American Journal of Infection Control 47 (2019) 394–399

Contents lists available at ScienceDirect

American Journal of Infection Control

journal homepage: www.ajicjournal.org

Major Article

Clostridioides difficile colonization and infection in patients with newly diagnosed acute leukemia: Incidence, risk factors, and patient outcomes

Clyde D. Ford MD [a,*], Bert K. Lopansri MD [c,d], Brandon J. Webb MD [b,d], Jana Coombs BS [d], Launce Gouw MD [a], Julie Asch MD [a], Daanish Hoda MD [a]

[a] *Intermountain Acute Leukemia Program, LDS Hospital, Salt Lake City, UT*
[b] *Department of Medicine, Division of Infectious Diseases and Geographic Medicine, Stanford University, Stanford, CA*
[c] *Department of Medicine, Division of Infectious Diseases, University of Utah, Salt Lake City, UT*
[d] *Department of Medicine, Division of Infectious Diseases and Clinical Epidemiology, Intermountain Healthcare, Salt Lake City, UT*

Key Words:
Clostridioides difficile
Leukemia
Antibiotics
Infection

Background: The frequency, risk factors, and outcomes for *Clostridioides difficile* infection (CDI) in patients with newly diagnosed acute leukemia (AL) admitted for induction therapy are unclear.
Methods: We studied 509 consecutive patients with AL admitted between 2006 and 2017 and conducted a prospective *C difficile* surveillance and ribotyping analysis in a subset of these.
Results: The incidence of CDI was 2.2/1,000 inpatient days during induction, and CDI was rare after discharge. CDI was highest in patients with acute myelogenous leukemia. A hospitalization shortly before admission and administration of a greater number of antibiotics increased the risk for CDI. No single class of antibiotics conveyed an increased risk. All cases were successfully treated, and CDI was not associated with an increase in length of stay, costs, or mortality. In a subgroup analysis, 16% of patients with acute myelogenous leukemia and 4% with other leukemia types were colonized on admission. Colonization was associated with a higher risk of CDI. Ribotyping of available isolates showed 27 different strain types with 014/020 and 027 being the most frequent.
Conclusions: The number of antibiotics administered are a major risk factor for CDI in patients with AL. However, CDI appears to have minimal clinical impact in this population.
© 2018 Association for Professionals in Infection Control and Epidemiology, Inc. Published by Elsevier Inc. All rights reserved.

Clostridioides difficile infection (CDI) is the most common cause of antibiotic-associated diarrhea. Although CDI has been most often attributed to acquisition in a hospital setting, community-onset infection is increasing.[1] Moreover, a number of CDI cases have no epidemiologic or molecularly confirmed links to known sources.[2] *C difficile* may cause large hospital outbreaks from the emergence and dominance of certain ribotypes and hypervirulent strains.[3,4,5]

Hospitalized patients with acute leukemia (AL) have been reported to be at significantly increased risk for CDI,[6,7,8] and CDI has been associated with increased mortality, length of stay (LOS), and cost.[8] Most patients with newly diagnosed AL are admitted to the hospital and receive induction therapy. The goal is to obtain a complete remission, in which case the patient may proceed to consolidation or maintenance treatment with the expectation of improved survival and quality of life. During induction, patients typically spend several weeks in the hospital during which time they are severely immunosuppressed, often infected, frequently on prolonged courses of broad-spectrum antibiotics, and housed on units with other patients who are at risk for toxigenic *C difficile* colonization or CDI.

There are currently insufficient data on the incidence, risk factors, and consequences of CDI for newly diagnosed patients admitted for induction therapy. Because CDI is not a common event, prior studies

*Address correspondence to Clyde D. Ford, MD, Intermountain Acute Leukemia and Blood and Marrow Transplant Program, LDS Hospital, Eighth Ave and C St, Salt Lake City, UT 84143.
E-mail address: clyde.ford@imail2.org (C.D. Ford MD).
Funding/support: This work was supported by a grant from the Intermountain Healthcare Medical and Research Foundation (grant no. 20600035); the Utah Cancer Registry is funded by the National Cancer Institute's Surveillance, Epidemiology, and End Results Program (contract no. HHSN2612013000017I) and the United States Center for Disease Control and Prevention's National Program of Cancer Registries (cooperative agreement no. NU58DP0063200-01), with additional support from the Utah Department of Health and the University of Utah.
Conflicts of interest: B.K.L. received research support from Cubist/Merck and OpGen in support of projects unrelated to this study. B.K.L. is a member of an advisory board for Merck & Co. There are no other conflicts of interest or financial disclosures to report.

https://doi.org/10.1016/j.ajic.2018.09.027
0196-6553/© 2018 Association for Professionals in Infection Control and Epidemiology, Inc. Published by Elsevier Inc. All rights reserved.

have increased sample sizes by combining patients admitted for AL induction and those with other hematologic malignancies,[7, 9,10,11,12] or comingling admissions for induction with postinduction hospitalizations for a variety of indications.[6,13] In contrast to patients with AL admitted for induction, the other patients usually have relatively short durations of neutropenia and antibiotic administration and, thus, may not reflect the same risk of CDI. In this study, we describe a single-center experience with a large consecutive population of patients admitted with newly diagnosed AL. We include a prospective study of *C difficile* colonization in a subgroup of these patients and characterize the distribution of *C difficile* ribotypes on our unit.

METHODS

Patients and treatments

We studied 509 consecutive patients with newly diagnosed acute myelogenous leukemia (AML), acute lymphoblastic leukemia (ALL), biphenotypic leukemia , or chronic myelogenous leukemia in blast phase who were admitted between October 2006 and August 2017. Suitably fit patients who consented received induction therapy. Patients were housed in individual rooms, most with high-efficiency particulate air filtration and positive-pressure airflow. Hand hygiene was required before entering the room. Patients had central venous catheters and received prophylactic proton pump inhibitors. Patients were not monitored for *C difficile* colonization, and those diagnosed with CDI were placed into contact isolation (gloves and gowns). The hospital diagnostic test for the presence of toxigenic *C difficile* in the stool evolved over the course of the study as follows: toxins A/B by enzyme immunoassay (bioMerieux, Cambridge, MA) prior to November 2010, nucleic acid amplification test for toxin A (Meridian Bioscience, Cincinnati, OH) from November 2010 to January 2014, and glutamate dehydrogenase (GDH) and toxins A/B (Alere, Waltham, MA) with reflex to polymerase chain reaction (PCR) for toxin B (Cepheid, Inc, Sunnyvale, CA) after January 2014. In September 2015, a multiplex molecular panel to detect 24 gastrointestinal pathogens including *C difficile* was introduced, and samples positive for *C difficile* were reflexed to GDH/toxin detection in reverse of the normal algorithm. Afebrile neutropenic patients received antimicrobial prophylaxis, usually levofloxacin, penicillin, and micafungin. Empirical treatment for febrile neutropenia was a carbapenem, cefepime, or piperacillin/tazobactam.

Patient data

Clinical data were acquired from our program's Acute Leukemia Database, laboratory data from the Intermountain Healthcare Enterprise Data Warehouse, and cost data from the hospital case mix database. Total patient costs (direct + indirect), adjusted to 2017 dollars, were estimated by relating total hospital costs to charge codes. Cost data were available for over 98% of the patients, including all with CDI. Costs for patients dying during the interval being evaluated were included. For data on antibiotic exposure, patients were considered to have received an antibiotic if 1 or more doses were administered on the day under consideration, and the total number of days on each antimicrobial was calculated. The total number of days that each specific antibiotic was administered was then acquired. Population-based data on AL was provided by the Utah Cancer Registry.

Definitions

CDI: the presence of (1) unformed stools, (2) a positive stool test for *C difficile* toxin or toxin genes, and (3) a diagnosis of CDI by the clinical staff. Toxigenic *C difficile* colonization: a positive stool test not accompanied by diarrhea or other potentially related symptoms or signs of CDI. Colonization on admission: *C difficile* colonization detected in a first stool submitted during the first week of hospitalization. Hospital-acquired *C difficile*: a negative admission stool followed by *C difficile* colonization and/or CDI during hospitalization. The day of admission was defined as hospital day 0.

Assessment for C difficile *colonization*

Stool samples are routinely ordered at admission and weekly thereafter for detection of vancomycin-resistant *Enterococcus*. Portions of these stools were saved by the nursing staff for the present study. Human fecal samples were stored at −80°C. After thawing, samples were inoculated onto *C difficile* ChromID agar plates (bioMérieux, Marcy l'Etoile, France) and incubated at 35°C for 48 hour. Grey-to-black colonies were sub-cultured on Trypticase Soy agar with 5% Sheep Blood (Becton, Dickinson and Company, Sparks, MD) and incubated for 48 hours under anaerobic conditions. The identity of uncertain isolates was confirmed by matrix-assisted laser desorption ionization-time of flight. Pure isolates were frozen at −80°C. The presence of GDH and toxins A and B were determined using C diff Alere Quik Chek Complete (Alere North America, LLC, Orlando, FL). The presence of toxin genes by PCR was detected using the Cepheid Xpert *C difficile* PCR/EPI test (Cepheid, Sunnyvale, CA).

PCR ribotyping

C difficile ribotyping was performed based on a previously described[14] semi-automated method combining amplification of the 16S-23S intergenic spacer region with DiversiLab chip kit and software. DNA was extracted using the UltraClean Microbial DNA Isolation Kit (Qiagen, Germantown, MD), amplified using a GeneAmp PCR System 9700 (Applied Biosystems, Foster City, CA), and loaded onto DiversiLab DNA chips (bioMérieux, Durham, NC). Fragments were resolved using the Agilent 2100 Bioanalyzer (Agilent, Santa Clara, CA) and analyzed using the DiversiLab web-based software. Strains were considered identical if they had $\geq$97% identity and no bands were different on visual inspection of the electropherograms. Results were compared with those of control strains obtained from American Type Culture Collection (Manassas, VA), and through Bei Resources (National Institute of Allergy and Infectious Diseases, National Institutes of Health, Manassas, VA).

Statistical analysis

Cumulative incidences of colonization and CDI during hospitalization and overall survival were estimated using the Kaplan-Meier method. For overall survival, patients were censored at last follow-up or when they proceeded to allogeneic hematopoietic stem-cell transplantation, hazard ratio (HR) (95% confidence interval [CI]) and *P* values for the figures were calculated using the log-rank test. For multivariable comparison of risk factors and antibiotic administrations for patients with and without CDI, Cox proportional-hazards models incorporating all variables were used to estimate HR and 95% CI. Potential risk factors for CDI were identified from the literature and included age, gender, history of diabetes, hospitalization within 2 months of admission, antibiotic administration within 3 months of hospitalization, Karnofsky performance status, admission serum albumin, inpatient days of severe neutropenia, number of antibiotics administered during admission, and total days of antibiotics during admission. Antibiotics with a frequency of administration adequate for analysis were divided into groups as follows: cephalexin/nafcillin, daptomycin/linezolid, vancomycin, fluoroquinolones, third- and fourth-generation cephalosporins, carbapenems, extended-spectrum penicillins, and antifungal agents, with the number of days each was received recorded. Individual patient outcomes were compared using

2-tailed Fisher's exact or Mann-Whitney U tests. A P value of $<.05$ was considered statistically significant.

RESULTS

Characteristics of the 509 patients are summarized in Table 1. Patient ages, genders, and AML predominance are as expected for this cohort. The median follow-up for deceased patients was 3 (range 0.1-118) months and for surviving patients 11 (range 0.1-125) months. Thirty-eight patients (7%) did not receive anti-leukemic therapy, because of either age, an inadequate performance status, and/or patient preference. Fifty-five patients (11%) died during hospitalization at a median of hospital day 12 (range 0-65).

Frequency, recurrence, and risk factors for CDI

Thirty-one patients (6%) were diagnosed with CDI for an overall incidence of 2.2 CDI/1,000 inpatient days. All patients were successfully treated, receiving a median of 18 days of oral metronidazole and/or vancomycin. Patients were often treated until neutropenia resolved. Four of 19 patients receiving initial metronidazole were changed to vancomycin because of the clinical perception of metronidazole failure.

Only 1 of the patients with CDI had a recorded history of prior episode (a patient with a second pre-existing hematologic malignancy), and only 3 patients had CDI detected following discharge. Two of these patients were undergoing hematopoietic stem-cell transplantation and 1 patient was receiving re-induction therapy for leukemic relapse.

The cumulative incidence of CDI for the entire patient cohort is shown in Figure 1A. This increased linearly during the first 3 weeks, and then plateaued at the time when many patients had increasing absolute neutrophil counts and were discontinuing broad-spectrum antibiotics. Patients with AML were more than twice as likely as those with other leukemic subtypes to develop CDI ($P = .049$; Fig 1B).

We compare some potential risk factors between patients with and without CDI in Table 2. CDI was not associated with older age, female gender, a lower admission serum albumin, or a history of diabetes. A recent prior hospitalization and, administration of a greater number of antibiotics, conveyed increased risk. The association of the antimicrobial groups of agents, recorded as the number of days administered, with CDI was investigated using a Cox multivariable analysis. No antibiotic grouping was found to be predictive for CDI. There was a trend for carbapenems to be protective (HR 0.38 [95% CI 0.13-1.1]; $P = 0.07$). AML patients were more likely than ALL patients to have received antibiotics during the prior 3 months (41%-28%, $P = 0.02$) and received a greater number of antibiotics (median 5 [range 0-9] vs median 3 [range 0-9]; $P < 0.0001$) and more days of antimicrobials (median 31 [range 0-118] vs 24 [0-53; $P < 0.0001$) during hospitalization.

Table 1
Characteristics of the 509 patients admitted with newly diagnosed AL

Group, characteristic	Value
Number of patients	509
Age, median (range), y	58 (18-88)
Gender	
Male	286 (56%)
Female	223 (44%)
Diagnosis	
AML	404 (79%)
Secondary AML	60 (12%)
ALL	93 (18%)
BPL	8 (2%)
CML-BP	4 (1%)
Prior hospitalization (2 mo)	157 (31%)
Prior antibiotics (3 mo)	197 (39%)
History of diabetes	82 (16%)
Received induction therapy	471 (93%)
Hospital length of stay, median (range), d	29 (1-117)
Deaths in hospital	55 (11%)
Patients with CDI during hospitalization	31 (6%)
CDI following hospitalization	3 (0.6%)
Bacteremia during hospitalization	85 (17%)
Patients receiving HSCT	132 (26%)

AL, acute leukemia; *AML*, acute myelogenous leukemia; *ALL*, acute lymphoblastic leukemia; *BPL*, biphenotypic leukemia; *CDI*, *Clostridioides difficile* infection; *CML-BP*, chronic myelogenous leukemia in blast phase; *HSCT*, hematopoietic stem-cell transplantation.

CDI and patient outcomes

We investigated several outcomes for their association with CDI (Table 3). Compared to patients without CDI, those with CDI showed a trend towards longer LOS but no differences in incidence of bacteremia, median or overall survival (Fig. 1C), number of hospital deaths, or costs.

C difficile *colonization*

We evaluated 100 patients without diarrhea who submitted a stool during the first week of hospitalization (median day 2). Twelve (6 toxigenic) of 75 (16%) patients with AML and 1 (1 toxigenic) of 25 (4%) patients with other leukemic types were colonized. The cumulative rate of acquisition of toxigenic *C difficile* during hospitalization for the 93 patients with toxigenic *C difficile* negative admission stools is shown in Figure 1D. Colonization was detected in 7 (8%) of the patients.

C difficile *colonization and CDI*

Two of the 7 (29%) patients colonized on admission with toxigenic *C difficile* and 3 of the 93 (3%) not colonized were diagnosed with CDI (Risk ratio 8.9 [95% CI 1.8-44.6%], $P = 0.04$) during hospitalization. This corresponds to incidences of 11.2 CDI/1,000 inpatient days and 1.1 CDI/1,000 inpatient days, respectively.

C *difficile ribotypes*

To estimate the number of toxigenic *C difficile* strain types on the unit and their individual prevalence, we PCR-ribotyped an available *C difficile* positive stool from 90 admissions (Fig. 2). Twenty-seven ribotypes were identified. Four ribotypes made up 50% of the samples. The most common ribotype was 014/020 followed by ribotype 027.

DISCUSSION

To our knowledge, this is the first large series of newly diagnosed patients with AL that examines the incidence, risk factors, and consequences of CDI associated with leukemic induction. Newly diagnosed patients typically have extended hospital stays, prolonged courses of broad-spectrum antibiotics, and an increased risk of environmental exposures to toxigenic *C difficile*. These factors might be expected to place these patients at an especially high risk. Conversely, our CDI incidence is similar to that reported for patients hospitalized with various hematologic malignancies,[6,8,9,13] which is increased, but not greatly so, over general hospitalized populations.[15]

A number of risk factors for CDI have been suggested in prior studies of hematologic malignancies. There has been disagreement over the predictive value of older age and female gender.[6,8,11,12,13,16] We found no association with these demographic parameters. Also, we

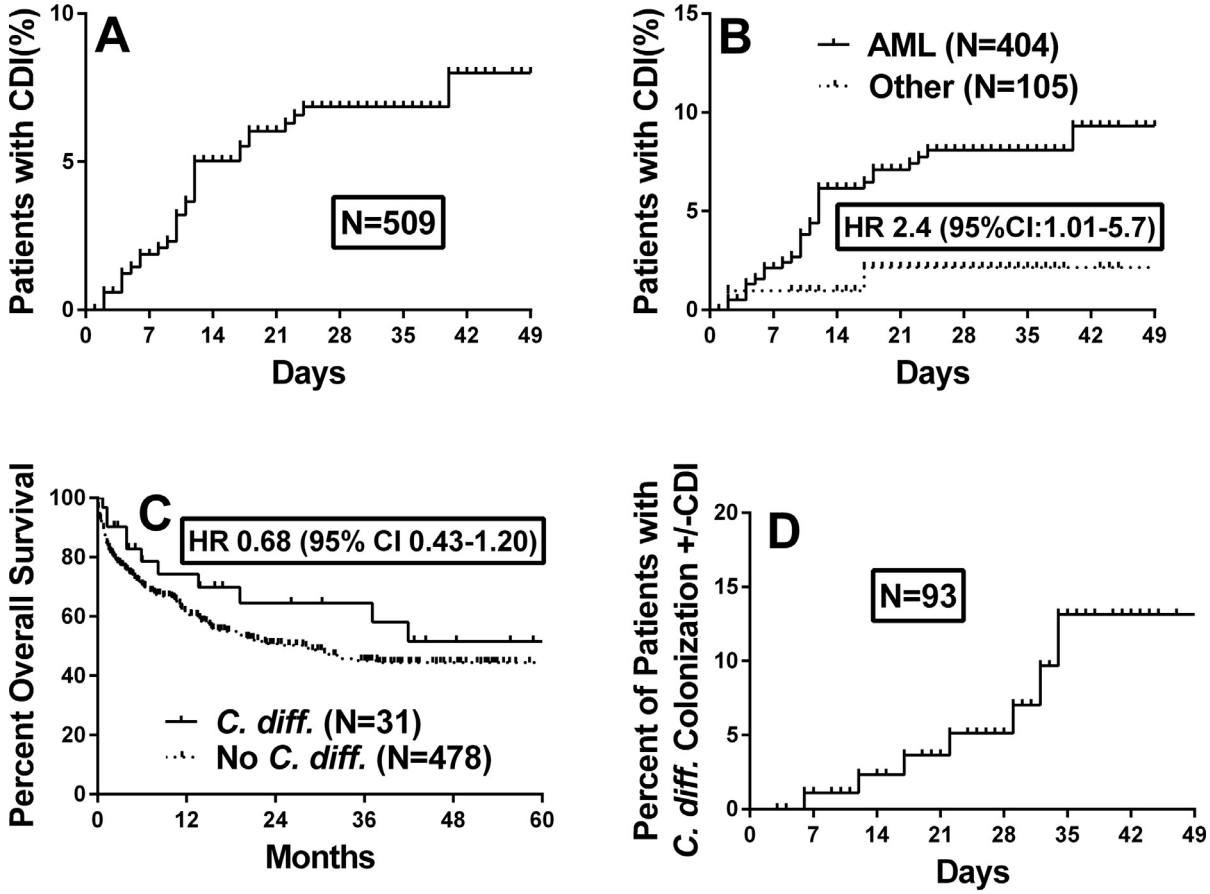

Fig 1. (A) Cumulative rate of *Clostridioides difficile* infection (CDI) for all patients. (B) Cumulative rate of CDI for patients with acute myelogenous leukemia (AML) compared to other types of acute leukemia. (C) Overall survivals for patients with and without CDI during admission for potential leukemic induction. (D) Cumulative rate of CDI for patients with an admission stool sample that was negative for toxigenic *C difficile* testing. Hazard ratio (HR) and confidence interval (CI) were calculated using the log-rank test.

Table 2
Comparison of 31 patients with and 478 patients without CDI during hospitalization for newly diagnosed AL

Group, characteristic	Multivariable HR*	*P* value
Patient demographics		
Age	1.01 (0.98-1.03)†	.61
Gender female	1.02 (0.51-2.1)	.96
Patient history		
Diabetes	1.8 (0.74-4.4)	.19
Hospitalization prior 2 mo	2.6 (1.2-5.8)	.02
Antibiotics prior 3 mo	0.39 (0.14-1.08)	.07
Admission co-morbidity		
Karnofsky performance Status	0.99 (0.97-1.02)	.55
Admit serum albumin, g/dL	1.04 (0.53-2.0)	.92
Hospital parameters		
Severe neutropenia (d)	0.44 (0.17-1.2)	.10
Antibiotics (no.)	1.2 (1.04-1.5)	.02
Antibiotics (d)	0.74 (0.65-0.84)	< .01

AL, acute leukemia; *HR*, hazard ratio.
*All variables in Table 2 were included in the model.
†(HR [95% confidence interval]).

could not confirm a correlation with admitting measures of co-morbidity such as serum albumin[7] or a history of diabetes.[8,16]

Our analysis shows that patients with AML are at higher risk for CDI. At least in part, this relates to the greater number of antibiotics in our AML cohort. It may be that other differences between AML and ALL patients will be found to be important. For example, the two groups receive distinct induction chemotherapy regimens. Whether individual chemotherapeutic agents increase infection risk by mechanisms other than myelosuppression is unclear.

Several authors have examined the relationship between various classes of antibiotics and CDI in patients with hematologic malignancies. These have identified ceftazidime,[6] cephalosporins,[11] or carbapenems.[13] To our knowledge, this study is the largest to address this question, and we could not identify an association with any antibiotic classes. Of additional interest was a trend for carbapenems to be protective, possibly because of their activity against *C difficile*.[18]

Our data suggest that the number of antibiotics are a greater risk factor than antimicrobial classes, possibly because of increased effects on gut flora. Also, a recent prior hospitalization, which in our patients was usually because of pre-diagnosis fever and/or infection, also seems to increase CDI. This may be due to an increased risk of *C difficile* colonization, as suggested by Behar et al.[17] A number of our patients received outpatient antibiotics for various local infections. However, antibiotic exposure within 3 months of admission, which has also been reported to increase *C difficile* colonization,[18] did not increase CDI.

Our results show that patients admitted for induction and those admitted post-induction for various leukemia-related indications (median about 2 admissions/patient in our experience) are 2 distinct risk groups for CDI. The latter typically have short admissions (median 5 days in our experience), may or may not receive antibiotics or chemotherapy, and rarely develop CDI. Thus, analyses that combine the longer induction admissions with the shorter subsequent ones[6,12] will inevitably identify longer LOS, more days of neutropenia,

Table 3
Comparisons of outcomes between Patients with and without *Clostridioides difficile* infection

Outcome	CDI	No CDI	*P* value
Patients (no.)	31	478	—
Lengths of stay, d	31 (13-58)	29 (1-117)	0.054
Bacteremia during hospitalization	4 (13%)	83 (17%)	0.48
Overall survival (median), mo	NR*	28.1	—
Deaths in hospital	1 (3%)	54 (11%)	0.23
Costs, median (range) $x10^4			
Hospitalization	9.2 (0.30-21)	9.3 (0.08-48)	0.54
First 3 mo following admit	13.4 (2.1-32)	12.3 (0.2-70)	0.89
First year following admit	19.1 (2.1-42)	17.6 (0.2-113)	0.74

*The median overall survival had not been reached at the time of the study.

and a greater number of antibiotic days as risk factors for CDI. Whether these are simply markers for the longer induction hospitalizations or directly contribute to CDI pathophysiology is less clear. Conceivably a longer LOS may increase opportunities for *C difficile* acquisition, more antimicrobials may cause greater disruption of gastrointestinal microbiota, and, perhaps, the immunosuppression associated with the neutropenic period may result in decreased CDI resistance.[19] For newly diagnosed patients, who typically present with neutropenia, begin antibiotics at admission, and develop CDI in the midst of neutropenia and antibiotic administration, LOS, days of antibiotics, and days of neutropenia would not emerge as risk factors.

At least 1 group has reported that blood-stream infection rates, in this case with vancomycin-resistant *Enterococcus*, are increased in patients with CDI.[20] We suggest that which organism is cultured from the blood is probably more dependent on patient colonization status, and whether a BSI with any organism occurs relates more to patient susceptibility factors, such as immune and mucosal compromise.[21] Thus, it may be more appropriate to ask if CDI increases the overall risk for bacteremia. If so, mucosal inflammation and break down, especially in the setting of neutropenia, could promote translocation of bacteria into the blood stream, and/or CDI could be a marker for greater microbiota disruption, which has been associated with sepsis.[22] However, in our patient cohort, CDI, at least in the relatively mild form experienced by our patients, did not increase the risk for bloodstream infections.

Concerns about CDI on units caring for patients with hematologic malignancies raise the question whether all patients should undergo admission screening for *C difficile* colonization. The low rate of colonization at admission and during hospitalization combined with the relatively benign nature of CDI in our patients suggest that routine screening is not warranted, unless, perhaps, in the setting of an outbreak or if hypervirulent strains are suspected. If patients are screened on admission, a negative stool suggests an increased consideration of other causes of subsequent diarrhea.

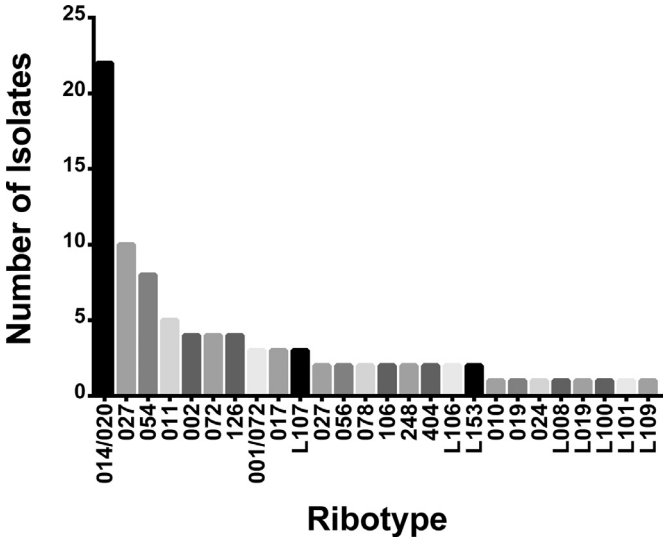

Fig 2. Prevalence of 27 ribotypes obtained from an available stool from 90 patient admissions between 2015 and 2017. Ribotypes preceded by "L" could not be matched with control strains obtained from the American Type Culture Collection.

There are few data on the effect of CDI on the outcomes of LOS, overall survival, and cost for patients with hematologic malignancies. In a large "nationwide analysis" combining hospitalizations of patients with acute and chronic leukemia, it was concluded that mortality, LOS, and costs are increased with CDI.[3] Similar findings in patients with malignancies were reported in a large regional multihospital discharge database.[23] In these studies, however, the patients without CDI had significantly shorter hospitalizations (mean 5 and 10 days, respectively). Since cost is driven primarily by LOS, and patients with unresolved comorbidities unrelated to CDI would tend to stay in the hospital longer, the relation of CDI itself to these outcomes has been unclear. Our results show that CDI itself seems to make no significant contribution to LOS, mortality, and cost in our patient population.

We found that ribotype 014/020 was the most common on our unit followed by 027. The predominance of 014/020 strains is consistent with previous epidemiologic surveys showing predominance of 014/020 in the Western United States and 027 in all other regions of the United States.[24] The clinical significance and outcomes of CDI from ribotype 014/020 has yet to be defined. We did not observe severe outcomes or increased mortality in our patients with 027.

A strength of our study is our large consecutive patient series. Limitations include a retrospective single institutional study with local practice patterns. Because of the relative homogeneity of our patient population, we were unable to assess some important issues, such as the association of CDI with administration of proton pump inhibitors (received by 96% of patients) or anti-leukemic treatment (93%). In addition, complete data on antibiotic administration prior to hospitalization were not uniformly available, so antimicrobial exposures may have been underestimated in some patients. The infrequent occurrence of CDI despite our large sample limited the power of some of our statistical analyses. Last, our patient cohort was not entirely a representative sample of all newly diagnosed patients in Utah. Being a referred population, our patients differed in expected ways. Comparison with data from the Utah Cancer Registry showed that our subgroup of patients were younger (median 58 vs 64 years), and a greater percentage received anti-leukemic therapy (median 93% vs estimated 80%).

CONCLUSIONS

CDI is relatively infrequent among newly diagnosed patients with AL and has little, if any, effect on patient outcomes. CDI is more common in patients with AML than other types of leukemia. Risk factors for CDI include a prior recent hospitalization and, a greater number of antibiotics. *C difficile* colonization on admission seems to be more frequent in patients with AML and conveys a greater risk of CDI. *C difficile* ribotypes 014/020 and 027 are most frequent on our unit.

Acknowledgments

The authors would like to thank the physicians, nurses, and other hospital staff who cared for the patients, Peter Jones for help with data abstraction, Gregory Snow, PhD for help with the statistical analysis, Tasha Fernley for assisting with the laboratory procedures, Sam Pettingill for providing the cost data, and the Utah Cancer Registry.

References

1. Bloomfield LE, Riley TB. Epidemiology and risk factors for community-associated *Clostridium difficile* infection: a narrative review. Infect Dis Ther 2016;5:231-51.
2. Eyre DW, Cule ML, Wilson DJ, Griffiths D, Vaughan A, O'Connor L, et al. Diverse sources of *C. difficile* infection identified on whole-genome sequencing. N Engl J Med 2013;369:1195-205.
3. Johnson S, Samore MH, Farrow KA, Killgore GE, Tenover FC, Lyras D, et al. Epidemics of diarrhea caused by a clindamycin-resistant strain of *Clostridium difficile* in four hospitals. N Engl J Med 1999;341:1645-51.
4. McDonald LC, Killgore GE, Thompson A, Owens RC, Kazakova SV, Sambol SP, et al. An epidemic, toxin gene-variant strain of *Clostridium difficile*. N Engl J Med 2005;353:2433-41.
5. Belmares J, Johnson S, Parada JP, Olson MM, Clabots CR, Bettin KM, et al. Molecular epidemiology of *Clostridium difficile* over the course of 10 years in a tertiary care hospital. Clin Infect Dis 2009;49:1141-7.
6. Schalk E, Bohr URM, Konig B, Scheinpflug K, Mohren M. *Clostridium difficile*-associated diarrhoea, a frequent complication in patients with acute myeloid leukaemia. Ann Hematol 2010;89:9-14.
7. Dubberke ER, Reske KA, Yan Y, Olsen MA, McDonald FVJ. *Clostridium difficile*-associated disease in a setting of endemicity: identification of novel risk factors. Clin Infect Dis 2007;45:1543-9.
8. Luo R, Greenberg A, Stone CD. Outcomes of *Clostridium difficile* infection in hospitalized leukemia patients: a nationwide analysis. Infect Control Hosp Epidemiol 2015;36:794-801.
9. Gorschluter M, Glasmacher A, Hahn C, Schakowski F, Ziske C, Molitor E, et al. *Clostridium difficile* infection in patients with neutropenia. Clin Infect Dis 2001;33:786-91.
10. Delmee M, Vandercam B, Avesani V, Michaux JL. Epidemiology and prevention of *Clostridium difficile* infections in a leukemia unit. Eur J Clin Microbiol 1987;6:623-7.
11. Cannon CM, Musuuza JS, Barker AK, Duster M, Juckett MB, Aurora E, et al. Risk of *Clostridium difficile* infection in hematology-oncology patients colonized with toxigenic *C. difficile*. Infect Cont Hosp Epidemiol 2017;38:718-20.
12. Shah K, Curtin BF, Chu C, Hwang D, Flasar MH, von Rosenvinge E. Characteristics of *Clostridium difficile* infection in patients hospitalized with myelodysplastic syndrome or acute myelogenous leukemia. World J Clin Oncol 2017;8:398-404.
13. Vehreschild MJGT, Weitershagen D, Biehl LM, Tacke D, Waldschmidt D, Tox U, et al. *Clostridium difficile* infection in patients with acute myelogenous leukemia and in patients undergoing allogeneic stem cell transplantation: epidemiology and risk factor analysis. Biol Blood Marrow Transplant 2014;20:823-8.
14. Westblade LF. Development and evaluation of a novel, semiautomated *Clostridium difficile* typing platform. J Clin Microbiol 2013;51:621-4.
15. Dubberke ER, Reske KA, Olsen MA, McMullen KM, Mayfield JL, McDonald C, et al. Evaluation of *Clostridium difficile*-associated disease pressure as a risk factor for *C. difficile*-associated disease. Arch Intern Med 2007;167:1092-7.
16. Apostolopoulou E, Raftopoulos V, Terzis K, Elefsiniotis I. Infection probability score: a predictor of *Clostridium difficile*-associated disease onset in patients with haematological malignancy. Europ J Oncol Nursing 2011;15:404-9.
17. Behar L, Chadwick D, Dunne A, Jones CI, Proctor C, Rajkumar C, et al. Toxigenic *Clostridium difficile* colonization among hospitalized adults; risk factors and impact on survival. J Infect 2017;75:20-5.
18. Kundrapu S, Sunkesula VCK, Jury LA, Cadnum JL, Nerandzic MM, Musuuza JS. Do piperacillin/tazobactam and other antibiotics with inhibitory activity against *Clostridium difficile* reduce the risk for acquisition of *C. difficile* colonization? BMC Infect Dis 2016;16:159-66.
19. Na'amnih W, Adler A, Miller-Roll T, Cohen D, Carmeli Y. Risk factors for recurrent *Clostridium difficile* infection in a tertiary hospital in Israel. Eur J Clin Microbiol Infect Dis 2018;37:1281-8.
20. Roghmann MC, McCarter RJ, Brewrink J, Cross AS, Morris Jr JG. *Clostridium difficile* infection is a risk factor for bacteremia due to vancomycin-resistant Enterococci (VRE) in VRE-colonized patients with acute leukemia. Clin Infect Dis 1997;25:1056-9.
21. Ford CD, Gazdik MA, Lopansri BK, Webb B, Mitchell B, Coombs J, et al. Vancomycin-resistant Enterococcus colonization and bacteremia and hematopoietic stem cell transplantation outcomes. Biol Blood Marrow Transplant 2017;23:340-6.
22. Baggs J, Jernigan JA, Halpin AL, Epstein L, Hatfield KM, McDonald LC. Risk of subsequent sepsis within 90 days after a hospital stay by type of antibiotic exposure. Clin Infect Dis 2018;66:1004-12.
23. Magee G, Strauss ME, Thomas SM, Brown H, Baumer D, Broderick KC. Impact of *Clostridium difficile*-associated diarrhea on acute care length of stay, hospital costs, and readmission: a multicenter retrospective study of inpatients, 2009-2011. Am J Infect Control 2015;43:1148-53.
24. Tickler IA, Goering TV, Whitmore JD, Lynn AN, Persing DH, Tenover FC. Strain types and antimicrobial resistance patterns of *Clostridium difficile* isolates from the United States, 2011 to 2013. Antimicrob Agents Chemother 2014;58:4214-8.