



The Impact of Switching to Two-Step Testing on Reducing Rates of Hospital Acquired Clostridioides Difficile Infection

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ABSTRACT

Background

Clostridioides difficile infection (CDI) diagnosis is challenging. Positive polymerase chain reaction (PCR) in colonized patients can impact hospital-acquired CDI (HACDI) rates. A negative toxin A/B enzyme immunoassay (EIA) as a second step can help determine colonization.

Objective

We aimed to study the impact of a two-step testing on HACDI rates and treatment.

Methods

Two-step testing consisted of positive PCR followed by EIA. Patients with positive PCR / negative EIA were retrospectively included and further classified based on treatment.

Results

Ninety-six patients were included and. Sixty-five (68%) were treated. HACDI was avoided in 18 cases (18.8%). There were more HACDI avoided in the non-treated compared to the treated group (32.3% vs 12.3%; $p=0.026$). Most non-treated patients were tested on medical-surgical units (77.4%), 49.2 % of the treated patients were tested in emergency or intensive care units. Treated patients were more likely to have leukocytosis and / or fever (66.2%) compared to non-treated patients (29%; $p=0.0009$). There was no difference in abdominal pain, diarrhea, or constipation.

Most patients had an abdominal CT (70.8%), of which colitis was found in 48.5%. Treated patients were more likely to have colitis on CT vs non-treated patients (43.1% vs 16.1%; $p<0.011$).

Compared to non-treated patients, treatment did not affect home disposition or 30-day readmission rates (80% vs 71%, $P=0.436$) and (25 % vs 29%, $P=0.63$) respectively.

Discussion

Two-step testing led to decreased HACDI rates without affecting discharge disposition or readmission rates in patients with PCR positive / EIA negative results regardless of treatment.

Keywords: Two-step testing, Clostridioides difficile, Hospital- Acquired

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Introduction

Clostridioides difficile, formerly known as *Clostridium difficile*, is a Gram-positive spore-forming bacterium (Lawson et al., 2016). It was first identified in 1978 as a major cause

for pseudomembranous colitis and antibiotic-associated diarrheal illness (Bartlett et al., 1987) and is the leading cause for nosocomial bacterial diarrhea in the western world. The diarrhea from *C. difficile* is the result of the release of toxins from pathogenic strains (Kelly and Kyne, 2011). Toxin A and



toxin B contributes to the pathogenesis of *Clostridioides difficile* infections (CDI) (Voth and Ballard, 2005) which may vary from mild diarrhea to fulminant colitis and toxic megacolon (Maroo and Lamont, 2006). Risk factors associated with the development of CDI are advanced age, current or past antibiotics use, and hospitalization (Bartlett and Gerding, 2008). Systemic antibiotics use raises the risk of contracting *C. difficile* infection 7-10 folds during the treatment course as well as for the following 4 weeks after systemic antibiotics use (Hensgens et al., 2012). The intestinal microbiome plays a vital role in the immune response, nutrition, and pathogen resistance. Antibiotics can disrupt the gut flora and lead to acute or chronic disease (Dethlefsen et al., 2008). The destabilization of the gut microbiota allows for *C. difficile* bacterial overgrowth and resultant CDI (Leffler and Lamont, 2015).

CDI tests have various degrees of sensitivity, making diagnosis challenging. For many years, the primary testing for CDI was done by enzyme immunoassay (EIA) targeting toxin A and B. EIA provided a rapid, convenient, and economical way for detection of the toxins, which is what prompted its adaptation by many laboratories (Burnham and Carroll, 2013). Both monoclonal and polyclonal antibodies are used for the detection of the toxins, but the specificity and sensitivity vary from 40% to 100% depending on the study (Burnham et al., 2013). As a result, nucleic acid-based techniques gained popularity and oftentimes have replaced EIA for the detection of CDI (Burnham and Carroll, 2013). Polymerase chain reaction (PCR) positive tests in colonized patients can impact rates of hospital-acquired CDI (HACDI) and lead to unnecessary treatment with increased cost (Polage et al., 2015). Using PCR alone without diagnostic stewardship could lead to detection of *C. difficile* DNA in a colonized patient in the absence of CDI, such as in laxative use or in patients with chronic diarrhea. A negative toxin A/B EIA as a second step can help determine colonization but is not as sensitive and could result in potentially missing or not treating a true clinical case of CDI if used alone. We aimed to study the impact of a two-step testing strategy on rates of HACDI and CDI treatment outcomes.

Methods

The project represents a quality improvement initiative aimed at reducing the incidence of HACDI through implementation of a two-step testing. We conducted a retrospective chart review in a 359-bed community teaching hospital in the United States from March 2020 to July 2021, after implementation of two-step testing in March 2020. HACDI is defined as a case of CDI that is acquired after 96 hours of admission. Colonization is defined as asymptomatic carriage of *C. difficile*. Two-step testing consisted of *C. difficile* DNA PCR, which if positive, was followed by toxin A/B EIA (Figure 1). If the EIA was found to be positive, the patient was determined to likely have *C. difficile* infection. If EIA was negative, the patient was deemed to either have *C. difficile* colonization or true infection determined by provider's judgement based on clinical symptoms, laboratory values and imaging. Patients older than 18 years with positive

PCR and negative EIA, who were tested in either the emergency department or an inpatient unit were included and further classified based on CDI treatment status. CDI treatment consisted of oral vancomycin or fidaxomicin when used for treatment of active infection (not for prophylaxis while on systemic antibiotics due to known colonization). The primary outcome was the number of HACDI cases avoided. HACDI was determined if the stool sample collected ≥ 4 days after inpatient admission tested positive irrespective of testing results prior to admission according to the National Healthcare Safety Network (NHSN) definition. Secondary outcomes included location at the time of testing, symptoms, leukocytosis, discharge disposition and 30-day readmission. Fisher's exact test was used for categorical variables (GraphPad software was used). Patient consent and (institutional review board approval was not required for this quality-improvement project.

The Standardized Infection Ratio (SIR) for CDI per the CDC NHSN is a summary metric that compares the number of observed healthcare facility-onset incident *C. difficile* events in a facility to the number predicted based on a national baseline. The SIR in fiscal year 2019, 2020, and 2021 was calculated.

Results

Ninety-six patients were included. Sixty-five patients (68%) were treated while 31 (32%) were not. HACDI was avoided in 18 cases (18.8%) with the help of two-step testing (there were 18 cases that would have met the definition of HACDI if the second step was not completed). Ten (56%) of those patients received no treatment or prophylactic CDI antibiotics. There were more HACDI avoided in the non-treated group compared to the treated group (32.3% vs 12.3%; $p=0.026$).

Overall, most toxin-negative patients initially had *C. difficile* testing ordered on a medical-surgical unit (Table 1). Most non-treated patients were tested on medical-surgical units (77.4%), whereas 49.2 % of the treated patients were tested in more acute areas such as emergency, step-down, or intensive care units.

Treated patients were more likely to have leukocytosis, fever, or both (66.2%) compared to non-treated patients (29%; $p=0.0009$), who were more likely to have neither of these symptoms (Table 2). There was no difference in abdominal pain, diarrhea, bloody stool, or constipation between treatment groups.

Most patients had an abdominal CT scan (70.8%) and of those, colitis was found in 48.5% (Table 2). Patients in the treated group were more likely to have had a CT scan completed that showed colitis versus the non-treated patients (43.1% vs 16.1%; $p<0.011$).

Finally, compared to the non-treated patients, treatment did not affect home disposition on discharge (80% vs 71%, $p=0.436$) as seen in Table 3. Additionally, Table 3 demonstrates that treatment did not affect 30-day readmission rate (25 % vs 29%, $p=0.63$). All six readmissions which

were deemed to be *C. difficile*-related were in the treated patients.

The SIR for CDI in fiscal year 2019, 2020, 2021 was calculated as 0.862, 0.952, 0.355 respectively corresponding to HACDI events of 30, 23, and 9 respectively.

Discussion

As more hospitals turn to two-step testing, more data is generated to support the use of the new protocols to reduce turnaround time, duration of stay, and overall cost to the healthcare system (Qutub et al., 2019; Polage et al., 2015).

Our investigation into the outcomes of two-step CDI testing implementation revealed that this strategy may be useful in reducing both HACDI rates and unnecessary treatment of *C. difficile* colonized patients. Many hospitals began shifting their focus to reducing rates of HACDI since the introduction of Center for Medicare and Medicaid Service's (CMS) hospital-acquired condition (HAC) reduction program. It has been reported in the literature that reducing HACDI is possible through multidisciplinary bundled approaches while using a GDH/toxin immunochromatographic assay/nucleic acid amplification test diagnostic algorithm (Schultz et al., 2018). Our hospital implemented the two-step *C. difficile* testing in addition to a multidisciplinary team approach that included infection prevention, microbiology laboratory, antimicrobial stewardship, clinical informatics, the clinical effectiveness system director, and infectious diseases physicians. Herein, we sought to evaluate the effect of changing *C. difficile* testing to a two-step method using DNA PCR and toxin A/B EIA, aiming to reduce HACDI rates in a multidisciplinary effort. Our results indicated this approach was helpful in reducing the HACDI rate in our institution by 18.8%, and in reducing the need for antibiotics such as oral vancomycin, as 32% of patients were not treated. A similar study design using two-step testing with PCR/EIA, found a 27.5% decrease in antibiotic use secondary to negative EIA, deeming patients as being colonized and not infected (Zhang et al., 2019). The impact on oral vancomycin use could influence CDI recurrence prevention since decreasing the use of oral vancomycin is important to avoid intestinal microbiome changes. It has been shown that oral vancomycin induces drastic changes in the human intestinal microbiota (Isaac et al., 2017). Johnson et al. showed that recurrence rate in patients treated with vancomycin is higher compared to patients treated with fidaxomicin (43% vs 29%), which is thought to be due to the wide spectrum of vancomycin leading to change in microbiota (Johnson et al., 2012). Furthermore, decreasing oral vancomycin use could affect the rates of vancomycin-resistant *C. difficile*. Resistant *C. difficile* is an emerging concern for hospitals (Greentree et al., 2022).

The patients identified as PCR positive and toxin negative were still placed on contact precautions until discharge. The two-step testing algorithm decreased the number of patients that were unnecessarily treated for CDI at our hospital. In our project, most of the untreated patients were tested on the medical-surgical units compared to only half of the treated patients being tested on medical-surgical units, while the other

half was tested in the emergency department, intensive care unit, and stepdown units. This may suggest that patients tested in higher acuity settings were more likely to be treated regardless of toxin results. Similarly, the adoption of two-step testing using NAAT/toxin has been shown by Dolan et al. to decrease CDI treatment, but most toxin-negative patients were still treated (Dolan et al., 2021).

Although three or more watery, non-bloody stools in a 24-hour period are the hallmark of CDI, abdominal pain associated with fever generally classifies the illness as moderate (Korman, 2015). Our project revealed that treated patients were more likely to have fever and/or leukocytosis, which might indicate treatment was pursued for at least moderate infection. Leukocytosis with WBC above 15,000 cells/ μ L, serum albumin <3 g/dL, and/or a serum creatinine level ≥ 1.5 compared to baseline are usually seen in severe disease (Surawicz et al., 2013). Although 81 of 96 patients in our quality improvement project presented with leukocytosis, the degree of white blood cell elevation, albumin level, and creatinine level was not gathered making severity classification not feasible. The findings of colitis on CT imaging in only 48.5% of our patients who had an abdominal CT is consistent with prior studies which showed that considerable amount of CDI patients had normal abdominal CT scans (39%) (Boland et al., 1994).

This project was limited by its small sample size, single center location, and risk of reviewing errors. The retrospective design may introduce unmeasured confounders and increase the risk of selection bias.

Conclusion

CDI two-step testing led to decreased HACDI rates without affecting discharge disposition or readmission rates in patients with PCR positive and toxin EIA negative results regardless of treatment status. More studies are needed to further evaluate the effect of two-step testing on HACDI rates and other outcome measures.

Declarations of conflict of interest:

No conflict of interest exist for any of the authors.

Funding:

No funding was received.

Ethics:

No institutional review board (IRB) approval was required for this project since it was a quality improvement project. This was confirmed with the IRB team.

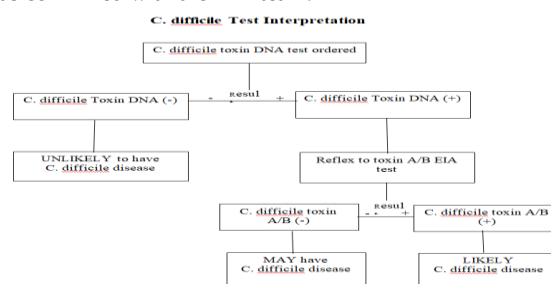


Figure 1: *C. difficile* test interpretation

Patient Location at the time of <i>C. difficile</i> testing	Total patients N=96	Treated patients N=65	Untreated patients N=31	P-value (treated versus untreated)
Emergency department	22 (22.9%)	19 (29%)	3 (9.7%)	0.039
ICU	9 (9.4%)	7 (10.8%)	2 (6.5%)	0.714
Step-down unit	8 (8.3%)	6 (9.2%)	2 (6.5%)	1.000
Medical-surgical floor	57 (59.4%)	33 (50.8%)	24 (77.4%)	0.015

Table 1: patients location at the time of *C. difficile* testing

	Total patients N=96	Treated patients N=65	Untreated patients N=31	P-value (treated versus untreated)
Leukocytosis alone	29	23 (35.4%)	6 (19.4%)	0.154
Fever alone	4	3 (4.6%)	1 (3.2%)	1.000
Both	19	17 (26.2%)	2 (6.4%)	0.028
Leukocytosis + fever + both	52	43 (66.2%)	9 (29%)	0.0009
Neither leukocytosis nor fever	44	22 (33.8%)	22 (71%)	0.0009
Abdominal pain	34 (35.4%)	26 (40%)	8 (25.8%)	0.254
Diarrhea	86 (89.2%)	58 (89.2%)	28 (90.3%)	1.000
Bloody stool	5 (5.2%)	3 (4.6%)	2 (6.5%)	0.657
Constipation	2 (2.1%)	2 (3.1%)	0 (0%)	1.000
No CT Scan done	28 (29.2%)	15 (23.1%)	13 (41.9%)	0.091
Colitis on CT scan	33 (34.4%)	28 (43.1%)	5 (16.1%)	0.011
No colitis on CT scan	35 (36.4%)	22 (33.8%)	13 (41.9%)	0.500

Table 2: signs and symptoms associated with *C. difficile* infection

	Total patients N=96	Treated patients N=65	Untreated patients N=31	P-value (treated versus untreated)
Discharged home	74 (77.1%)	52 (80%)	22 (71%)	0.436
Discharged to SNF/LTAC	8 (8.3%)	4 (6.2%)	4 (12.9%)	0.268
Not admitted	2(2.1%)	1 (1.5%)	1 (3.2%)	0.544
Transferred to another hospital	3 (3.1%)	1 (1.5%)	2 (6.5%)	0.243
CMO during stay	1 (1%)	1 (1.5%)	0 (0%)	1.000
Left against medical advise	2 (2.1%)	1 (1.5%)	1 (3.2%)	0.544
Expired	6 (6.3%)	5 (7.8%)	1 (3.2%)	0.660
Any readmission	25 (26%)	16 (24.6%)	9 (29%)	0.630
<i>C. difficile</i> -related admission	6 (6.3%)	6 (9.2%)	0 (0%)	0.172
<i>C. difficile</i> -unrelated admission	19 (19.8%)	10 (15.4%)	9 (100%)	0.170

Table 3: Patient disposition

SNF: skilled nursing facility, LTAC: long-term acute care,
CMO: comfort measure only

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