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Basic Study

Characteristics of *Clostridium difficile* infection in patients hospitalized with myelodysplastic syndrome or acute myelogenous leukemia

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Abstract**AIM**

To evaluate factors associated with *Clostridium difficile* infection (CDI) and outcomes of CDI in the myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) population.

METHODS

After IRB approval, all MDS/AML patients hospitalized at the University of Maryland Greenebaum Comprehensive Cancer Center between August 2011 and December 2013 were identified. Medical charts were reviewed for demographics, clinical information, development of CDI, complications of CDI, and mortality. Patients with CDI, defined as having a positive stool PCR done for clinical suspicion of CDI, were compared to those without CDI in order to identify predictors of disease. A *t*-test was used for comparison of continuous variables and chi-square or Fisher's exact tests were used for categorical

variables, as appropriate.

RESULTS

Two hundred and twenty-three patients (60.1% male, mean age 61.3 years, 13% MDS, 87% AML) had 594 unique hospitalizations during the study period. Thirty-four patients (15.2%) were diagnosed with CDI. Factors significantly associated with CDI included lower albumin at time of hospitalization ($P < 0.0001$), prior diagnosis of CDI ($P < 0.0001$), receipt of cytarabine-based chemotherapy ($P = 0.015$), total days of neutropenia ($P = 0.014$), and total days of hospitalization ($P = 0.005$). Gender ($P = 0.10$), age ($P = 0.77$), proton-pump inhibitor use ($P = 0.73$), receipt of antibiotics ($P = 0.66$), and receipt of DNA hypomethylating agent-based chemotherapy ($P = 0.92$) were not significantly associated with CDI.

CONCLUSION

CDI is common in the MDS/AML population. Factors significantly associated with CDI in this population include low albumin, prior CDI, use of cytarabine-based chemotherapy, and prolonged neutropenia. In this study, we have identified a subset of patients in which prophylaxis studies could be targeted.

Key words: *Clostridium difficile*; Acute myeloid leukemia; Cytarabine-based chemotherapy; Myelodysplastic syndrome; Neutropenia

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Core tip: This study evaluates factors associated with the development and outcomes of *Clostridium difficile* infection (CDI) in patients with Myelodysplastic syndrome (MDS) or acute myelogenous leukemia (AML). Our findings demonstrate a high incidence of CDI with 15.2% of patients diagnosed with CDI during the 28-mo study period. Risk factors associated with the development of CDI include low albumin, prior history of CDI, chemotherapy within 30 d of hospitalization, cytarabine-based chemotherapy within 30 d of hospitalization, and increased duration of neutropenia and hospitalization.

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INTRODUCTION

Clostridium difficile is a gram-positive, spore-forming, anaerobic bacterium that is the major cause of nosocomial diarrhea in the developed world. Over the last two decades the rate, morbidity, mortality, and costs of *C. difficile* infection (CDI) have risen dramatically^[1].

Data from the United States Centers for Disease Control and Prevention show that the discharge diagnosis rate of CDI doubled from the 1990's into the 2000's^[2,3]. CDI rates have increased considerably since that time, with a current estimate of almost half a million cases and 29000 deaths per year occurring in the United States alone^[1]. This increase has not only been observed in hospitalized, elderly, and immunocompromised patients, but also in younger adults without significant comorbidities^[4]. Patients who develop CDI have significant increases to their length of hospitalization^[5]. According to a recent systematic review, attributable mean CDI costs range from \$8911 to \$30049 for hospitalized patients^[6]. The sheer burden of CDI necessitates a search for more effective means of preventing and combating this infection.

Current statistics indicate that approximately 53000 new cases of leukemia will be diagnosed in the United States this year, 20000 of which will be acute myeloid leukemia (AML)^[7]. Patients receiving treatment for myelodysplastic syndrome (MDS) or AML are at increased risk for developing CDI given their frequent neutropenic episodes, as well as exposure to antibiotics and chemotherapy^[8]. Antineoplastic agents have antimicrobial properties, and numerous chemotherapeutic drugs have been associated with the development of CDI, including cisplatin, etoposide, bleomycin, paclitaxel, vinblastine, 5-fluorouracil, cyclophosphamide, methotrexate, doxorubicin, and cytarabine-based regimens^[8]. Several risk factors for CDI in leukemia patients have been recently identified, which include receipt of chemotherapy, age > 65 years, admission at a teaching hospital, increased length of stay, diagnosis of acute rather than chronic leukemia, sepsis, and neutropenia^[9,10].

The aim of this study is to evaluate factors associated with CDI and outcomes of CDI in the MDS and AML population. Outcomes of interest include mortality and severe morbidity such as Intensive Care Unit (ICU) admission, need for surgical intervention, or recurrence of CDI.

MATERIALS AND METHODS

The Institutional Review Board of the University of Maryland, Baltimore, approved this study and waived the requirement for informed consent (IRB# HP-00058296). All patients with a diagnosis of MDS or AML were identified through an electronic medical record database utilized by the University of Maryland Medical Center (UMMC). Inclusion criteria were: Age greater than or equal to 18 years, a diagnosis of MDS or AML, and hospitalization at the UMMC Greenebaum Comprehensive Cancer Center between August 2011 and December 2013. Charts were reviewed for demographics, clinical information, development of CDI, complications of CDI, and mortality. The starting point of data collection was identified as August 2011, when UMMC began to utilize the illumigene® *C. difficile* DNA amplification assay (Meridian Bioscience, Inc.). The assay uses loop-

Table 1 Characteristics of Patients with *C. difficile* infection
n (%)

Variable (per patient)	CDI (<i>n</i> = 34)
Diagnosis	
AML	31 (91)
MDS	3 (9)
Gender	
Male	15 (44.1)
Female	19 (55.9)
PPI therapy ¹	22 (64.7)
Prior history of CDI	5 (14.8)
Receipt of chemotherapy ²	31 (91)
Type of chemotherapy	
Cytarabine-based chemotherapy	21 (61.7)
DNA hypomethylating agent-based chemotherapy	11 (32.3)
Death/referral to hospice	8 (23.5)
Severity of CDI ³	
Mild-moderate	29 (85.2)
Severe	4 (11.7)
Severe-complicated	1 (2.9)
Total number of CDI episodes during hospitalization	
1	31 (91)
2	3 (9)
Recurrence of CDI	4 (11.7)
ICU admission	8 (23.5)
Bowel perforation	0
Need for surgical intervention	1 (3)

¹PPI therapy defined as use of PPI documented at the time of hospital admission; ²Receipt of chemotherapy defined as being given within 30 d of hospital admission; ³Severity as defined by the SHEA/IDSA Guidelines^[12]. CDI: *Clostridium difficile* infection; AML: Acute myeloid leukemia; MDS: Myelodysplastic syndrome; PPI: Proton-pump inhibitor; ICU: Intensive care unit.

mediated isothermal DNA amplification to detect the *tcdA* 5' region present in all toxigenic *C. difficile*, and has a sensitivity and specificity of 95.2% and 95.3%, respectively^[11]. Our facility currently does not implement a two-step detection method for CDI.

Demographics and clinical data were recorded per patient encounter and included: Documented diagnosis of MDS or AML, age at diagnosis, gender, proton pump inhibitor (PPI) use during hospitalization or the within 30 d prior to hospitalization, any prior documented history of CDI, type of chemotherapy received during hospitalization or within 30 d prior to hospitalization, antibiotic use during hospitalization or within 30 d prior to hospitalization, total length of stay in days, albumin level at admission, duration of neutropenia during hospitalization, current episode of CDI as a recurrence, and documentation of death or referral to hospice. Data collected included factors previously associated with CDI and focused on investigating the primary aim of our study as described above. CDI was defined as a positive stool *C. difficile* test done in the setting of diarrhea, defined as the passage of 3 or more unformed stools in 24 or fewer consecutive hours^[12]. Our laboratory policy does not permit *C. difficile* testing on formed stool, thus we are reasonably confident all patients had diarrhea. Recurrence of CDI was defined as CDI in the setting of a positive *C. difficile* stool assay as well as receipt of

CDI treatment in the 8 wk prior to the current episode. Severity of CDI was determined based on the criteria set forth by the Society for Healthcare Epidemiology of America (SHEA) and Infectious Diseases Society of America (IDSA) guidelines^[12]. Chemotherapeutic regimens were defined as cytarabine-based, DNA hypomethylating agent-based, or other regimens. Neutropenia was defined as an absolute neutrophil count of 500 cells/ μ L or less.

MDS and AML patients with CDI were compared to those patients that were not diagnosed with CDI in order to identify factors related to disease. A *t*-test was used for comparison of continuous variables and χ^2 or Fisher's exact tests were used for categorical variables, as appropriate (SAS, version 9.2). Statistical significance was defined as *P* < 0.05. As some patients were hospitalized multiple times, data analysis was performed on variables per hospital encounter. Total days of neutropenia as well as total days of hospitalization during the study period were analyzed per patient. A biomedical statistician performed the statistical review.

RESULTS

We identified 223 patients with MDS or AML that had 594 unique hospitalizations between August 2011 and December 2013. Sixty point one percent of the patients were male, the mean age was 61.3 years, 87% had AML, and 13% had MDS. Thirty-four of the patients (15.2%) were diagnosed with CDI during the study period. Of these, 44% were male, the mean age was 59.2 years, 91% had AML, 9% had MDS, and 35% were on a PPI at time of admission. Sixty point seven percent received cytarabine-based chemotherapy, and 32.3% received DNA hypomethylating agent-based chemotherapy. None of the patients with MDS who developed CDI received cytarabine-based chemotherapy. Eighty-five percent received antibiotics during hospitalization or within the 30 d prior to hospitalization. Twelve percent had recurrent CDI, eight required intensive care unit admission, and one underwent colectomy for CDI. According to the classification criteria set forth by the SHEA/IDSA guidelines, 85.2% had mild-moderate disease, 11.7% had severe disease, and 2.9% had severe-complicated disease^[12]. Twenty-three point five percent of these patients died or were referred to hospice (Table 1).

Several factors were significantly associated with CDI when analyzed by hospital encounter (Table 2), including a lower albumin at the time of hospitalization (mean 2.8 g/dL in the CDI group vs 3.5 g/dL in the non-CDI group, *P* < 0.0001), prior history of CDI (*P* < 0.0001), receipt of any chemotherapy in within 30 d of hospitalization (92.1% in the CDI group vs 78.8% in the non-CDI group, *P* = 0.048), and receipt of cytarabine-based chemotherapy within 30 d of hospitalization (63.4% in the CDI group vs 45.5% in the non-CDI group, *P* = 0.015).

As some factors did not lend themselves to a per-hospital encounter analysis, we performed a per patient

Table 2 Comparison of myelodysplastic syndrome and acute myeloid leukemia patients with and without *Clostridium difficile* infection *n* (%)

Variable	No CDI (<i>n</i> = 556)	CDI (<i>n</i> = 38)	Significance (<i>P</i> value)	No CDI (<i>n</i> = 189)	CDI (<i>n</i> = 34)	Significance (<i>P</i> value)
Per encounter analysis						
Age on admission, mean (95%CI)	58.4 (57.0-59.8)	59.2 (54.6-63.9)	0.77			
Albumin level (g/dL) on admission, mean (95%CI)	3.5 (3.4-3.5)	2.8 (2.6-3.1)	< 0.0001			
AML (<i>vs</i> MDS) diagnosis	506 (91.0)	35 (92.1)	0.82			
Male gender	338 (60.8)	18 (47.4)	0.1			
Female gender	218 (39.2)	20 (52.63)	0.1			
Use of PPI therapy ¹	206 (37.0)	13 (34.21)	0.73			
Prior history of CDI	15 (2.7)	10 (23.32)	< 0.0001			
Antibiotic use	465 (84)	31 (83)	0.66			
Any chemotherapy ²	438 (78.8)	35 (92.1)	0.048			
Cytarabine-based chemotherapy ²	253 (45.5)	25 (65.79)	0.015			
DNA hypomethylating agent-based chemotherapy ² (<i>n</i>)	165 (29.7)	11 (29.0)	0.92			
Other chemotherapy ²	25 (4.5)	0 (0)	0.18			
Death or referral to hospice	82 (14.8)	8 (21.05)	0.29			
Per patient analysis						
Total days of neutropenia during study period				13.7 (11.3-16.0)	21.6 (14.5-28.7)	0.014
Total days of hospitalization during study period				22.7 (19.9-25.5)	40.8 (28.9-52.7)	< 0.0001

¹PPI therapy defined as use of PPI documented at the time of hospital admission; ²Receipt of chemotherapy defined as being given within 30 d of hospital admission. CDI: *Clostridium difficile* infection; MDS: Myelodysplastic syndrome.

analysis (Table 2) for total days of neutropenia during the study period (mean 21.6 d in the CDI group *vs* 13.7 d in the non-CDI group, *P* = 0.014), and total days of hospitalization during the study period (mean 40.8 d in the CDI group *vs* 22.7 d in the non-CDI group, *P* = 0.005).

DISCUSSION

Our findings demonstrate a high incidence of CDI in our MDS and AML population with 15.2% of patients diagnosed with CDI during the 28-mo study period. This is comparable to previous reports. In a retrospective study of AML patients receiving chemotherapy, the incidence of CDI was 18%^[13]. In another similar study, the incidence was 12%^[14]. Within this overall high-risk group, we identified several factors associated with CDI. Specifically, CDI is significantly associated with low albumin level at time of hospitalization, prior history of CDI, receipt of any chemotherapy within 30 d of hospitalization, receipt of cytarabine-based chemotherapy within 30 d of hospitalization, total length of neutropenia and total length of hospitalization.

Similar to previously published findings, we found a higher rate of CDI in women, though this result was not statistically significant (*P* = 0.10)^[1]. While other studies have identified associations between age and PPI use and risk for CDI^[13], age (*P* = 0.77) and PPI use (*P* = 0.73) were not associated with CDI in our population. In addition, use of DNA hypomethylating agent-based chemotherapy (*P* = 0.92) was not associated with CDI. No differences in mortality or referral to hospice rates during the study period were identified between CDI and non-CDI groups (*P* = 0.29). It is well established that the greater the antibiotic exposure, the greater the risk of CDI^[12,13]. However, infections during a neutropenic

state are associated with high mortality rates, and thus antibiotic prophylaxis is indicated in patients with high-risk neutropenia per American Society of Clinical Oncology guidelines^[15]. Fluoroquinolones are generally the agents of choice in these situations. The emergence of the NAP1/BI/027 hypervirulent strain is associated with an increased incidence of CDI over the past 15 years^[16]. Fluoroquinolone resistance characterizes the NAP1/BI/027 strain^[16], which may be one reason for increased risk of CDI in this population. In our study, 85% of patients received antibiotic therapy. Interestingly, antibiotic usage was not significantly associated with CDI (*P* = 0.66). This likely reflects insufficient power to detect a difference given the high rate of antibiotic use in this population. Previous studies examining strategies to improve antibiotic prescribing practices of providers have shown mixed results in the reduction of CDI incidence^[17]. However, reducing the duration and potency of antibiotics used, particularly after initial presentation of CDI, would be an interesting area of study for the MDS and AML population.

Consistent with our findings, low albumin levels have previously been established as a risk factor for the development of CDI^[18]. A low albumin level may indicate poor baseline health status, malnutrition, or the presence of other comorbidities such as cirrhosis or nephrotic syndrome, all which may increase susceptibility to CDI^[19,20]. Also, low albumin may be found in cases of diarrhea and loss of protein due to mucositis/enterocolitis in patients after chemotherapy for AML. A prior history of CDI was associated with CDI, as demonstrated in previous studies^[21]. Prior history of CDI may predispose a patient to future episodes of CDI due to patient colonization, environmental contamination, or the presence of persistent risk factors.

The majority of patients in our study had a confir-

med diagnosis of AML and received treatment with cytarabine-based chemotherapy. Based on our findings, any chemotherapy, and cytarabine-based therapy in particular, was associated with development of CDI. This may be related to neutropenia, as total days of neutropenia was also significantly increased in patients that developed CDI. Chemotherapeutics are also known to disrupt enteric bacterial populations and the resulting dysbiosis may predispose to CDI^[8]. While there is a paucity of data on the effect of different chemotherapeutic regimens on the gastrointestinal microbiome, cytotoxic changes may create a favorable environment for the proliferation of *C. difficile*. Microbial data suggests that chemotherapeutics may select for colonization of *C. difficile* and *Enterococcus faecium*^[22].

We evaluated several factors that did not prove to be significantly associated with CDI in our MDS and AML population, including age, gender, PPI use, use of DNA hypomethylating agent-based chemotherapy, and antibiotic use. In theory, PPI therapy may increase the risk of CDI by increasing the ability of *C. difficile* spores to survive in the lumen of the gastrointestinal tract. While there has been controversy regarding their significance, a meta-analysis demonstrated a significant association between PPI use and risk of developing CDI (OR = 1.74, 95%CI: 1.47-2.85)^[23]. Within the same study there appears to be increased risk with concomitant use of antibiotics and PPIs, and increased risk of recurrence with PPI use^[23]. Non-cytarabine based chemotherapy, which in the case of our study was primarily DNA-hypomethylating agents, was not associated with CDI. We hypothesize that cytarabine-based agents are generally more caustic and induce a greater period of neutropenia, thus providing a more favorable environment for CDI in comparison to less cytotoxic agents.

We believe that our findings will inform future CDI prophylaxis studies in the high-risk MDS and AML population. We have identified a subset of this population, namely those with low albumin, prior CDI, or receipt of cytarabine-based chemotherapy, who can be identified at time of hospital admission as being especially high-risk for CDI. Recently, metronidazole prophylaxis has been proposed as a possible strategy for CDI prevention, however data specifically looking at patients with malignancies has not been supportive of prophylactic antibiotic treatment to prevent CDI^[24,25]. In addition, the anti-toxin monoclonal antibody bezlotoxumab was recently approved by the FDA, and a toxoid vaccine in phase III clinical study is likely to be available soon^[26,27]. Studies of these agents for CDI prophylaxis in our high-risk patient population are warranted.

Our study is not without limitations. Our study is retrospective and took place in a single tertiary medical center. We included primarily AML patients with a high degree of medical complexity, and our findings may not be generalizable to other populations. Additionally, many of the patients had prolonged hospital stays or numerous admissions throughout the testing period,

and our study design was ill-equipped to evaluate temporal relationships between chemotherapy and CDI onset. Another limitation is our inability to analyze the degree in which antibiotics predict development of CDI in this population. While antibiotic usage was not found to be associated with CDI in our study, the widespread use of antibiotics makes this difficult to assess. While antibiotic exposure is not necessary for the development of CDI, it is likely to contribute to our population's overall CDI risk^[10].

In conclusion, CDI is common in our MDS/AML population. Factors significantly associated with CDI include low albumin, prior history of CDI, use of cytarabine-based chemotherapy, and prolonged neutropenia. Length of hospitalization is also associated with CDI; however, this is likely both a cause and effect of CDI. Prophylactic strategies to lower the burden of CDI in MDS/AML patients are needed. In this study, we have identified a subset of this high-risk population in which prophylaxis studies could be targeted. These findings are novel and increase our understanding of CDI in this patient population as well as open new frontiers of research.

COMMENTS

Background

Acute myelogenous leukemia (AML) and Myelodysplastic syndrome (MDS) are blood borne malignancies that require strong treatments with heavy doses of chemotherapy, which leaves these patient's susceptible to opportunistic infections. *Clostridium difficile* infection (CDI) remains a major cause of nosocomial diarrhea and is of significant importance to the immunosuppressed population, such as those receiving chemotherapies for AML and MDS.

Research frontiers

CDI has been recognized as a major contributor of increased morbidity and mortality in hospitalized patients. New treatment regimens, such as vaccinations, immunotherapy, and fecal transplantation are currently undergoing evaluation. It is essential to identify certain susceptible populations in which targeted therapy for CDI can be investigated. Patients with AML and MDS are particularly susceptible to CDI and further characterization of CDI in this population is warranted.

Innovations and breakthroughs

The authors have found that CDI is common in this specific patient populations. Factors significantly associated with CDI in this population include low albumin, prior CDI, use of cytarabine-based chemotherapy, and prolonged neutropenia. The authors have identified a subset of patients in which prophylaxis studies could be targeted

Applications

By identifying and characterizing CDI within this specific patient population, the authors have identified a cohort of patients that would benefit from future novel CDI therapies and possible CDI prophylaxis. The authors have also identified risk factors that would enable providers to recognize patients that are particularly susceptible for identifying CDI and adjusting their management accordingly.

Terminology

CDI was defined as a positive stool *C. difficile* test done in the setting of diarrhea, defined as the passage of 3 or more unformed stools in 24 or fewer consecutive hours. Recurrence of CDI was defined as CDI in the setting of a positive *C. difficile* stool assay as well as receipt of CDI treatment in the 8 wk prior to the current episode. Severity of CDI was determined based on the

criteria set forth by the Society for Healthcare Epidemiology of America (SHEA) and Infectious Diseases Society of America guidelines. Chemotherapeutic regimens were defined as cytarabine-based, DNA hypomethylating agent-based, or other regimens. Neutropenia was defined as an absolute neutrophil count of 500 cells/ μ L or less.

Peer-review

The authors have shown that CDI is common in the MDS/AML population. Factors significantly associated with CDI in this population include low albumin, prior CDI, use of cytarabine-based chemotherapy, and prolonged neutropenia. The findings are worthy of sharing with the scientific community.

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