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MAJOR ARTICLE

Patient Outcomes With Prevented vs Negative *Clostridioides difficile* Tests Using a Computerized Clinical Decision Support Tool

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Background. Overtesting and overdiagnosis of *Clostridioides difficile* infection are suspected to be common. Reducing inappropriate testing through interventions designed to promote evidence-based diagnostic testing (ie, diagnostic stewardship) may improve *C. difficile* test utilization. However, the safety of these interventions is not well understood despite the potential risk for missed or delayed diagnoses.

Methods. This retrospective case–control study examined the outcomes of patients admitted to the University of Virginia Medical Center following introduction of a computerized clinical decision support tool without hard-stops designed to reduce inappropriate tests. Outcomes were compared between patients with a prevented *C. difficile* nucleic acid amplification test and those with a negative result. Chart reviews were performed for patients with a subsequent positive within 7 days, as well as those patients who received *C. difficile*–active antibiotics after implementation of the computerized clinical decision support tool.

Results. Multivariate analysis of 637 cases (490 negative, 147 prevented) showed that a prevented test was not significantly associated with the primary composite outcome (inpatient mortality or intensive care unit transfer) compared with a negative test (adjusted odds ratio, 0.912; $P = .747$). Fifty-four of 147 (37%) prevented tests were followed by a completed test within 7 days; 11 of these results were positive, resulting in a potential delay in diagnosis. Individual case reviews found that either clinical changes warranted the delay in testing or no adverse events occurred attributable to *C. difficile* infection. *C. difficile* treatment without a positive test was not identified.

Conclusions. Diagnostic stewardship of *C. difficile* testing using computerized clinical decision support may be both safe and effective for reducing inappropriate inpatient testing.

Keywords. *Clostridioides difficile*; computerized clinical decision support tool; diagnostic stewardship.

Clostridioides difficile is the most common cause of hospital-acquired infection (HAI) in the United States, resulting in significant cost, length of stay, morbidity, and mortality among hospitalized patients [1, 2]. Identifying disease accurately is essential for appropriate management and to avoid overtreatment. Guidelines recommend testing only in patients with signs and symptoms of infection coupled with risk factors (eg, receipt of antibiotics, gastrointestinal surgery, advanced age) and acknowledge the low yield of certain duplicate *C. difficile* testing [3, 4]. However, adherence to these guidelines by hospital providers historically has been mixed at best [5].

Over the last decade, >70% of hospitals have adopted highly sensitive *C. difficile* nucleic acid amplification testing (NAAT) in favor of less sensitive tests [6]. NAAT cannot distinguish between colonization and infection, and studies suggest that overdiagnosis may occur in nearly half of hospitalized patients when using NAAT [7, 8]. CDI overdiagnosis is thought to be due to inappropriate testing of patients with low pretest probability for infection [9]. False-positive tests potentially lead to overtreatment and ensuing unnecessary cost, antimicrobial resistance, and adverse drug effects.

Diagnostic stewardship of *C. difficile* test overuse and false positives may prevent unnecessary treatment; test underuse risks missed or delayed diagnoses and potential harm related to untreated conditions [10]. One common diagnostic stewardship strategy is the use of computerized clinical decision support (CCDS), or integrated software designed to educate providers and promote adherence to evidence-based guidelines. CCDS has been shown to improve provider performance [11]. However, in some circumstances CCDS may be unhelpful or even backfire, leading to unintended consequences and possibly

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patient harm [12–15]. Although a limited number of studies examining various CCDS diagnostic stewardship strategies to improve *C. difficile* test utilization have not demonstrated overt patient harm [12, 16–20], adverse patient outcomes have not been systematically examined.

We recently reported a 41% reduction in overall *C. difficile* testing following introduction of a CCDS tool bundled with provider education and a financial incentive program designed to promote appropriate testing in addition to significant reductions in duplicate negatives (≤3 days after a previous negative) and duplicate positives (≤14 days following a previous positive) [21]. Importantly, providers were allowed to override testing recommendations. National Healthcare Safety Network (NHSN)–reported hospital-onset *C. difficile* infection (HO-CDI) laboratory-identified events (occurring on hospital day ≥4) were also significantly reduced following institution of the bundled CCDS intervention, compared with pre-intervention [21]. Similar findings were seen among high-risk solid organ transplant recipients [22]. In addition, we demonstrated that the intervention was cost-effective and helped providers to accurately identify patients unlikely to have CDI (based on NAAT cycle threshold) [23, 24]. Although increased CDI-related complications or deaths were not noted hospital-wide during the study period [21], the safety of this intervention among patients with tests prevented by the CCDS was not known. In this study, we performed a retrospective analysis of outcomes for patients who were identified as having a potentially high risk for delayed diagnosis by the CCDS in order to assess patient safety with this intervention.

METHODS

Setting and Participants

The cohort included all admitted patients to the University of Virginia Medical Center (a 619-bed tertiary care hospital) between the CCDS go-live date December 5, 2016, and June 30, 2017. We hypothesized that the CCDS discouraged testing in patients with low pretest probability for infection, and therefore *C. difficile* NAAT orders "prevented" by CCDS guidance were compared with *C. difficile*–negative patients. Patients <2 years of age were excluded due to differing recommendations for testing in this age group [25]. NAATs were performed using the GeneXpert platform (Cepheid, Sunnyvale, CA, USA).

For the purposes of this study, a test was considered prevented if a *C. difficile* NAAT order was initiated in the computerized physician order entry (CPOE) system, triggering the CCDS tool, but the order was closed before it was completed. Subsequent repeated triggers were excluded to prevent duplicates, but any completed *C. difficile* test order within 7 days of a prevented test was reviewed for potential delays in diagnosis. The total delay in time was defined as the time period between initial trigger of a noncompleted *C. difficile* test order and the placement of a subsequent completed *C. difficile* test order.

Computerized Clinical Decision Support Intervention

A full description of the CCDS tool has been previously published, including a video demonstration [21]. Briefly, the 2-part CCDS tool consisted of a series of questions that an ordering provider had to answer before ordering a *C. difficile* NAAT. First, a duplicate-order information screen listed *C. difficile* test results within 28 days. Next, there was an algorithm of questions prompting the provider to consider the appropriate indications for testing (eg, "Has the patient had ≥ 3 liquid stools in 24 hours without another source?") and recommended course of action based on the response (eg, "*C. difficile* NAAT not indicated. Please Cancel.") [26]. A test could be completed in a total of 3–5 clicks, depending on the answers to the questions. A test could be ordered regardless of provider responses or lack of indication.

Data Collection

Baseline and outcome data were collected from the hospital's central data repository, a database that contains administrative, clinical, pharmacy, and laboratory data gathered from the electronic medical record. Baseline clinical data included the closest available measurement within ±48 hours of the CCDS trigger time for each test. The Charlson Comorbidity Index was used as an independent variable to estimate comorbidity burden at the time of each test attempt [27]. NAAT cycle thresholds were collected from the GeneXpert machine. While not part of our primary statistical analysis, data for *C. difficile*–positive patients were also collected. Data from a random sample of 10 cases were validated by chart review.

All outcomes occurred during the remainder of the hospitalization following the CCDS trigger. A composite primary end point of all-cause inpatient mortality or subsequent transfer to an intensive care unit (ICU) after the trigger but during the same hospitalization was used to evaluate for potential serious adverse events due to delayed CDI diagnosis and treatment.

Clinical case reviews were performed using the electronic medical records of patients treated with anti–*C. difficile* antibiotics without an associated positive test in order to assess treatment without an established diagnosis as a potential "workaround" to the CCDS. Anti–*C. difficile* antibiotics were defined as metronidazole (intravenous or enteral), vancomycin (oral, enteral, or per rectum), or fidaxomicin. Cases with a subsequent positive result were reviewed, and clinical CDI determinations were made based on 2014 NHSN clinical criteria for CDI [28] to better understand the potential impacts of delays in diagnosis that may have been caused by the CCDS. In addition, prevented cases with the primary outcome underwent detailed chart review to determine a primary clinical reason for ICU transfer and/or mortality.

Statistical Methods

P values for categorical variables were obtained using the Fisher exact test. An independent-samples *t* test was used for continuous variables (2-tailed, equal variances not assumed) except for variables without a normal distribution (Charlson comorbidity index, creatinine, length of stay), for which the Mann-Whitney *U* test was used. A multivariate logistic regression model was created including prevented or negative tests to evaluate the association between a prevented test (primary independent variable) and the composite outcome. Analyses were performed using statistical software R, version 3.4.1 (R Core Team, Vienna, Austria). This study received approval from the University of Virginia Internal Review Board (#20082).

RESULTS

Cohort Analysis

A total of 637 test attempts (490 negative and 147 prevented) that met inclusion criteria were identified from 594 individual patients. One hundrd twenty repeated prevented test attempts and 2 repeated negative results were not included because they occurred within 7 days of an initial attempt. Negative and prevented test groups had similar baseline characteristics (Table 1).

There was no statistical difference in the primary outcome (death or ICU transfer) between the groups (Table 2). Prevented group patients had shorter lengths of stay (median, 9 days negative vs 6 days prevented; $P = .004$) but were more likely to have a subsequent sample submitted to the laboratory within 7 days of the initial trigger (6.7% negative vs 36.7% prevented; $P < .001$). *C. difficile*–positive patients from the study period showed the highest rates of mortality as well as the composite outcome, compared with both the negative and prevented test groups. No difference was seen in use of anti–*C. difficile* treatment between the 2 groups (22.4% of patients in the negative group vs 22.4% in the prevented group). A significantly higher proportion of prevented patients were treated with oral vancomycin during the 7-day period after CCDS trigger compared with the negative group (Table 2).

To determine whether empiric CDI treatment was used as a workaround to the CCDS tool, the reason for administration of *C. difficile*–active antibiotic therapy was examined following the test trigger for all patients in the prevented group. Review of the subgroup of 29 cases (10 prevented, 19 negative) treated with oral vancomycin identified 6 patients (0 in the prevented group) without a recent positive test to justify treatment (defined as during the hospitalization or within the previous 28 days). Of these 6 patients, 3 cases represented empiric oral vancomycin treatment while awaiting the results of a subsequently negative test (followed by discontinuation of the drug), 2 cases received extended vancomycin tapers for recurrent CDI, and the remaining 1 immunocompromised patient was treated for presumed CDI despite a negative result. Chart reviews of the 30 prevented cases treated with metronidazole (intravenous or oral) revealed none to have received therapy inappropriately (16 patients were treated for reasons unrelated to CDI, 11 received metronidazole in relation to a recent positive *C. difficile* test, and 3 were treated empirically until a subsequent completed

Table 1. Baseline Patient Characteristics

Characteristic	Negative (n = 490)	Prevented (n = 147)	*P*	Positive (n = 131)
Age, mean (SD), y	57.7 (17.4)	60.1 (19.5)	.177	60.4 (15.7)
Gender, male	241 (49.2)	70 (47.6)	.778	69 (52.7)
Charlson comorbidity index, median (IQR)[a]	0 (0–3)	0 (0–4)	.357	0 (0–4)
0	264 (56.2)	74 (52.1)		71 (54.2)
1–2	72 (15.3)	21 (14.8)		18 (13.7)
3–4	49 (10.4)	20 (14.1)		14 (10.7)
≥5	85 (18.1)	27 (19.0)		28 (21.3)
Race			.309	
White	373 (76.1)	114 (77.6)		103 (78.6)
Black	102 (20.8)	32 (21.8)		25 (19.1)
Asian	4 (0.8)	1 (0.7)		0 (0.0)
Other	11 (2.2)	0 (0)		3 (2.3)
Serum creatinine, median (IQR),[b] mg/dL	1.0 (0.7–1.7)	1.0 (0.7–1.4)	.202	1.0 (0.7–1.7)
Vasopressors[c]	34 (6.9)	7 (4.8)	.444	
WBC, mean (SD),[d] 10^9/L	11.7 (9.5)	10.1 (6.9)	.031	11.9 (8.0)
ICU	144 (29.4)	34 (23.1)	.144	37 (28.2)

Data are presented as No. (%) unless otherwise indicated. *P* values are for negative/prevented comparisons.

Abbreviations: ICU, intensive care unit; IQR, interquartile range; WBC, white blood cell count.

[a]Charlson comorbidity index data not available for 25 cases (20 negative, 5 prevented).

[b]Baseline creatinine data not available for 11 patients (1 negative, 10 prevented).

[c]At time of test trigger.

[d]Baseline white blood cell count data not available for 16 patients (8 negative, 8 prevented, 2 positive).

Table 2. Outcomes After a Negative, Prevented, or Positive *C. difficile* Test

Outcomes	Prevented (n = 147)	Negative (n = 490)	*P*	Positive (n = 131)	*P*
Inpatient mortality or ICU transfer	23 (15.6)	94 (19.2)	.395	29 (22.1)	.166
Inpatient mortality	4 (2.7)	32 (6.5)	.101	14 (10.7)	.007
ICU transfer	22 (15.0)	72 (14.7)	.999	17 (13.0)	.634
Length of stay, median (IQR), d	6 (3–13.5)	9 (4–20)	.004	9 (4–19)	.012
New/increased leukocytosis (WBC >11×10^9/L)[a]	32 (25.2)	142 (31.6)	.189	51 (37.0)	.039
Serum creatinine increase >1.5×[a]	15 (11.5)	60 (12.7)	.888	12 (8.2)	.356
Colectomy	0 (0.0)	10 (2.0)	.127	1 (0.7)	.321
Repeat test performed within 7 d of initial attempt	54 (36.7)	33 (6.7)	<.001	2 (1.3)	<.001
Negative	43 (29.3)	32 (6.5)	<.001	1 (0.7)	<.001
Positive	11 (7.5)	1 (0.2)	<.001	1 (0.7)	.003
Rejected by laboratory	3 (2.0)	2 (0.4)	.083	0 (0.0)	.079
2nd repeat test within 7 d[b]	5 (3.4)	4 (0.8)	.034	0 (0.0)	.023
Anti-CDI treatment[c]	33 (22.4)	110 (22.4)	.999		
Metronidazole (IV/PO)[d]	30 (20.4)	103 (21.0)	.908		
Vancomycin (PO)	10 (6.8)	13 (2.7)	.024		
Vancomycin (PO) w/o a (+) test[e]	0 (0.0)	6 (2.0)	.345		

Data presented as No./total available data (%) unless otherwise indicated. *P* values represent comparisons with prevented group.

Abbreviations: CDI, *Clostridioides difficile* infection; dx, diagnosis; ICU, intensive care unit; IQR, interquartile range; IV, intravenous; PO, per os (includes medications administered rectally or per enteric tube); PR, per rectum; WBC, white blood cell count.

[a]White blood cell and creatinine data missing for 41 and 18 cases, respectively.

[b]Results of all second repeated tests within 7 days of the initial test attempt were negative.

[c]Treatment for CDI refers to PO vancomycin or PO metronidazole at any point after CCDS trigger until hospital discharge. Treatment was not assessed for positives.

[d]Chart review revealed no prevented patients who received metronidazole for CDI without a recent positive test result to justify treatment.

[d]Cases of oral vancomycin treatment without a recent positive test identified by chart review.

test result was negative, followed by discontinuation). No patients received fidaxomicin or vancomycin per rectum.

Logistic Regression

The final logistic regression model included baseline parameters with a published association with CDI-related morbidity and mortality (age [29] and CCI [30]) in addition to predictors identified by univariate analyses (race, leukocytosis, vasopressor use, or ICU location) (Table 3). Age was included as a continuous variable based on its linear relationship with CDI [29]. Multicollinearity among predictors was not detected. When adjusting for other covariates, a prevented test was not associated with inpatient mortality or ICU transfer (odds ratio, 0.912; 95% confidence interval, 0.513–1.571; $P = .747$) (Table 4).

Case Reviews

Among the 23 prevented test cases with inpatient mortality or subsequent transfer to an ICU, 10 had a subsequently negative result within 24 hours. Of the remaining 13 cases, 5 occurred in the setting of sepsis attributed to a nongastrointestinal source (pneumonia, 3; soft tissue infection, 1; and bloodstream infection, 1), 7 were attributed to primary etiologies other than sepsis (intracranial hemorrhage, 3; cardiogenic shock/congestive heart failure, 2; status epilepticus, 1; and abdominal

Table 3. Univariate Analyses of Associations Between Baseline Characteristics and Combined ICU Transfer or Inpatient Mortality

Baseline Characteristics	OR (95% CI)	*P*
Age	0.996 (0.986–1.008)	.528
Male gender	1.176 (0.787–1.760)	.428
Charlson comorbidity index	0.940 (0.870–1.008)	.097
White race (reference = nonwhite)	1.737 (1.044–3.027)	.041
WBC, 10^9/L	1.063 (1.038–1.090)	<.001
Serum creatinine, mg/dL	1.050 (0.910–1.195)	.475
Vasopressors	6.11 (3.184–11.822)	<.001
ICU	4.301 (2.833–6.561)	<.001
Prevented test (reference = negative test result)	0.781 (0.466–1.267)	.332

Abbreviations: CI, confidence interval; ICU, intensive care unit location at time of trigger; OR, odds ratio; WBC, white blood cell count.

Table 4. Multivariate Analysis of Factors Associated With ICU Transfer or Inpatient Mortality

Baseline Characteristics	AOR (95% CI)	*P*
Age	0.992 (0.979–1.005)	.208
Charlson comorbidity index	0.954 (0.875–1.032)	.255
White race (vs nonwhite)	1.706 (0.971–3.140)	.073
WBC, 10^9/L	1.046 (1.021–1.074)	<.001
Vasopressors	3.467 (1.718–7.016)	<.001
ICU	2.792 (1.752–4.446)	<.001
Prevented test	0.912 (0.513–1.571)	.747

Abbreviations: AOR, adjusted odds ratio; CI, confidence interval; ICU, intensive care unit location at time of trigger; WBC, white blood cell count.

compartment syndrome, 1), and 1 patient was undergoing CDI treatment for a previously positive result.

Following the initial trigger, 11 patients in the prevented group and 1 patient in the negative group went on to have a subsequent positive result within 7 days. The time delay in testing and clinical characteristics for these patients were reviewed (Table 5). The majority (9/11) had a polymerase chain reaction cycle threshold value (ie, ≤26.4–28.0) that predicted high organism burden, which is correlated with increased likelihood of disease (high cycle thresholds [7, 31–34]), and all 11 patients were treated for CDI. Patients with a delay of <30 minutes (patients #1–4) had few to no clinical changes documented in the chart to explain the delay. Patients with delays between 30 minutes and 24 hours (patients #5–8) all had significant clinical changes that may have influenced diagnostic decision-making. On retrospective chart review, patients #6 and #8 met clinical criteria for *C. difficile* testing at the time of the prevented test and thus may have had their tests delayed by the CCDS for ~8 and ~19 hours, respectively; however, neither patient suffered serious adverse events directly attributable to CDI during their admissions. Patients with a >24-hour delay did not meet clinical criteria for disease at the time of CCDS trigger (patients #9–11) or had a negative initial result (patient #12). Patients whose initial test was prevented and then met criteria at the time of the subsequent positive test (#7, 9, and 10) were found to have significant documented changes in clinical status that justified reconsideration for testing, such as more frequent diarrhea or fever.

DISCUSSION

We observed that tests prevented by our CCDS tool for *C. difficile* testing were not associated with increased serious adverse outcome results upon individual case review or when collectively compared with *C. difficile*–negative patients. Prevented tests were associated with shorter length of stay and similar rates of other CDI-related complications (new or increased leukocytosis, acute kidney injury, or colectomy) compared with *C. difficile*–negative patients. Empiric *C. difficile* treatment without *C. difficile* testing was not observed as an unintended consequence of the tool, similar to findings by Drees et al., who also did not observe significant vancomycin utilization without *C. difficile* testing following launch of a CCDS tool [20]. Importantly, thorough chart review of the subset of patients with a subsequent positive result following a prevented test revealed no delays in diagnosis >24 hours in patients who met CDI criteria at the time of the initial prevented test attempt, suggesting that the CCDS tool is not discouraging appropriate testing (ie, discouraging testing in patients with an elevated risk for CDI). Furthermore, all but 1 patient with a delay >24 hours had significant changes in their pretest probability for CDI to warrant retesting. The single remaining case actually had an initial negative result followed by a positive result 156 hours later.

We hypothesize that minimal time delays <30 minutes do not contribute to a significant delay in appropriate treatment but rather reflect more thoughtful use of diagnostic tests. Minimal time delays may represent providers evaluating the patient or reviewing the medical record before deciding to test following questions prompted by the CCDS tool.

Our study has relevant implications for hospitals and providers seeking to improve diagnostic management of CDI. In an era of rising health care costs, diagnostic stewardship is increasingly used to reduce unnecessary testing, and recent studies have recognized CCDS as a useful adjunctive strategy in the context of CDI [12, 17]. However, few have closely examined patient outcomes associated with these interventions.

Maintaining or improving patient safety is essential to improving quality in health care. Assessing harm among patients affected by diagnostic stewardship is especially challenging, and when reviewed in the context of *C. difficile*, outcomes have only been assessed in aggregate. A unique aspect of our CCDS tool allowed us to electronically capture patients for whom a test was attempted but not performed and stratify outcomes associated with prevented tests. This is one of few studies to assess patient outcomes associated with introduction of a CCDS that significantly reduced *C. difficile* testing [35]. To our knowledge, this is the first publication to systematically compare outcome measures using providers' interactions with a CCDS tool as a marker for prevented tests.

Several weaknesses of our study should be acknowledged. The composite outcome was designed to identify the most severe outcomes of infection; however, we did not capture less severe end points such as prolonged hospital stay. Although gross trends in *C. difficile*–related complications (ie, colectomies, mortality) were not observed postintervention [21], sample sizes may have been inadequate to detect differences. Our analysis was powered to detect an 8% higher univariate composite outcome rate (ie, 27.2% vs 19.2%) compared with negative controls. We also did not capture patient-level morbidity or mortality of patients for whom a test order was not initiated in the first place, for example, tests prevented or delayed by institutional behavior changes engendered by the bundled provider education efforts related to the tool. Conversely, prevented tests did not necessarily reflect the altered intention to order a *C. difficile* test, and about a third of prevented tests ultimately resulted in a completed test order within 7 days. Case reviews complemented population-level analyses and provided deeper insight into a select group of patients thought to be at highest risk for having a delay in diagnosis; however, by focusing on patients with a positive result within 7 days of the trigger, it is possible that not all patients at risk were reviewed.

Updated Infectious Diseases Society of America–Society For Healthcare Epidemiology of America guidelines for *C. difficile* infection, published in February 2018, now recommend 2 options to optimize use of *C. difficile* NAAT: (1) a multistep

Table 5. Case Series and Time Delays of Positive *C. difficile* Results Within 7 Days of an Initial Prevented or Negative Test

No.	Time Delay (H:M)	Prior CDI	Age, Pertinent Conditions, Diagnoses	Clinical CDI Determination[a] Initially Positive	NAAT Cycle Threshold[b]	Clinical Changes During Delay	Subsequent Hospital Course	
			Initial prevented test (n = 11)					
1[b]	00:01	Yes	75 y, chronic leukemia, septic shock	Yes GI-GE (I, VII, VIII, IX)	Yes GI-GE (I, VII, VIII, IX)	21.7	None	Multiple comorbid conditions, respiratory failure due to multifocal pneumonia, and poor prognosis; aggressive care withdrawn; died on HD 15.
2	00:01	No	45 y, paraplegia, hip abscess	No (III)	No (III)	26.4	None	Abscess drained. Due to incidental bowel wall thickening on CT, chronic diarrhea, and anticipated antibiotics, team decided to treat if +. Remained stable through discharge HD 12.
3	00:24	Yes	65 y, end-stage renal disease, confusion, and diarrhea	Yes GI-GE (I, VII, VIII)	Yes GI-GE (I, VII, VIII)	24.3	None	Confusion quickly improved (thought due to polypharmacy). Discharged HD 3.
4[c]	00:24	Yes	22 y, cystic fibrosis status post–lung transplant <1 y ago, shock, respiratory failure	No (IX)	No (IX)	20.2	None	Fungal pneumonia discovered on admission. Diarrhea in setting of tube feeds prompted + test on HD 6. Discharged home HD 86. Readmitted for progressive respiratory failure, rejection, and discharged to hospice 5 months later.
5	7:27	No	57 y, hypertension, aortic dissection (emergent repair)	No (VII)	No (III, VII)	31.0	Abdominal pain prompted abdominal CT with finding of colitis.	No significant diarrhea noted but treated in light of CT finding, + test, and history of CDI. Discharged home in stable condition HD 13.
6[c]	7:41	Yes	59 y, dementia, alcohol withdrawal, and electrolyte abnormalities	Yes GI-GE (I, VII, VIII)	Yes GI-GE (I, VII, VIII)	24.5	Poor clinical historian. Team learned of recent undertreated CDI diagnosis.	Resumed CDI treatment and discharged on HD2. Diarrhea continued and lymphocytic colitis diagnosed (endoscopy/biopsy) on subsequent admission. Cardiac arrest, died 1 month later related to new-onset CHF.
7	18:26	No	52 y, leukemia, chemotherapy (elective)	No (VIII)	Yes GI-GE (I, VIII)	22.3	Additional loose stool overnight.	Discharged same day as positive result with outpatient CDI treatment.
8	19:11	No	45 y, hypothyroidism, diarrhea, and hypokalemia	Yes GI-GIT (III, V, VI, VII)	Yes GI-GE (I), GI-GIT (III, V, VII)	35.0	Persistent abdominal pain, CT finding of nonspecific bowel wall thickening.	CDI treatment started empirically after CT and before test resulted +. Hypokalemia and diarrhea improved before discharge home HD 7.
9	66:51	No	59 y, ulcerative colitis, toxic ingestion, and UTI	No (IX)	Yes GI-GE (I)	18.6	Intervening antibiotic started for UTI followed by worsening of chronic diarrhea.	CT of abdomen, done for abdominal pain, was normal. Pain/diarrhea improved with treatment of UTI and CDI. Discharged home.
10[c]	128:44	No	44 y, acute leukemia, blast crisis	No (V)	Yes GI-GE (I, VIII, IX)	23.8	Fever and acute-onset diarrhea on the day of completed test order.	Febrile neutropenia due to multidrug-resistant bacteremia. Small bowel obstruction due to neoplastic mesenteric infiltration (confirmed on laparotomy). Ultimately discharged to hospice HD 36 with refractory leukemia and died.
11	180:23	No	55 y, mechanical heart valve, subarachnoid hemorrhage	No	No	21.3	New diarrhea after tube feed initiation, laxatives.	Diarrhea improved. Slow recovery from subarachnoid hemorrhage. Discharged home 3 weeks later.

Table 5. Continued

No.	Time Delay (H:M)	Prior CDI	Age, Pertinent Conditions, Diagnoses	Clinical CDI Determination[a] Initially Positive	NAAT Cycle Threshold[b]	Clinical Changes During Delay	Subsequent Hospital Course
Initial negative test (n = 1)							
12	156:05	No	76 y, colon cancer, diarrhea, and renal failure	Yes GI-GE (I, VIII)	Yes GI-GE (I), GI-GIT (III, VII, VIII)	20.3	Worsening diarrhea and new colitis compared with CT 7 d prior.	Renal failure improved and discharged following initial negative test. A positive test occurred 6 d later on subsequent admission with diarrhea. Improved after treatment.

Abbreviations: CDI, *C. difficile* infection; CHF, congestive heart failure; CT, computed tomography; GI-GE, gastroenteritis; GI, gastrointestinal; GTI, gastrointestinal tract infection; HD, hospital day; NAAT, nucleic acid amplification test; UTI, urinary tract infection.

[a]Based on 2014 National Healthcare Safety Network surveillance clinical criteria for gastrointestinal system infections due to *C. difficile*, gastroenteritis, and/or gastrointestinal tract infection [28]: gastroenteritis: (I) acute-onset diarrhea (>12 hours) without a likely noninfectious cause; gastrointestinal tract infection: (II) histopathologic evidence of infection (ie, pseudomembranous colitis) OR pathologic findings on (III) imaging or (IV) endoscopy plus at least 2 of the following without a recognized cause other than *C. difficile*: (V) nausea, (VI) vomiting, (VII) abdominal pain or tenderness, (VIII) diarrhea, or (IX) fever (temperature ≥38°C, regardless of cause) [28].

[b]Inpatient mortality.

[c]Discharged to hospice or death within 6 months of initial test attempt.

algorithm that includes *C. difficile* toxin EIA plus NAAT or (2) NAAT alone if accompanied by "preagreed institutional criteria for patient stool submission," which amounts to an endorsement of diagnostic stewardship as an acceptable option for improving test performance [3]. However, evidence for what factors contribute to the efficacy and/or safety (or, conversely, lack of efficacy and/or hazards) of *C. difficile* diagnostic stewardship interventions are lacking [36]. For example, our CCDS was intentionally designed so that providers could override its recommendations based on clinical discretion as a safety precaution, and 23.1% of all inpatient tests were ordered despite the CCDS indicating a potentially inappropriate test (Supplementary Table 1). However, other centers commonly employ more stringent restrictions to testing, or "hard stops," such as mandatory telephone approval ("hard stops") or protocol order canceling (eg, canceling tests requests with concurrent laxative use) that could imaginably generate scenarios of delayed or missed diagnosis and patient harm [20].

As diagnostic stewardship interventions are increasingly adopted, future trials will be required to address patient safety concerned with reducing tests for CDI and other HAIs. Outcomes measures should ideally be collected prospectively and stratified to patients at highest risk for adverse events related to reduced testing. In addition, the tradeoffs of improved test utilization through CCDS-based diagnostic stewardship require further study to weigh the possible disadvantages of increased workload, provider frustration, and alarm fatigue as increasing levels of decision support are incorporated into the CPOE.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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