CONCISE COMMUNICATION

Clinical Characteristics and Outcomes of Hematologic Malignancy Patients With Positive *Clostridium difficile* Toxin Immunoassay Versus Polymerase Chain Reaction Test Results

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In a cohort of inpatients with hematologic malignancy and positive enzyme immunoassay (EIA) or polymerase chain reaction (PCR) *Clostridium difficile* tests, we found that clinical characteristics and outcomes were similar between these groups. The method of testing is unlikely to predict infection in this population, and PCR-positive results should be treated with concern.

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Both infection and colonization with *Clostridium difficile* are common in patients with hematologic malignancy; 10%–29% of patients are positive by culture on admission.[1,2] However, while there is increasing recognition that molecular-based polymerase chain reaction (PCR) testing for *C. difficile* toxin lacks specificity for detecting infection as opposed to colonization,[3,4] determining true infection in patients with hematologic malignancy may be particularly difficult given the high prevalence of diarrhea due to other etiologies (eg, chemotherapy or antibiotics)[5,6] and the absence of typical signs and symptoms of infection such as leukocytosis or fever due to the effect of disease and/or therapy. Similarly, while studies have suggested lower rates of both characteristics predictive of infection and poor outcomes in patients with PCR versus enzyme immunoassay (EIA) positive tests,[7,8] it is unknown whether these findings apply to patients with hematologic malignancy. Therefore, we aimed to compare clinical characteristics and outcomes between patients with EIA- versus PCR-positive *C. difficile* test results in a cohort of inpatients with hematologic malignancy.

METHODS

We performed a retrospective cohort study of patients admitted to the Hospital of the University of Pennsylvania (HUP), a 776-bed tertiary-care medical center from January 1, 2015, to March 31, 2017. Patients with active hematologic malignancy and a positive *C. difficile* test during hospitalization were included.

Stool samples ordered for *C. difficile* testing were processed by the HUP Clinical Microbiology Laboratory. The testing algorithm uses a commercial EIA for detection of toxin A, B, and glutamate dehydrogenase (GDH) (C Diff Quik Check Complete, Alere, Waltham, MA). Samples that are negative for toxin A and B but positive for GDH are subsequently tested using PCR for toxin genes (BD MAX Cdiff Assay, Becton Dickinson, Franklin Lakes, NJ).

Clinical data were collected using medical record review, including demographics, comorbidities, antibiotic use in the previous month, clinical signs and symptoms (including fever, diarrhea, number of bowel movements, abdominal pain, and imaging evidence of colitis), and medication use in the 72 hours prior to the positive test. Clinical outcomes were also collected, including toxic megacolon, colectomy, recurrent *C. difficile* disease in the 90 days after index testing, as well as all-cause intensive care unit (ICU) transfer, in-hospital mortality, and hospital readmission. Clinical characteristics and outcomes of patients with EIA- versus PCR-positive *C. difficile* test results were compared using the χ^2 or the Fischer exact test for categorical variables and the Wilcoxon rank-sum test for continuous variables using Stata version 14.2 software (StataCorp, College Station, TX). For all calculations, a 2-tailed P value $< .05$ was considered significant.

RESULTS

Over the 27-month study period in the hospital's dedicated hematology oncology units, 11.6% of *C. difficile* tests were positive. Of the 182 patients admitted with hematologic malignancy who had a positive *C. difficile* test result, 101 patients (55%) had a PCR(+)/EIA(−) result, and 81 patients (45%) had an EIA(+) result. Among patients without neutropenia, leukocytosis (white blood cell count >15,000 cells/mm^3) at the time of testing was significantly more common in the EIA(+) group (ie, 26%) versus the PCR(+)/EIA(−) group (ie, 11%; $P = .02$) (Table 1). There was no difference in rates of severe CDI,[9] fever, diarrhea, or imaging evidence of colitis between the 2 groups. Stool output trended towards being higher in the PCR(+)/EIA(−) group, with a median of 4 bowel movements per 24 hours compared to a median of 3 bowel movements per 24 hours in the EIA(+) group ($P = .15$).

Receipt of medications associated with an increased risk for CDI, including acid suppressants (52%) and systemic antibiotics (80%), were similar in both groups. There were relatively high rates of recent use of laxatives (30%), but this was not significantly different between the 2 groups.

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TABLE 1. Clinical Characteristics of Patients With Hematologic Malignancy With EIA- Versus PCR-Positive *C. difficile* Test Results

Characteristics	Total Population (n = 182) No. (%)	EIA Positive (n = 81) No. (%)	PCR Positive (n = 101) No. (%)	*P* Value
Age, y (IQR)	62 (53–68)[a]	62 (55–68)[a]	62 (52–68)[a]	.74
Race, white	140 (77)	61 (75)	79 (78)	.64
Malignancy				
Acute myeloid leukemia	81 (45)	36 (44)	45 (45)	.91
Multiple myeloma	41 (23)	19 (23)	22 (22)	
Non-Hodgkin's lymphoma	26 (14)	10 (12)	16 (16)	
Other	34 (19)	16 (20)	18 (18)	
C. difficile test collected <72 h after admission	33 (18)	17 (21)	16 (16)	.37
History of stem cell transplant	67 (37)	35 (43)	32 (32)	.11
History of *C. difficile*[b]	22 (12)	13 (16)	9 (9)	.14
Prior hospitalization[c]	103 (57)	48 (59)	55 (54)	.51
Chronic gastrointestinal disease[d]	32 (18)	18 (23)	14 (14)	.13
Neutropenia[e]	64 (35)	24 (30)	40 (40)	.14
Leukocytosis[f]	21(18)	15 (26)	6 (11)	.02
Fever[g]	68 (37)	27 (33)	41 (41)	.31
Albumin (IQR)[h]	2.9 (2.4–3.4)	2.7 (2.2–3.3)	3.0 (2.5–3.5)	.11
Severe *C. difficile* infection[i]	22 (12)	13 (16)	9 (9)	.14
Diarrhea[j]	133 (73)	57 (70)	76 (75)	.46
Stool count (IQR)[k]	3 (2–5)[a]	3 (2–5)[a]	4 (2–6)[a]	.15
Radiographic evidence of colitis	15 (8)	6 (7)	9 (9)	.71
Medications[l]				
Proton-pump inhibitor	73 (40)	32 (40)	41 (41)	.93
Histamine-2 antagonist	30 (16)	15 (19)	15 (15)	.50
Corticosteroid	73 (40)	39 (48)	34 (34)	.05
Loperamide	10 (6)	5 (6)	5 (5)	.74
Laxative[m]	54 (30)	21 (26)	33 (33)	.32
Docusate	46 (25)	19 (23)	27 (27)	.61
Antibiotics[c]				
Any antibiotic	145 (80)	65 (80)	80 (79)	.83
Anti-pseudomonal[n]	119 (65)	55 (68)	64 (64)	.52

NOTE. IQR, interquartile range; EIA, enzyme immunoassay; PCR, polymerase chain reaction
[a]Median, interquartile range (IQR).
[b]A positive *C. difficile* test by PCR or EIA within the prior year.
[c]Within the prior 30 days.
[d]Graft-versus-host disease, inflammatory bowel disease (Crohn's disease or ulcerative colitis), irritable bowel syndrome, short gut syndrome.
[e]Absolute neutrophil count < 500 cells/mm^3 within 72 h of the index *C. difficile* test.
[f]Total white blood cell count (WBC) >15,000 cells/mm^3 among nonneutropenic patients.
[g]Temperature >38°C (100.4°F).
[h]Within 72 h (n = 110).
[i]Serum albumin <3 g/dL plus WBC ≥15,000 cells/mm^3 or abdominal tenderness.
[j]Listed as diarrhea or liquid stool by provider.
[k]Highest number of stools per 24-h period over 72 h prior to the testing date.
[l]Within the previous 72 h of the testing date.
[m]Includes sennosides, polyethylene glycol, milk of magnesia, bisacodyl, lactulose.
[n]Cefepime, meropenem, piperacillin-tazobactam, and levofloxacin.

We observed high rates of adverse outcomes in the cohort, including an in-hospital mortality rate of 18% and an ICU transfer rate of 25%, but these were similar between the 2 groups (Table 2). Toxic megacolon was uncommon but occurred in 2 patients (2%) in the PCR(+)/EIA(−) group compared to zero in the EIA(+) group ($P = .20$). Most

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TABLE 2. Outcomes of Patients With Hematologic Malignancy and EIA- Versus PCR-Positive *Clostridium difficile* Test Results

Outcomes	Total Population, (n = 182), No. (%)	EIA Positive (n = 81), No. (%)	PCR Positive (n = 101), No. (%)	*P* Value
In-hospital mortality[a]	33 (18)	18 (23)	15 (15)	.18
ICU transfer[b]	45 (25)	23 (28)	22 (22)	.30
Toxic megacolon	2 (1)	0 (0)	2 (2)	.20
Colectomy	4 (2)	1 (1)	3 (3)	.42
C.difficile recurrence	21 (12)	7 (9)	14 (14)	.27
GVHD of the GI tract	11 (6)	6 (7)	5 (5)	.48
Treatment[c]				
None	4 (2)	0 (0)	4 (4)	.07
Oral vancomycin	118 (65)	57 (70)	61 (60)	.16
Days, median (IQR)	15 (10–21)	15 (10–22)	14 (10–21)	.83
Oral metronidazole	107 (59)	43 (53)	64 (63)	.16
Days, median (IQR)	10 (4–14)	8 (3–14)	11 (6–15)	.03
Intravenous metronidazole	49 (27)	21 (26)	28 (28)	.79
Days, median (IQR)	6 (3–12)	6.5 (3.5–9.5)	6 (3–15)	.64

NOTE. EIA, enzyme immunoassay; PCR, polymerase chain reaction; ICU, intensive care unit; GVHD, graft-versus-host disease; GI, gastrointestinal.
[a]Within 90 days.
[b]Within 30 days.
[c]Patients may have received >1 antibiotic for treatment.

patients received treatment with oral vancomycin (59%). Two patients in the PCR(+)/EIA(−) group did not receive treatment; neither developed a measured adverse outcome.

DISCUSSION

We compared clinical characteristics and outcomes in patients with hematologic malignancy and an EIA- versus PCR-positive *C. difficile* test result after positive GDH screening. We have demonstrated that clinical characteristics and outcomes are similar in this cohort, whether results are positive by EIA or PCR. In addition, the results of our study highlight the significant morbidity and mortality of patients with *C. difficile* in this population, with high rates of ICU transfer and death.

Particularly in a population characterized by high rates of colonization with *C. difficile*,[1,2] it is important to differentiate infection versus colonization. However, our results suggest that among patients with hematologic malignancy, the testing modality (ie, EIA vs PCR) cannot be used to reliably distinguish between *C. difficile* infection and colonization. Specifically, clinical factors typically associated with active or more severe infection[9] were similar between the 2 groups. Complicating the appropriate diagnosis of CDI in this population, there was a high rate of use of laxative and stool softeners in the 72 hours prior to *C. difficile* testing in both groups.

Clinical outcomes were also similar between hematologic malignancy patients with PCR(+)/EIA(−) versus EIA(+) *C. difficile* test results. Morbidity and mortality were high, likely reflecting the overall complexity and severity of illness of patients hospitalized with hematologic malignancy. However, those outcomes specific to CDI were also similar between both groups, with rates of recurrent CDI of 12% within 90 days and cases of toxic megacolon identified in the PCR(+)/EIA(−) group.

Our results differ from studies of general medical patients that have found those with toxin EIA(+) *C. difficile* results to have both a greater prevalence of CDI clinical characteristics and worse outcomes compared to those with PCR(+)/EIA(−) results.[7,8] A prospective study without GDH screening found those with PCR(+)/EIA(−) results to have a lower prevalence of leukocytosis, fewer number of stools, and lower rates of adverse outcomes, including mortality and recurrent CDI.[7] However, the 30-day mortality of 0.6% in the PCR(+)/EIA(−) group in this study compared to 15% in our study highlights the significant difference in study populations. Another recent study also demonstrated higher rates of leukocytosis, fever, and severe CDI as well as recurrent CDI with an EIA(+) result versus PCR(+)/EIA(−) result after GDH screening, but these results showed no difference in mortality between the groups.[8] Notably, our study included only samples collected through routine clinical care and were tested via a multistage process, which included a *C. difficile* GDH screening test. While we compared EIA and PCR test results, these tests were conducted for patients who had had a positive GDH screen. In a multicenter study comparing clinical outcomes among general medical patients, GDH screening was shown to perform similarly to cytotoxigenic culture and had similar sensitivity to PCR.[10] However, it is possible that our results

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differ somewhat from prior studies where GDH screening was not performed.

Our study has potential limitations. First, given the relatively limited sample size available for clinical outcomes, we were unable to perform a multivariable analysis for the association between *C. difficile* testing method and patient outcomes. Additionally, our study focused on the care of hematology oncology patients at an academic institution and may not be generalizable to populations with different characteristics.

In conclusion, our findings highlight the importance of evaluating the characteristics and performance of *C. difficile* testing algorithms specifically in high-risk populations. Additionally, considering the high morbidity and mortality associated with *C. difficile* in this population, future studies are needed focusing on optimal methods of differentiating colonization versus infection, as well as preventing *C. difficile* disease in patients with hematologic malignancy.[11]

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