity, as defined by the Society for Healthcare Epidemiology of America and the Infectious Diseases Society of America clinical practice guidelines for CDI in adults.[8] The guidelines define 3 stages of disease severity: mild to moderate, severe, and severe-complicated. Mild-to-moderate CDI is defined by leukocytosis with a white blood cell count of <15,000 cells/μL and a serum creatinine level <1.5 times the premorbid level. Severe CDI is defined by leukocytosis with a white blood cell count of ≥15,000 cells/μL or a serum creatinine level ≥1.5 times the premorbid level. Finally, severe-complicated infection is associated with one of the following serious sequelae: hypotension or shock, ileus, or toxic megacolon. Oral vancomycin or metronidazole was considered effective antimicrobial therapy for mild-to-moderate infections. Oral vancomycin, with or without metronidazole, was considered effective therapy for infections that were classified as either severe or severe-complicated.

Patients in the postimplementation cohort were enrolled in the study if they met all of the inclusion criteria. The preimplementation cohort was compiled by matching patients to the postimplementation cohort in a 1:2 ratio and stratifying them based on disease severity. The primary objective of the study was to determine the time (in hours) to initiation of effective antimicrobial therapy as previously defined. Secondary outcomes included time to order entry of effective antimicrobial therapy, time to initiation of contact enteric precautions, all-cause in-hospital mortality, overall length of stay (LOS), 30-day readmission, and infection-related LOS.

A portion of each cohort was excluded from the final analysis that examined the time from CDI detection to initiation of contact enteric precautions. Patients were excluded from this analysis for a number of reasons, including if contact precautions were implemented prior to CDI detection, if there was no order for contact precautions in the medical record, or if contact precautions were implemented as a result of a computer-generated automated order at the time of CDI detection. Not all patients received an automated order at the time of CDI detection because of a change in the computer software. Therefore, to more accurately examine the impact of human intervention, patients with an automated order for contact precautions were excluded. The additional exclusions resulted in 12 patients in the preimplementation cohort and 19 patients in the postimplementation cohort being considered for the secondary end point analysis of time from CDI detection to initiation of contact precautions.

Statistical analysis

The Shapiro-Wilk test for normality was used to determine data distributions. Data were analyzed using a χ^2 or Fisher exact test for univariate association between qualitative variables and categorical data. An independent samples *t* test was used for 2-group comparisons of parametric data and a Mann-Whitney *U* test was used for nonparametric 2-group comparisons of continuous data. SPSS statistical software version 23 (IBM Armonk, NY) was used for all statistical comparisons. All data were analyzed using 95% confidence intervals, and *P* values of <.05 were considered statistically significant.

RESULTS

Characteristics of patient populations

The postimplementation cohort included patients who were admitted between April 14, 2016, and January 3, 2017. Supportive clinical data were used to determine disease severity. Among patients who were included in the postimplementation cohort, 31.8% were classified as mild-to-moderate infection, 27.3% were classified as severe infection, and 40.9% were classified as severe-complicated infection. In both cohorts, the presence of hypotension or shock was the only qualifying parameter for severe-complicated infection. There were no reported cases of ileus or toxic megacolon. Patients in the preimplementation cohort were matched in a 2:1 fashion based on disease severity. The preimplementation cohort included patients who were admitted between January 3, 2016, and April 13, 2016. This time frame was used to obtain a 2:1 ratio between pre- and postimplementation cohorts. The total number of patients included in the study was 66 (22 postimplementation vs 44 preimplementation). The median age was 71.5 years (interquartile range, 60.5-82.8 years) and 68 years (interquartile range, 58.3-78.5 years) in the pre- and postimplementation cohorts,