Easily Modified Factors Contribute to Delays in Diagnosis of *Clostridium difficile* Infection: a Cohort Study and Intervention

Sirisha Kundrapu,^a Lucy A. Jury,^b Brett Sitzlar,^b Venkata C. K. Sunkesula,^a Ajay K. Sethi,^c Curtis J. Donskey^{a,b}

Department of Medicine, Infectious Diseases Division, Case Western Reserve University School of Medicine, Cleveland, Ohio, USA^a; Geriatric Research, Education and Clinical Center, Cleveland Veterans Affairs Medical Center, Cleveland, Ohio, USA^b; Department of Population Health Sciences, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin, USA^c

Although rapid laboratory tests are available for diagnosis of *Clostridium difficile* infection (CDI), delays in completion of CDI testing are common in clinical practice. We conducted a cohort study of 242 inpatients tested for CDI to determine the timing of different steps involved in diagnostic testing and to identify modifiable factors contributing to delays in diagnosis. The average time from test order to test result was 1.8 days (range, 0.2 to 10.6), with time from order to stool collection accounting for most of the delay (mean, 1.0 day; range, 0 to 10). Several modifiable factors contributed to delays, including not providing stool collection supplies to patients in a timely fashion, rejection of specimens due to incorrect labeling or leaking from the container, and holding samples in the laboratory for batch processing. Delays in testing contributed to delays in initiation of treatment for patients diagnosed with CDI and to frequent prescription of empirical CDI therapy for patients with mild to moderate symptoms whose testing was ultimately negative. An intervention that addressed several easily modified factors contributing to delays resulted in a significant decrease in the time required to complete CDI testing. These findings suggest that health care facilities may benefit from a review of their processes for CDI testing to identify and address modifiable factors that contribute to delays in diagnosis and treatment of CDI.

Clostridium difficile is the most important cause of health care-associated diarrhea in developed countries (1). During the past decade, the emergence of an epidemic *C. difficile* strain, termed North American pulsed-field gel electrophoresis type 1, has been associated with dramatic increases in the incidence and severity of *C. difficile* infection (CDI) in North America and Europe (1–3). In the context of these changes in the epidemiology of *C. difficile*, accurate and efficient strategies to diagnose CDI are crucial to guide management and prevent transmission. Enzyme immunoassays for glutamate dehydrogenase or for toxins A and B and real-time PCR assays for toxin genes can provide rapid CDI test results in the laboratory (4–8); the enzyme immunoassays for toxins A and B are recommended only as part of multistep testing algorithms (4, 7). However, delays in completion of CDI diagnostic testing are common in clinical practice. Identification of easily modified factors that contribute to these delays could benefit infection control programs and clinicians who manage patients with CDI.

Scheurer et al. (9) recently reported that the mean time from onset of symptoms to collection of samples for *C. difficile* testing was 2.2 days. Similarly, we reported that the mean time from onset of diarrhea to diagnosis of infection was 2 days in our hospital and 4 days in our long-term-care facility (10). In a hospital that tested for CDI using stool culture and external toxin analysis, Frenz and McIntyre (11) found that the mean time from onset of diarrhea to collection of samples for testing was 4.7 days and the mean time from sample collection to treatment was 7.7 days; an educational intervention and substitution of a *C. difficile* toxin A enzyme immunoassay for culture resulted in significant reductions in these times to 0.8 days and 2.8 days, respectively. Here, we examined the timing of different steps involved in diagnostic testing for CDI in our facility and sought to identify modifiable factors contributing to delays in diagnosis.

MATERIALS AND METHODS

Setting. The Cleveland Veterans Affairs Medical Center includes a 215-bed hospital and 165-bed long-term-care facility. Routinely, diagnostic testing for CDI was performed using an enzyme immunoassay for glutamate dehydrogenase (Wampole *C. diff* Chek-60; Inverness Medical, Princeton, NJ) as an initial screen, with positive tests being confirmed with a commercial PCR assay (Xpert *C. difficile*; Cepheid, Sunnyvale, CA). Completion of the glutamate dehydrogenase and PCR assays in the laboratory requires ~35 min and ~1 h, respectively. The glutamate dehydrogenase tests were often batched with specimens being run once at midday; samples arriving in the laboratory in the afternoon were often held to be run the following day. The laboratory rejected formed stool samples and performed repeat tests only if 7 days had elapsed after a prior test. The hospital's Institutional Review Board approved the study protocol.

Study design. We conducted a 6-month cohort study from October 2011 to March 2012 of inpatients being tested for CDI. All inpatients being tested for CDI were eligible for inclusion. Patients were excluded if they denied having unformed stools, declined to participate, or were discharged or died before being enrolled. A diagnosis of CDI was based on a positive PCR test from unformed stool in the absence of alternative explanations for diarrhea. For each patient, we determined the time required to complete different steps in the testing process. Information on the number of bowel movements per day was obtained through interviews with patients and/or family members and nurses and by review of the electronic medical record. The times of placement of orders for CDI testing, collection of stool specimens, accessing of the specimens in the Microbiology Laboratory, and completion of test results were obtained

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Address correspondence to Curtis J. Donskey, curtisjd123@yahoo.com.

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through review of the electronic medical record. CDI diagnostic testing was considered timely if the time from the CDI test order to the availability of the test result was less than or equal to 1 day. Diagnostic testing was considered delayed if the time from CDI test order to the availability of the test result was greater than 1 day.

Patient characteristics. The electronic medical record and patient interviews were used to determine variables that included age, sex, number of unformed bowel movements per day, paraplegia or quadriplegia, dementia, presence of a colostomy or rectal tube, mobility (measured routinely by nursing staff on a scale of 1 to 4 as a component of the Braden score for prediction of pressure ulcer risk as follows: 1, complete immobility; 2, very limited mobility; 3, slightly limited mobility; and 4, no mobility limitation), and test order location (medicine, surgery, intensive care unit, spinal cord injury, and long-term-care facility).

Qualitative assessment of reasons for and impact of delays in testing. Interviews were conducted with all patients and with a subset of nurses and physicians caring for the patients to obtain information on potential reasons for and impact of delays in testing. On the day the CDI tests were ordered before or after stool collection, patients and nurses were asked open-ended questions regarding why delays in specimen collection might occur. In addition, nurses were asked if they were aware of the order for stool collection, when they had been notified of the order, and if and when stool collection supplies were placed in the rooms. Patients were asked if they were aware that they were to provide stool specimens. Interviews with nurses were discontinued after 40 interviews were completed because each of the major nursing divisions (i.e., medicine, surgery, intensive care, spinal cord injury, and long-term-care facility) had participated in at least 5 interviews. Physicians caring for patients receiving empirical CDI therapy were interviewed in person or by phone regarding whether delays in diagnostic testing contributed to the decision to prescribe empirical CDI therapy. Interviews with physicians were discontinued after 22 interviews were completed because each of major services (i.e., medicine, surgery, spinal cord injury, and long-term-care facility) had participated in at least 5 interviews.

Intervention to decrease delays in testing. After completion of the investigation of reasons for delays in CDI testing, a 4-month intervention was performed from April 2012 to July 2012 to determine the impact of an intervention designed to address easily modified factors contributing to delays. We implemented an intervention to address several easily modified factors contributing to delays as follows: (i) the original specimen container with a loose-fitting lid was replaced by a screw cap container; (ii) CDI testing was made a priority laboratory test (i.e., priority tests are to have processing initiated upon arrival in the laboratory) with the expectation that test results would be available within 2 h of arrival of the sample in the laboratory; (iii) CDI testing was made a priority test for transport to the laboratory (i.e., transport staff were called to pick up and deliver stool specimens rather than waiting for scheduled pickup times); (iv) nurses received education on the importance of timely CDI testing and on appropriate labeling of specimens; and (v) physicians received education on the importance of communicating directly with nursing staff to alert them when CDI test orders were placed.

Although not considered crucial for the intervention, we also elected to change the laboratory testing protocol from a 2-step procedure to PCR as a standalone test. Based on discussions with the Microbiology Laboratory staff, the impact of making CDI testing a priority and changing from a 2-step to a 1-step test strategy was relatively minor. No additional training was required since the PCR assay was already the second step in the 2-step algorithm. Because the PCR assay used is not labor-intensive and single tests can be processed, laboratory personnel stated that the overall testing process was easier and less labor-intensive. Stool specimens were set up for the PCR assay as they arrived in the laboratory until 8 p.m.; specimens received after 8 p.m. were processed the next morning.

Statistical analysis. Distributions of clinical and demographic characteristics were compared for patients with a timely diagnosis (defined as less than or equal to 1 day from test order to diagnosis) versus a delayed

diagnosis (defined as greater than 1 day from test order to diagnosis). The times from test order to test result were compared for the baseline period versus the last 3 months of the 4-month intervention period. The Student *t* test and Wilcoxon rank sum test were used for normally and non-normally distributed data, respectively. Pearson's chi-square test, Fisher's exact test, and the Mann-Whitney U test were used for categorical data. Data were analyzed with the use of SPSS statistical software version 10.0 (SPSS Inc., Chicago, IL) and STATA 11 (StataCorp, College Station, TX).

RESULTS

Of 272 inpatients with orders for CDI testing, 30 (11%) were excluded, including 8 who declined to participate, 15 who did not have unformed stool, and 7 who were not available for enrollment due to discharge or death (Fig. 1). Of the 242 patients enrolled, 51 were not tested by the Microbiology Laboratory because stool samples either were not collected or were rejected without resubmission of samples. Of the 191 patients tested by the Microbiology Laboratory, 151 had negative test results; of those patients, 21 (14%) received empirical therapy for CDI. Of the 51 patients with orders for testing but not tested by the Microbiology Laboratory, 6 (12%) received empirical CDI therapy. Thus, 27 of 67 (40%) CDI treatment regimens were prescribed as empirical therapy for patients with negative CDI test results ($n = 21$) or with no stool samples collected for testing ($n = 6$).

Time from CDI test order to stool collection. At baseline, the mean time from CDI test order to stool collection was 1.0 day (range, 0 to 10). There was no correlation between the number of bowel movements per day and time from order to stool specimen collection (correlation coefficient, -0.02 ; $P = 0.84$). The percentages of patients whose stool samples were collected within 1 day were higher in the intensive care unit (67%) and long-term-care facility (63%) than in the medical/surgical wards (45%) and spinal cord injury unit (14%) ($P = 0.04$).

Time from stool specimen collection to receipt in the laboratory. At baseline, the mean time from collection of stool specimens to receipt in the laboratory was 0.4 days (range, 0.05 to 3). A total of 52 of 56 (93%) specimens with >0.5 day of time from collection to documentation of receipt in the laboratory were collected between 3 p.m. and 8 a.m.

Time from receipt in the laboratory to availability of test result. At baseline, the mean time from receipt in the laboratory to completion of test results was 0.4 days (range, 0.05 to 5). Two factors contributed to delays in processing of stool specimens in the Microbiology Laboratory. First, 38 of 191 (20%) stool specimens submitted were rejected and clinicians were asked to order another specimen. The most common reason (20/38; 53%) for rejection of specimens was leakage of stool from the specimen container (i.e., collection cups that did not have a screw cap top frequently leaked). Other reasons for rejection of specimens included improper labeling of specimens and an insufficient amount of specimen collected. Second, specimens were sometimes batched or held for the next day, particularly if they arrived in the laboratory in the afternoon.

Overview of time from CDI test order to result. Figure 2 provides an overview of the time from placement of orders for CDI testing to availability of test results for each of the 203 patients with stool samples collected for analysis during the baseline period, including 191 patients whose tests were completed and 12 patients whose samples were rejected by the Microbiology Laboratory with no additional specimens submitted. For the 191 patients with completed tests, the average time from test order to test

FIG 1 Distribution of subjects enrolled in the cohort study of patients with orders for *Clostridium difficile* infection (CDI) testing. *, 38 of 191 specimens tested were initially rejected by the laboratory due to leaking, improper labeling, or submission of an insufficient or wrong specimen and were resubmitted.

result was 1.8 days (range, 0.2 to 10.6), with the time from order for testing to stool collection accounting for most of the delay (mean, 1.0 day; range, 0 to 10). The time from test order to result was >1 day for 158 of 191 (83%) patients with completed tests and >2 days for 67 of 191 (35%) patients with completed tests. For the 38 patients diagnosed with CDI who did not receive empirical treatment, the average time from test order to initiation of CDI therapy was 1.7 days (range, 0.5 to 5.8). Of the 23 CDI patients requiring >1 day from CDI test order to diagnosis, 14 (61%) had delays primarily due to delays in collection, 6 (26%) had delays primarily due to rejected specimens (leaking and improper labeling) requiring recollection of specimens, and 3 (13%) had delays primarily due to delays in laboratory processing.

Characteristics of patients with timely versus delayed testing. As shown in Table 1, there were no significant differences in the assessed characteristics of the 33 patients whose CDI testing was timely (i.e., test order to result ≤ 1 day) versus the 158 patients whose testing was delayed (i.e., test order to result > 1 day).

Qualitative assessment of reasons for and impact of delays in testing. Interviews with patients, family members, and nurses were conducted on average 0.5 days after placement of the CDI order (interquartile range, 0 to 1 days). Twenty-four (10%) of 242 patients stated they were unaware that a stool specimen had been requested, and an additional 16 (7%) were aware of the request but collection materials had not yet been provided. Of 40 nurses interviewed, 8 (20%) were not yet aware of the order for CDI testing. The nurses stated that multiple factors contributed to delays in stool collection, including delays in being made aware of the order for testing, frequent patient absences from the ward for

testing or procedures, and patients not providing a specimen in a timely fashion due to confusion or infrequent bowel movements.

All 22 physicians who were approached agreed to be interviewed. All of the physicians suggested that the decision to begin empirical therapy for patients with suspected CDI was influenced by the anticipation that there might be delays in testing. All of the physicians agreed with the statement that they would be willing to defer initiation of treatment for suspected CDI with mild to moderate symptoms if they were assured that test results could be available within 6 h.

Intervention to decrease delays in testing. Table 2 shows a comparison of the 6-month baseline period and final 3 months of the intervention period (i.e., months 2 through 4). During the intervention period, 130 specimens were submitted to the laboratory for CDI testing. In comparison to the baseline period, the proportion of specimens rejected due to factors such as leaking, improper labeling, and wrong or insufficient specimens was reduced, but the reduction was not statistically significant (15 of 130 [12%] versus 46 of 241 [19%]; $P = 0.08$). In comparison to the baseline period, the time from test order to completion of diagnostic testing was significantly reduced during intervention (mean, 0.8 days [range, 0.1 to 8.2; standard deviation, 1.5] versus 1.8 days [range, 0.2 to 10.6; standard deviation, 0.8]; $P < 0.001$).

DISCUSSION

Despite the use of a fairly rapid laboratory test algorithm for CDI, the average time from placement of test orders to availability of test results in our facility was 1.8 days, with time from test order to stool collection accounting for much of the delay. We identified

FIG 2 Times from order for *Clostridium difficile* infection (CDI) testing to availability of test results for 203 individual patients with stool samples collected for analysis. A total of 191 patients had tests completed, and 12 did not (i.e., samples were rejected by the Microbiology Laboratory, and no additional specimens were submitted). The median time from test order to test result was 1.2 days (range, 0.2 to 10.6 days).

multiple factors that contributed to delays in diagnosis, some of which were amenable to simple interventions. These modifiable factors included delays in communication of the test order to nursing, not providing stool collection supplies to patients in a

timely fashion, rejection of specimens due to incorrect labeling or leaking from the container, and laboratory delays due to batch processing of specimens for once-daily glutamate dehydrogenase testing. In contrast to a previous study from our institution (10),

TABLE 1 Baseline characteristics of the 191 patients with completed CDI testing, according to the time from test order to the availability of test results^a

Patient or facility characteristic	All patients (n = 191)	CDI testing in <1 day (n = 33)	CDI testing in >1 day (n = 158)	P value ^b
Median age (yr) (interquartile range)	64 (60–74)	63 (61–73.5)	64 (60–74)	0.70
Male sex	186 (97.3)	33 (100)	153 (97)	0.58
Median no. of unformed bowel movements per day (interquartile range)	4 (3–5)	4 (3–6)	4 (3–5)	0.83
Clinical condition				
Paraplegia or quadriplegia	9 (4.7)	1 (3.0)	8 (5.0)	1.00
Dementia	10 (5.2)	2 (6.0)	8 (5.0)	0.68
Colostomy or rectal tube	9 (4.7)	0 (0.0)	9 (5.7)	0.30
Median mobility score ^c (interquartile range)	3 (3–4)	3 (3–4)	3 (3–4)	0.16
Test order location				
Medicine	129 (68.0)	22 (66.7)	107 (68.3)	1.00
Surgery	15 (7.8)	3 (9.1)	12 (7.6)	0.72
Intensive care unit	20 (10.5)	3 (9.1)	17 (10.7)	1.00
Spinal cord injury	8 (4.2)	0 (0.0)	8 (5.1)	0.35
Long-term-care facility	19 (9.9)	5 (15.1)	14 (8.7)	0.33

^a Data represent the number (%) of patients unless otherwise specified.

^b The Wilcoxon rank sum test was used for comparison of median values between groups. Fisher's exact test or Pearson's chi-square test was used to compare categorical variables.

^c The mobility score is a subcategory of the Braden score for prediction of pressure ulcer risk (1, complete immobility; 2, very limited mobility; 3, slightly limited mobility; 4, no mobility limitation).

TABLE 2 Comparison of the timing of CDI testing and the frequency of specimen rejection by the Microbiology Laboratory during the baseline and intervention periods^a

Parameter	Baseline period (6 mo)	Intervention period (3 mo) ^b	<i>P</i> value ^c
Total no. of specimens submitted	241	130	
No. of specimens initially submitted	203	118	
Rejected	50 (21)	18 (14)	0.47
Formed stool	4 (2)	3 (2)	0.69
Resubmission requested	46 (19)	15 (12)	0.08
Leaking container	24 (10)	2 (2)	0.002
Improper labeling	17 (7)	8 (6)	0.83
Wrong or insufficient specimen ^d	5 (2)	2 (2)	1.00
No. of specimens resubmitted	38	12	
CDI tests completed	191 (79)	112 (86)	0.12
Timing of CDI testing, mean no. of days (range)			
Test order to specimen collection	1.0 (0–10)	0.54 (0–6)	0.006
Specimen collection to receipt in laboratory	0.4 (0.05–3)	0.24 (0.05–1.5)	0.005
Receipt in laboratory to test result	0.4 (0.05–5)	0.12 (0.05–1.2)	<0.001
Test order to test result	1.8 (0.2–10.6)	0.8 (0.1–8.2)	<0.001

^a Data represent the number (%) of specimens unless otherwise specified. For the baseline period, the 241 total specimens submitted included 203 initial specimens and 38 resubmitted specimens; for the intervention period, the 130 total specimens submitted included 118 initial submissions and 12 resubmitted specimens.

^b The intervention period was 4 months long, but data were collected only for the final 3 months.

^c The Wilcoxon rank sum test was used for comparison of median values between groups. Fisher's exact test or Pearson's chi-square test was used to compare categorical variables.

^d Wrong specimens were urine samples submitted rather than stool.

delays in CDI testing were not more common in the long-term-care facility; this change may be related to the fact that the long-term-care facility has relocated from a separate facility to a building directly adjacent to the hospital.

An intervention that addressed several factors reduced the average time from CDI test order to result from 1.8 to 0.8 days. The intervention included some changes that were independent of the need for ongoing education of staff members. These included replacing a specimen container that frequently leaked with a screw cap container and making CDI testing a priority laboratory test and a priority for specimen transport. A majority of the reduction in testing time involved reducing the time from CDI test order to stool collection. To achieve more rapid stool collection, nurses and physicians received education on the importance of expediting CDI testing. Physicians were encouraged to communicate directly with nursing staff to alert them to new CDI test orders. To maintain improvements in timing of stool collection, an automated system is being implemented to alert nursing staff when new CDI orders are placed and monthly feedback on timing of stool collection is being provided to each nursing unit.

Expediting CDI testing could result in improved clinical and infection control outcomes (12, 13). First, expedited testing may limit the overuse of empirical CDI therapy (12). Forty percent of all CDI treatment regimens were prescribed as empirical therapy for patients with negative CDI test results or with no stool samples collected for testing. Such empirical therapy may have adverse effects. For example, oral metronidazole and oral vancomycin therapy have been associated with overgrowth of pathogens such as vancomycin-resistant enterococci and *Candida* spp. (14, 15). Interviews with physicians suggested that more rapid diagnostic testing might reduce prescription of empirical treatment for suspected CDI. Second,

expedited testing will reduce delays in initiation of therapy for patients with CDI. For 38 CDI patients who did not receive empirical treatment, the average time from test order to initiation of CDI therapy was 1.7 days. Finally, expedited testing may decrease *C. difficile* transmission by reducing delays in isolation of CDI patients (12). Alternatively, if all patients being tested for CDI are placed in contact precautions, expediting testing will reduce the time that patients with negative testing are maintained in isolation. Placement of patients in isolation may result in adverse effects, including reducing the amount of contact patients in isolation have with health care providers (16, 17).

Our study had some limitations. The study was conducted among inpatients in one facility with a patient population that includes mostly men. There is a need for additional studies in other facilities and in outpatient settings. The reduction in laboratory processing time achieved in our facility may not be feasible in some centers. The commercial PCR assay used in our facility is amenable to testing of individual samples in real time. Although we changed the laboratory procedure for CDI testing from a 2-step procedure to PCR as a standalone test, this change accounted for only a minor part of the reduction in testing time and similar reductions could have been achieved using the 2-step procedure. We are not aware of adverse effects on Microbiology Laboratory work flow related to making CDI testing a priority, but it is possible that this change resulted in delays in processing of other test results. Finally, we did not assess delays in recognition of CDI symptoms which may also contribute to delayed diagnosis of CDI (9–11).

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