HHS Public Access

Author manuscript

Infect Control Hosp Epidemiol. Author manuscript; available in PMC 2019 July 01.

Published in final edited form as:

Infect Control Hosp Epidemiol. 2018 July ; 39(7): 863–866. doi:10.1017/ice.2018.83.

Clinical characteristics and outcomes of hematologic malignancy patients with *Clostridium difficile* toxin immunoassay versus PCR positive test results

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Abstract

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

INTRODUCTION

Both infection and colonization with *Clostridium difficile* are common in patients with hematologic malignancy, with 10-29% of patients positive by culture on admission.[1-2] However, while there is increasing recognition that molecular-based testing (PCR) 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 (e.g., chemotherapy, antibiotics)[5,6] and 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 if these findings apply to patients with hematologic malignancy. Therefore, we aimed to compare clinical

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Potential conflicts of interest: All authors report no conflicts of interest relevant to this study.

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). Samples which 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).

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 chi-square or Fischer's exact test for categorical variables and the Wilcoxon rank-sum test for continuous variables (Stata 14.2, StataCorp LC, College Station, TX). For all calculations, a 2-tailed *P* value <0.05 was considered to be 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 (55%) patients had a PCR (+)/EIA (−) result, and 81 (45%) had an EIA (+) result. Among patients without neutropenia, leukocytosis (white blood cell count >15 thousand cells/mm^3) at the time of testing was significantly more common in the EIA (+) group (26%) versus PCR (+)/EIA (−) group (11%) (*P*=0.02) (Table 1). There was no difference in rates of severe CDI[9], fever, diarrhea, or imaging evidence of colitis between the two 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*=0.15).

Receipt of medications associated with an increased risk for *C.difficile* infection, 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 two groups.

We observed high rates of adverse outcomes in the cohort, including an in-hospital mortality rate of 18% and ICU transfer rate of 25%, but these were similar between the two groups (Table 2). Toxic megacolon was uncommon, but occurred in 2 (2%) of patients in the PCR (+)/EIA (−) group compared to 0 (0%) in the EIA (+) group (P=0.20). Most 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 demonstrate 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 (i.e., EIA versus PCR) cannot be used to reliably distinguish between *C. difficile* infection or colonization. Specifically, clinical factors typically associated with active or more severe infection[9] were similar between the two groups. Complicating the appropriate diagnosis of *C. difficile* infection 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 *C.difficile* infection 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 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 *C.difficile* infection with an EIA(+) result versus PCR (+)/EIA (−) result after GDH screening, but did not find a 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 are comparing EIA and PCR test results, these are among patients who have had a positive GDH screen. In a multi-center 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 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 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].

Acknowledgments

Financial support: This work was supported by the National Institutes of Health (grant no. T32-AI055435 to M.Z. and grant no. K01-AI103028 to J.H.H.) and by a CDC Cooperative Agreement, FOA#CK16-004-Epicenters for the Prevention of Healthcare Associated Infections. The funding agencies had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation, review, or approval of the manuscript.

The interim results of this study were presented at the Infectious Disease Society of America IDWeek as a poster (Presentation #1291) on October 6th, in San Diego, California

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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 No. (%) n=182	EIA Positive No. (%) n=81	PCR Positive No. (%) n=101	*P* Value
Age	62 (53-68)[a]	62 (55-68)[a]	62 (52-68)[a]	0.74
White race	140 (77)	61 (75)	79 (78)	0.64
Malignancy				
Acute myeloid leukemia	81 (45)	36 (44)	45 (45)	0.91
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 <72hrs within admission	33 (18)	17 (21)	16 (16)	0.37
History of stem cell transplant	67 (37)	35 (43)	32 (32)	0.11
History of *C.difficile*[b]	22 (12)	13 (16)	9 (9)	0.14
Prior hospitalization[c]	103 (57)	48 (59)	55 (54)	0.51
Chronic gastrointestinal disease[d]	32 (18)	18 (23)	14 (14)	0.13
Neutropenia[e]	64 (35)	24 (30)	40 (40)	0.14
Leukocytosis[f]	21(18)	15 (26)	6 (11)	0.02
Fever[g]	68 (37)	27 (33)	41 (41)	0.31
Albumin[h]	2.9 (2.4-3.4)	2.7 (2.2-3.3)	3.0 (2.5-3.5)	0.11
Severe *C.difficile* infection[i]	22 (12)	13 (16)	9 (9)	0.14
Diarrhea[j]	133 (73)	57 (70)	76 (75)	0.46
Stool count[k]	3 (2-5)[a]	3 (2-5)[a]	4 (2-6)[a]	0.15
Radiographic evidence of colitis	15 (8)	6 (7)	9 (9)	0.71
Medications[l]				
Proton-pump inhibitor	73 (40)	32 (40)	41 (41)	0.93
Histamine-2 antagonist	30 (16)	15 (19)	15 (15)	0.50
Corticosteroid	73 (40)	39 (48)	34 (34)	0.05
Loperamide	10 (6)	5 (6)	5 (5)	0.74

Characteristics	Total Population No. (%) n=182	EIA Positive No. (%) n=81	PCR Positive No. (%) n=101	*P* Value
Laxative[m]	54 (30)	21 (26)	33 (33)	0.32
Docusate	46 (25)	19 (23)	27 (27)	0.61
Antibiotics[c]				
Any antibiotic	145 (80)	65 (80)	80 (79)	0.83
Anti-pseudomonal Antibiotic[n]	119 (65)	55 (68)	64 (64)	0.52

NOTE. EIA, enzyme immunoassay; PCR, polymerase chain reaction

[a] Median, inter-quartile 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 < 500cells/mm^3 within 72 hours of the index *C. difficile* test

[f] Total white blood cell count (WBC) greater than 15,000 cells/mm^3, among non-neutropenic patients

[g] Temperature greater than 100.4 degrees Fahrenheit

[h] Within 72 hours, n=110

[i] Serum albumin <3g/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-hour period over 72 hours prior to the testing date

[l] Within the previous 72 hours of the testing date

[m] Includes sennosides, polyethylene glycol, milk of magnesia, bisacodyl, lactulose

[n] Cefepime, meropenem, piperacillin-tazobactam, and levofloxacin

TABLE 2

Outcomes of patients with hematologic malignancy and EIA versus PCR positive *C.difficile* test results

Outcomes	Total Population No. (%) n=182	EIA Positive No. (%) n=81	PCR Positive No. (%) n=101	*P* Value
In-hospital mortality[a]	33 (18)	18 (23)	15 (15)	0.18
ICU transfer[b]	45 (25)	23 (28)	22 (22)	0.30
Toxic megacolon	2 (1)	0 (0)	2 (2)	0.20
Colectomy	4 (2)	1 (1)	3 (3)	0.42
C.difficile recurrence	21 (12)	7 (9)	14 (14)	0.27
GVHD of the GI tract	11 (6)	6 (7)	5 (5)	0.48
Treatment[c]				
None	4 (2)	0 (0)	4 (4)	0.07
Oral vancomycin	118 (65)	57 (70)	61 (60)	0.16
Days	15 (10-21)[d]	15 (10-22)[d]	14 (10-21)[d]	0.83
Oral metronidazole	107 (59)	43 (53)	64 (63)	0.16
Days	10 (4-14)[d]	8 (3-14)[d]	11 (6-15)[d]	0.03
Intravenous metronidazole	49 (27)	21 (26)	28 (28)	0.79
Days	6 (3-12)[d]	6.5 (3.5-9.5)[d]	6 (3-15)[d]	0.64

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 more than one antibiotic for treatment

[d]Median, inter-quartile range (IQR)