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Predictors of *Clostridioides difficile* Infection-Related Complications and Treatment Patterns among Nucleic Acid Amplification Test-Positive/Toxin Enzyme Immunoassay-Negative Patients

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ABSTRACT The addition of toxin enzyme immunoassay (EIA) to nucleic acid amplification tests, including PCR, creates challenges in the diagnosis and management of *Clostridioides difficile* infection (CDI). There are limited data in large cohorts, with discordant results, that is, PCR-positive/EIA-negative (PCR^+/EIA^-) results. We conducted a retrospective cohort study on all PCR^+/EIA^- adult inpatients and assessed CDI-related complications and clinical failure. We identified 240 individuals. Twenty-three (9.6%) patients experienced a CDI-related complication, including 2 cases of megacolon, 1 colectomy, and 22 intensive care unit (ICU) admissions. In multivariable logistic regression analyses, baseline severe disease by Infectious Diseases Society of America (IDSA) criteria (odds ratio [OR], 5.84; 95% confidence interval [CI], 1.88 to 18.1; $P = 0.002$), baseline fulminant colitis (OR, 84.7; 95% CI, 14.3 to 500; $P < 0.001$), fever of >38.5°C (OR, 4.61; 95% CI, 1.42 to 15.0; $P = 0.011$), and proton pump inhibitor (PPI) use (OR, 3.50; 95% CI, 1.19 to 10.3; $P = 0.023$) were associated with increased odds of CDI-related complications. For 67 PCR^+/EIA^- patients who did not receive complete treatment, clinical failure was observed in 10 (15%) patients. A comparison of PCR^+/EIA^- patients who received complete treatment to all 112 PCR^+/EIA^+ patients showed no differences in CDI-related complications (11% and 13% for PCR^+/EIA^- and PCR^+/EIA^+ patients, respectively), 60-day all-cause mortality (17% and 18% for PCR^+/EIA^- and PCR^+/EIA^+ patients, respectively), or recurrent CDI (7% and 9% for PCR^+/EIA^- and PCR^+/EIA^+ patients, respectively). Predictors of CDI-attributable complications among PCR^+/EIA^- patients include baseline severe disease by IDSA criteria, baseline fulminant colitis, and fever of >38.5°C. Identifying the subgroup of PCR^+/EIA^- patients who could have true disease, and therefore allowing them to be targeted for treatment, is critical.

KEYWORDS *C. difficile*, CDI, *Clostridioides difficile*, toxin enzyme immunoassay

Clostridioides difficile is the most common cause of health care-associated infection. A surveillance study across 10 geographic areas in the United States estimated the number of incident *Clostridioides difficile* infections (CDI) in 2011 to be 453,000, and the estimated number of deaths was 29,300 (1). Prompt and accurate diagnosis is critical for patient care, yet it remains problematic, with no standalone test of high sensitivity and specificity capable of providing rapid results. Enzyme immunoassays (EIA) for toxins were previously favored over culture, but their sensitivity remains poor (2). Nucleic acid amplification tests, including PCR, have been shown to be highly sensitive in detecting gene targets of toxins A and B, but important limitations have been recognized. Individuals colonized with *Clostridioides difficile* without disease may test positive, and this low specificity has implications for patient overdiagnosis and overtreatment (3, 4).

To confront the problems of the aforementioned single tests, hospitals have ad-

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opted a strategy that often includes PCR plus EIA, for example, a so-called multistep algorithm, which is recommended in Infectious Diseases Society of America (IDSA) guidelines, particularly when there are no preagreed institutional criteria for patient stool submission (5). The European Society of Clinical Microbiology and Infectious Diseases (ESCMID) similarly recommends the use of a two-step algorithm (6). Clinicians are now encountering discordant results, that is, PCR-positive/EIA-negative (PCR^+/EIA^-) results. There is uncertainty at the bedside about how to manage these patients. The limited published studies are contradictory. It has been shown that patients with negative EIA results tend to develop less severe forms of CDI or no CDI at all (3, 7). However, it has also been shown that severe CDI can develop in PCR^+/EIA^- patients (8–10).

To address the need for additional data on the outcomes and management of large cohorts of these patients and, importantly, to identify predictors of CDI-attributable complications, we undertook the present study. Our institution added EIA for toxin to PCR^+ specimens beginning in June 2018, providing the consummate opportunity to study clinical characteristics, outcomes, and physician prescribing patterns over the following months.

MATERIALS AND METHODS

Study design and population. We conducted a retrospective cohort study on all adult (>18 years old) inpatients tested for CDI at the Cleveland Clinic Foundation (CCF) in Cleveland, OH, from June to December 2018, the first 6 months following the introduction of EIA for toxin to the existing PCR. Patients with or without a history of CDI were eligible for study. Approval was granted by the institutional review board, as was a waiver of written informed consent since the data were routinely collected for patient care and evaluation of the results posed minimal risk.

CDI testing data were retrieved from the infection prevention database, which is used for National Healthcare Safety Network reporting. Testing is performed on unformed stool samples by the clinical microbiology laboratory. Stool samples that are PCR^+ (Xpert *C. difficile* test; Cepheid, Sunnyvale, CA) are subsequently tested using EIA (Tox A/B Quik Chek; TechLab, Blacksburg, VA). The reported sensitivity of the Xpert *C. difficile* test ranges from 96 to 100% (6). The Tox A/B Quik Chek test has reported specificity between 94 and 100% (6). These newer-generation tests comply with guideline-recommended algorithms to perform a highly sensitive test first, followed by a highly specific test.

Prior to initiation of the two-step testing algorithm, there was no specific provider education or electronic medical record guidance on how to interpret these tests. The results released to clinicians were step wise; first, PCR results were reported, and second, a separate EIA result with no added interpretation was reported.

A comprehensive chart review was performed by two investigators (R.M. and JA.M.) in order to collect the following information: demographics, comorbidities, medication exposures (systemic antibiotics in the prior month, proton pump inhibitor [PPI] use within the prior 4 weeks, and laxative medication use in the 48 h prior to a positive test), clinical signs and symptoms at presentation, CDI-specific treatment, need for concomitant systemic antibiotics, and outcomes.

Outcomes. The primary outcome was a CDI-related complication. Predictors of CDI-related complications were assessed in all PCR^+/EIA^- patients. CDI-related complications were compared between PCR^+/EIA^+ patients and PCR^+/EIA^- patients who received complete treatment. Secondary outcomes included recurrent CDI within 60 days and death, and for those PCR^+/EIA^- patients who received incomplete or no treatment, clinical failure was defined as repeat testing, initiation of full treatment, or CDI-related complications within 60 days. Attributable mortality due to CDI was also determined. Follow-up began on the date of diagnosis and ended on the date of death or the date of the last available record.

Definitions. CDI-related complications were defined as a composite of toxic megacolon, need for colectomy, or admission to the intensive care unit (ICU) on the day of or following CDI diagnosis for the management of CDI. Recurrence was defined as a new episode of diarrhea associated with PCR^+/EIA^+ or PCR^+/EIA^- status and the need for *C. difficile*-specific therapy. PCR^+/EIA^- patients who did not receive complete treatment were assessed for clinical failure, which was defined as a composite of need for repeat testing or subsequent treatment within 60 days of initial testing. This was chosen as a marker of ongoing clinical suspicion of CDI; for example, a patient initially given no treatment subsequently given complete treatment for CDI was classified as a clinical failure in the no-treatment group.

Severity of CDI was defined according to the IDSA criteria, including white blood cell (WBC) count greater than 15,000 cells/ml or serum creatinine level greater than or equal to 1.5 mg/dl (5). Fulminant CDI was characterized by hypotension or shock, ileus, or megacolon on imaging study (6).

To understand clinician prescribing patterns, patients with discordant results were placed into one of the 3 following groups for comparison: (i) complete treatment, (ii) incomplete treatment, and (iii) no treatment. Complete treatment included any standard therapy recommended by IDSA guidelines (5). Incomplete treatment was defined as any regimen different from standard therapy (less-frequent doses or shorter duration, for example). Variables associated with giving complete treatment were assessed.

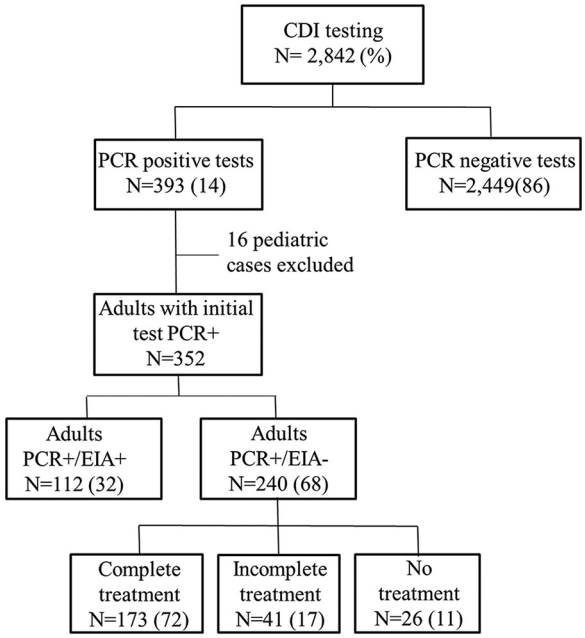

FIG 1 Flowchart depicting results of *C. difficile* testing and treatment at the Cleveland Clinic, June to December 2018.

Statistical analysis. Descriptive statistics were computed, and differences in characteristics across groups were analyzed by chi-square test or analysis of variance techniques. Multivariable analyses for factors associated with complete treatment and factors associated with CDI-related complications were performed using stepwise multiple logistic regression analysis. The criterion for entry into the model was significance at an α level of 0.15, while the criterion for remaining in the model was significance at an α level of 0.05. Odds ratios and corresponding 95% confidence intervals were calculated. Kaplan-Meier curves were used to show survival in PCR$^+$/EIA$^-$ patients given complete treatment and PCR$^+$/EIA$^+$ patients. They were also used to show the time to clinical failure in PCR$^+$/EIA$^-$ patients with incomplete treatment compared to no treatment. The probability differences between survival curves were compared using the log-rank test. All statistical tests were two tailed and utilized a 5% significance level. Analyses were performed using JMP 14 (SAS Institute, Cary, NC).

RESULTS

Characteristics. Out of 2,842 patients tested for CDI during the study period, 393 (14%) patients were PCR$^+$. Three hundred fifty-two patients met the inclusion criteria. Among these, 240 (68%) patients had discordant results (PCR$^+$/EIA$^-$) (Fig. 1). The mean patient age was 60 years, and 122 (51%) patients were female. Most patients were admitted from home or transferred from another hospital. Baseline conditions included high-severity comorbidities such as transplant ($n = 42$), hematologic malignancy ($n = 27$), and solid tumor ($n = 32$). Thirty-eight (16%) patients had a history of prior CDI (Table 1). The median time (range) from admission to positive PCR result in PCR$^+$/EIA$^-$ patients was 3 (0 to 85) days.

Of the 240 PCR$^+$/EIA$^-$ patients, 214 were treated, as follows: 173 (72%) patients were administered complete treatment, 41 (17%) patients were administered incomplete treatment, and 26 (11%) patients had no treatment. There was no difference across these treatment groups in the proportion of patients given systemic antibiotic therapy in the prior month (46%). Likewise, the proportion of patients on current systemic antibiotics at the time of CDI testing was similar across groups (45 to 50%). In the complete-treatment group, 158 (91%) patients received vancomycin as part of the prescribed regimen (147 vancomycin monotherapy), amounting to 2,107 days of therapy, with a mean of 13 days. Forty-one patients received incomplete treatment, which consisted of vancomycin administered four times per day for a shorter-than-guideline-concordant duration or two times per day. With regard to severity of illness, this was assessed only in patients administered complete treatment ($n = 173$). Ten (5.8%)

TABLE 1 Characteristics of 240 *C. difficile* PCR-positive, toxin-negative patients classified according to treatment given at the Cleveland Clinic, June to December 2018

Characteristic	Data for patients by treatment[a]		
	Complete	Incomplete	None
Group size	173 (72)	41 (17)	26 (11)
Mean (SD) age (yr)	60 (17)	62 (13)	59 (12)
Female sex	89 (51)	21 (51)	12 (46)
Origin prior to admission			
Home	125 (72)	29 (71)	17 (65)
Skilled nursing facility	3 (1.7)	1 (2.4)	1 (3.8)
Long-term acute care facility	1 (0.6)	0 (0)	0 (0)
Other hospital	44 (25)	11 (27)	8 (31)
Comorbid conditions			
Transplant	31 (18)	6 (15)	5 (19)
Hematologic malignancy	24 (14)	2 (5)	1 (4)
Solid tumor	22 (13)	8 (20)	2 (8)
Chemotherapy	26 (15)	4 (10)	1 (4)
Other immunosuppression	17 (10)	3 (7)	1 (4)
Inflammatory bowel disease	13 (8)	1 (2)	1 (4)
HIV	2 (1)	0 (0)	0 (0)
Systemic antibiotics in prior mo	79 (46)	19 (46)	12 (46)
History of prior CDI	23 (13)	8 (20)	7 (27)
Clinical features			
Hypotension	11 (6)	1 (2)	1 (4)
Ileus	17 (10)	3 (7)	1 (4)
White blood cell count >15,000 cells/ml	51 (29)	5 (12)	6 (23)
Serum creatinine >1.5 mg/dl	47 (27)	13 (32)	11 (42)
Imaging with colitis	17 (10)	3 (7)	1 (4)
In-hospital factors			
Hospital length of stay (median [IQR]) (days)[b]	11 (5–22)	14 (8–23)	14 (6–21)
Current treatment systemic antibiotics	77 (45)	20 (49)	13 (50)
Laxative use	43 (25)	13 (32)	10 (38)
Infectious disease consultation	58 (34)	24 (59)	14 (54)
Primary team being surgical	61 (35)	13 (32)	8 (31)
CDI severity			
Severe	70 (40)	NA	NA
Fulminant	10 (6)	NA	NA
Treatment			
Metronidazole	13 (8)	NA	NA
Vancomycin	147 (85)	NA	NA
Fidaxomicin	2 (1)	NA	NA
Combination[c]	11 (6)	NA	NA
Vancomycin days of therapy	2,107	NA	NA
Outcomes			
CDI-related complications	19 (11)	2 (5)	2 (8)
Megacolon	2 (1)	0 (0)	0 (0)
Colectomy	1 (1)	0 (0)	0 (0)
ICU care related to CDI	18 (10)	2 (5)	2 (8)
Recurrent CDI	12 (7)	NA	NA
All-cause mortality	29 (17)	6 (15)	1 (4)
Death attributable to CDI	4 (2)	0 (0)	0 (0)
Clinical failure	NA	7 (17)	3 (12)
Repeat testing	NA	7 (17)	2 (8)
Treatment initiated	NA	3 (7)	2 (8)

[a]Data are presented as number (%), unless otherwise stated. NA, not applicable.
[b]IQR, interquartile range.
[c]Includes patients who received vancomycin plus metronidazole with or without a vancomycin enema.

TABLE 2 Results of multivariable analyses of predictors of CDI-related complications among 240 PCR-positive, toxin-negative patients at the Cleveland Clinic, June to December 2018[a]

Variable	OR	95% CI	*P* value
Fever >38.5°C	4.61	1.42–15.0	0.011
PPI use	3.50	1.19–10.3	0.023
Baseline severe disease by IDSA criteria	5.84	1.88–18.1	0.002
Baseline fulminant colitis (hypotension or shock, ileus, or megacolon on imaging)	84.7	14.3–500	<0.001

[a]CDI-related complications are a composite of toxic megacolon, need for colectomy, or admission to the ICU on the day of or following CDI diagnosis.

patients met the criteria for fulminant colitis, while 70 (40%) patients were classified as severe CDI.

Primary outcome. The primary outcome of CDI-related complications (composite of toxic megacolon, need for colectomy, or admission to the ICU on the day of or following CDI diagnosis) was experienced by 23 (9.6%) PCR$^+$/EIA$^-$ patients. There were 2 cases of megacolon, 1 colectomy, and 22 ICU admissions. On univariate analyses, factors positively associated with a CDI-related complication included the following (all $P < 0.05$): baseline severe disease by IDSA criteria, baseline fulminant colitis, fever of >38.5°C, PPI use, systemic antibiotic use, and imaging showing ileus or colitis. In multivariable logistic regression analyses, baseline severe disease by IDSA criteria (odds ratio [OR], 5.84; 95% confidence interval [CI], 1.88 to 18.1; $P = 0.002$), baseline fulminant colitis (OR, 84.7; 95% CI, 14.3 to 500; $P < 0.001$), fever of >38.5°C (OR, 4.61; 95% CI, 1.42 to 15.0; $P = 0.011$), and PPI use (OR, 3.50; 95% CI, 1.19 to 10.3; $P = 0.023$) were associated with increased odds of CDI-related complications (Table 2).

The 173 PCR$^+$/EIA$^-$ patients who received complete treatment were compared to 112 PCR$^+$/EIA$^+$ patients (Table 3). A significantly higher proportion of PCR$^+$/EIA$^+$ patients met the criteria for severe disease at baseline (53% versus 40%, respectively; OR, 1.63; 95% CI, 1.01 to 2.65; $P = 0.04$). Apart from this association between toxin EIA positivity and baseline severe disease, the groups were comparable. Recurrent CDI rates were similar (7% and 9% for PCR$^+$/EIA$^-$ and PCR$^+$/EIA$^+$ patients, respectively), and there were no significant differences in CDI-related complications (11% and 13% for PCR$^+$/EIA$^-$ and PCR$^+$/EIA$^+$ patients, respectively) or 60-day all-cause mortality (17% and 18% for PCR$^+$/EIA$^-$ and PCR$^+$/EIA$^+$ patients, respectively). Kaplan-Meier curves of time to death showed no significant difference between the 2 groups (Fig. 2). Four deaths were attributed to CDI in PCR$^+$/EIA$^-$ patients compared to zero deaths in PCR$^+$/EIA$^+$ patients.

TABLE 3 Comparison of disease severity and outcomes between the PCR$^+$/EIA$^-$ complete-treatment group and PCR$^+$/EIA$^+$ group

Disease severity or outcome	No. (%) of adults with: PCR$^+$/EIA$^-$ (complete treatment) ($n = 173$)	PCR$^+$/EIA$^+$ ($n = 112$)	*P* value
CDI severity			
Severe	70 (40)	59 (53)	0.04
Fulminant	10 (6)	3 (3)	0.23
Severe or fulminant	80 (46)	62 (55)	0.13
CDI-related complications	19 (11)	14 (13)	0.69
Megacolon	2 (1)	0 (0)	
Colectomy	1 (0.6)	1 (1)	
ICU care related to CDI	18 (10)	14 (13)	
Recurrent CDI, 60 days	12 (7)	10 (9)	0.54
All-cause mortality, 60 days	29 (17)	20 (18)	0.8
Death attributable to CDI, 60 days	4 (2)	0 (0)	0.26

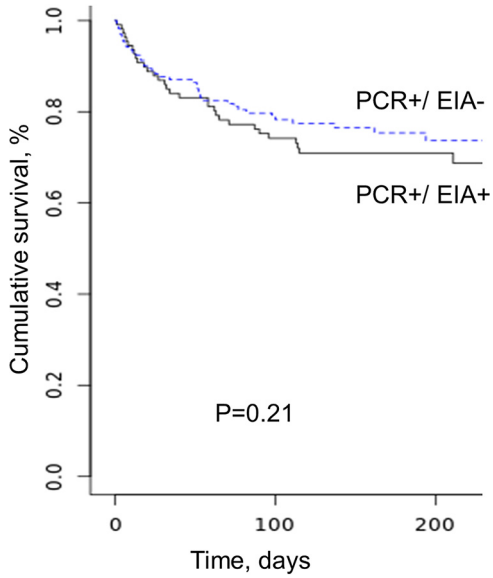

FIG 2 Kaplan-Meier survival curve of PCR$^+$/EIA$^-$ patients given complete treatment and PCR$^+$/EIA$^+$ patients at the Cleveland Clinic, June to December 2018.

For those PCR$^+$/EIA$^-$ patients who received incomplete or no treatment ($n = 67$), clinical failure (a composite of need for repeat testing or subsequent treatment) was observed in 10 (15%) patients (Fig. 3). Interestingly, 4/9 (44%) patients who underwent repeat testing were found to be PCR$^+$/EIA$^+$ at days 10, 11, 16, and 41.

Treatment patterns. In multivariable logistic regression analyses, a WBC count of >15,000 cells/ml (OR, 3.30; 95% CI, 1.48 to 7.34; $P = 0.003$) and hematologic malignancy (OR, 3.99; 95% CI, 1.10 to 14.4; $P = 0.035$) were associated with increased odds of treatment (Table 4). Infectious disease consultation was associated with not prescribing complete treatment (OR, 0.30; 95% CI, 0.16 to 0.56; $P < 0.001$).

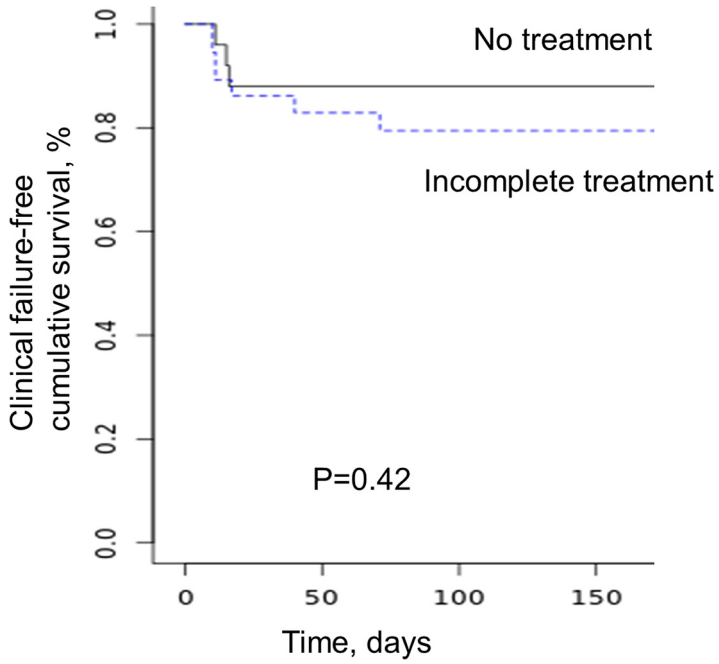

FIG 3 Kaplan-Meier clinical failure-free survival curve of 67 PCR$^+$/toxin- patients given incomplete treatment and no treatment at the Cleveland Clinic, June to December 2018.

TABLE 4 Results of multivariable analyses of predictors of full CDI treatment among 240 PCR-positive, toxin-negative patients at the Cleveland Clinic, June to December 2018

Variable	OR	95% CI	*P* value
WBC count >15,000 cells/ml	3.30	1.48–7.34	0.003
Hematologic malignancy	3.99	1.10–14.4	0.035
PPI use	0.58	0.31–1.08	0.088
Laxative use	0.54	0.27–1.08	0.080
History of prior episode of CDI	0.52	0.23–1.14	0.102
Infectious disease consultation	0.30	0.16–0.56	<0.001

Laxative and PPI use, as well as having a history of prior CDI, were associated with decreased odds of treatment, but the associations did not reach statistical significance ($P = 0.080$ to 0.102). There was no association between prescribing complete treatment and the use of concomitant systemic antibiotics.

DISCUSSION

In a large cohort of PCR$^+$/EIA$^-$ individuals with high-severity comorbidities, CDI-related complications were experienced by nearly 10%. This was largely driven by ICU admission for CDI. We observed that baseline severe disease by IDSA criteria, baseline fulminant colitis, fever of >38.5°C, and PPI use were associated with increased odds of CDI-related complications. We further documented that a similar proportion of PCR$^+$/EIA$^+$ and PCR$^+$/EIA$^-$ patients experience important outcomes such as CDI-related complications, recurrent CDI, and 60-day all-cause mortality. We characterized clinician prescribing patterns and showed that treatment with vancomycin was very common and that a WBC count of >15,000 cells/ml and hematologic malignancy were associated with increased odds of treatment, whereas infectious disease consultation was associated with not prescribing complete treatment.

How do clinicians identify PCR$^+$/EIA$^-$ individuals with true disease who would benefit from treatment? Identifying baseline clinical features of patients who ultimately develop CDI-related complications may help identify those with true disease. This is in contrast to some studies that would suggest there is no need to determine predictors of CDI-related complications because EIA for toxin accurately identifies those at risk for complications. One study showed that there were zero CDI-related complications in 30 days among 162 PCR$^+$/EIA$^-$ patients (3). In comparison, in the present study, almost 10% of PCR$^+$/EIA$^-$ patients were observed to have a CDI-related complication. This is similar to what has been shown in a cohort of 125 PCR$^+$/EIA$^-$ patients in Spain, where 4.8% had CDI-related complications and an additional 4.8% died due to CDI (7). It is also comparable to a study from Canada in which the proportion of patients with CDI-related complications was 9% among 110 PCR$^+$/EIA$^-$ patients (8). ESCMID guidelines nicely highlight this problem, in which PCR$^+$/EIA$^-$ results may indicate carriage or true disease (11). They emphasize that the decision to treat CDI is ultimately a clinical decision taking into account clinical signs and symptoms guided by laboratory results (6). Taken together, the above-mentioned findings seem to indicate that there are some PCR$^+$/EIA$^-$ patients who experience complications and need treatment. CDI remains a clinical diagnosis, and a negative EIA for toxin does not rule out disease.

One substantial contribution of the present study involves its multivariable model used to determine associations with CDI-related complications. These variables, which are readily apparent at the time of *C. difficile* laboratory results, may assist clinicians in targeting PCR$^+$/EIA$^-$ individuals with true disease for treatment. In published studies, the only similar model was derived from both PCR$^+$/EIA$^+$ patients and a much smaller number of PCR$^+$/EIA$^-$ patients (7). It is not informative in identifying predictors of CDI-related complications in PCR$^+$/EIA$^-$ patients, which is the most clinically relevant question. For example, Origüen and colleagues (7) identified concomitant antibiotics as a predictor of complications, but we analyzed a larger number of PCR$^+$/EIA$^-$ patients alone and found no significant association between systemic antibiotics and CDI-related complications. In patients at our center found to be PCR$^+$/EIA$^-$, baseline severe

disease by IDSA criteria, baseline fulminant colitis, and fever of >38.5°C predicted CDI-related complications and helped identify patients who could benefit from treatment moving forward.

An important comparison was made between PCR^+/EIA^+ patients and PCR^+/EIA^- patients who received complete treatment. More PCR^+/EIA^+ patients had baseline severe disease; however, we could not show any difference in important outcomes such as recurrent CDI, CDI-related complications, or 60-day all-cause mortality across the groups. This is in agreement with what has been shown about the performance of EIA for toxin (9, 12). Published studies evaluating outcomes of PCR^+/EIA^+ patients compared to those of PCR^+/EIA^- patients generally show similar proportions with CDI-related complications, recurrent CDI, and 60-day all-cause mortality (12–15).

The apparent similarity in outcomes between PCR^+/EIA^+ and PCR^+/EIA^- patients may in part relate to the groups we chose to compare. In the present study, the comparison was limited only to the PCR^+/EIA^- patients who received complete treatment. The proportion of patients with true disease in this group was probably higher than in the group not given complete treatment because some form of clinical assessment led to the recommendation for complete treatment. If there indeed were a number of patients in this group with true disease, recurrent CDI, CDI-related complications, and 60-day all-cause mortality would be expected to be similar in PCR^+/EIA^+ patients, which is what we observed.

To support this, *post hoc* we compared the incidence of CDI-related complications between PCR^+/EIA^- patients who did not receive complete treatment (6%) and PCR^+/EIA^+ patients (13%). We found increased odds of CDI-related complications among PCR^+/EIA^+ patients (OR, 2.24; 95% CI, 0.73 to 8.22; $P = 0.17$), but the association did not reach statistical significance due to a small sample size.

We believe a substantial amount of overtreatment occurred during the first 6 months despite adding EIA for toxin to the existing PCR. We found that a WBC count of >15,000 cells/ml and hematologic malignancy were associated with increased odds of treatment. The overall low threshold for treatment may arise from the distinctly immunocompromised patient population in the present study. At centers with fewer patients who underwent solid organ transplant, were diagnosed with hematologic malignancy, and received other immunosuppression, the threshold for treatment is likely higher, and the prescribing pattern may be very different. Interestingly, infectious disease consultation was associated with not prescribing complete treatment. This underscores the importance of individual patient assessment, particularly since it has been shown that the cause of diarrhea in hospitalized patients, even those with leukocytosis or hematologic malignancy, is most often not CDI (5). The present study validates this further. Eighty-six percent of *C. difficile* testing on patients with diarrhea was negative. Moreover, there were 67 PCR^+/EIA^- patients who were not administered complete treatment, and 63 (94%) patients were observed to do very well without complications. We suspect that baseline widespread testing, a low threshold to treat immunocompromised patients, and a learning curve with the 2-step approach led to overtreatment. These three are major challenges in optimizing the management of PCR^+/EIA^- patients after instituting a new testing algorithm, which thus far has not provided diagnostic clarity at the bedside. Despite the frequent treatment given, it almost entirely involved vancomycin, which is an advantage of the present study. Published reports have to date in this population have all been dominated by metronidazole, and patient outcomes on metronidazole may be less germane in the current treatment era.

There are important limitations to this study. The observational design was limited principally by confounding by indication, and the results of some comparisons should be interpreted cautiously. For example, there was an apparent association between PPI use and increased odds of CDI-related complications, almost certainly reflecting the increased use of PPI in critically ill patients in the ICU rather than a therapeutic complication of the PPI itself. We used the IDSA criteria for severity of CDI, which are based on expert opinion rather than being derived from and validated in prospective

studies, and these criteria are limited when applied to patients with kidney disease in particular. As a tertiary referral center, the setting involved patients with more complicated and comorbid conditions, representing a referral bias that may limit generalizability. These data also reflected the first 6 months since introducing EIA for toxin to the existing PCR and may not be generalizable to centers where multistep testing has been performed for longer periods.

In conclusion, the present study provides new data in a large cohort of PCR$^+$/EIA$^-$ individuals with high-severity comorbidities. There are variables associated with increased odds of CDI-related complications that may assist clinicians in targeting PCR$^+$/EIA$^-$ patients with true disease for treatment. This is critical for 2 reasons, as follows: (i) since the proportion of PCR$^+$/EIA$^-$ patients who experience important outcomes is similar to that of PCR$^+$/EIA$^+$ patients, there is a subgroup of PCR$^+$/EIA$^-$ patients who need to be treated; and (ii) since many PCR$^+$/EIA$^-$ patients experience no complications, there is a subgroup who do not need to be treated. Does my patient have CDI? As health systems contend with the continued challenges of CDI diagnostics, clinicians are asking this as they seek a prompt and accurate diagnosis. The present study highlights that individual clinical assessment beginning with whom to test (diagnostic stewardship) and concluding with whom to treat (antimicrobial stewardship) is currently the only way to deliver this.

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