Published in final edited form as:

Infect Dis Clin Pract (Baltim Md). 2020 January ; 28(1): 10–15. doi:10.1097/ipc.0000000000000798.

A Single-Center Experience and Literature Review of Management Strategies for *Clostridium difficile* Infection in Hematopoietic Stem Cell Transplant Patients

Aneela Majeed, MD, FACP¹, Marti M. Larriva, PharmD², Ahmad Iftikhar, MD³, Adeela Mushtaq, MD⁴, Patrick Campbell, PharmD², Mustafa Nadeem Malik, MD⁶, Abdul Rafae, MD⁶, Muhammad Abu Zar, MD⁶, Ahmad Kamal, MD⁶, Midhat Lakhani, MD⁶, Nageena Rani Khalid, MD⁶, Tirdad T Zangeneh, MD, FACP⁵, Faiz Anwer, MD, FACP^{6,7}

¹.Department of Medicine, Division of Infectious Diseases, Stanford University, Stanford, CA.

².Department of Pharmacy, University of Arizona, Tucson, AZ.

³.Department of Medicine, University of Arizona, Tucson, AZ.

⁴.Department of Medicine, University of Pittsburgh Medical Center, McKeesport, PA.

⁵.Department of Medicine, Division of Infectious Diseases, University of Arizona, Tucson, AZ.

⁶.Department of Medicine, Division of Hematology and Oncology, University of Arizona, Tucson, AZ 85724

⁷.Taussig Cancer Center, Department of Hematology, Medical Oncology, Cleveland Clinic, Cleveland, Ohio 44195

Abstract

Introduction—The aim of our study is to evaluate risk factors associated with the development of *C. difficile* infection (CDI) in hematopoietic stem cell transplant (HSCT) patients, determine its incidence and report outcomes of CDI in our patient population.

Methods—We performed a retrospective review of medical records of adult HSCT recipients diagnosed between 2013 and 2016 at our center. Logistic regression models were used to determine the relationship between risk factors and the odds of CDI.

Results—The overall incidence of CDI in HSCT patients was 9.4%. The incidence of CDI was higher in allogeneic HSCT (20%) versus autologous HSCT (4.8%). No statistically significant differences in age, gender, cancer type, transplant type were found between those who developed CDI and those who did not. However, patients with CDI had a longer length of stay (25 days) and used more antibiotics (30 days prior to and during admission for HSCT) than non-CDI patients (19 days). Only two of 17 patients (11.8%) with CDI experienced recurrence among 180 patients after

Corresponding Author: Faiz Anwer MD, FACP, Staff Physician, Cleveland Clinic, anwerf@ccf.org, Phone No.: 216-444-9964, Clinic mailing address: Taussig's Cancer Center, Street Address: 9500 Euclid Ave. /CA60 10201 Carnegie Ave. Cleveland, OH 44195.

Conflict of Interest:

This manuscript is original research, has not been previously published and has not been submitted for publication elsewhere while under consideration. Authors declare no conflict of interest with this manuscript.

HSCT. No patient suffered from toxic megacolon or ileus and no patient underwent colectomy. There was no mortality associated with CDI at our center.

Conclusion—CDI has an incidence rate of 9.4% in HSCT recipients. Established risk factors including age, gender, cancer type, and transplant type were not identified as risk factors in our population. However, longer LOS and use of greater than four lines of antibiotics were observed among those with CDI compared to those without CDI.

Keywords

Clostridium difficile; autologous hematopoietic stem cell transplant; allogeneic hematopoietic stem cell transplant

INTRODUCTION

C. difficile infection (CDI) is the most common cause of nosocomial infectious diarrhea (1, 2). It is the leading cause of enterocolitis and gastroenteritis associated deaths.(3, 4) The reported incidence of CDI in hematopoietic stem cell transplant (HSCT) recipients is between 5.7% to 24.7%.(5–7) The incidence is higher in allogeneic HSCT recipients, varying between 2–27 %.(5, 6, 8–14)

CDI rates in HSCT recipients are reported to be nine times higher than general medical patients and 1.4 times higher than in patients with cancer (24.0 vs 2.6 vs 16.8/10000 patient-days respectively).(14) Symptomatic CDI generally presents with diarrhea, abdominal distention, pain, fever, and leukocytosis.(15) Diarrhea is a common symptom in HSCT recipients and *C. difficile* associated diarrhea (CDAD) can be difficult to differentiate from other causes of diarrhea (e.g. chemotherapy, mucositis, and graft-versus-host disease (GVHD) of the gastrointestinal tract).(16–19)

There are several risk factors that are associated with the development of CDAD in HSCT patients. Some of these include myeloablative conditioning,(8, 20) allogeneic-HSCT,(13, 14, 21) longer duration of hospital or ICU stay,(6, 20–22) septicemia,(21) extremes of age,(6) prior vancomycin-resistant enterococci (VRE) colonization,(13) pre-transplant or pre ICU admission *C. difficile* colonization (CDC),(23) severe mucositis,(7) total body irradiation, (19, 24) GVHD,(9, 17, 24) neutropenia,(6, 19) duration and type of antibiotics used,(6, 7, 9, 22) immunosuppression(25) and proton pump inhibitor (PPI) use.(26) Age is considered to be one of the most important risk factors associated with death. (6, 27, 28) Factors which are associated with decreased risk of CDI, include colonization with *Bacteroidetes*, *Lachnospiraceae*, *Ruminococcaceae* species (29) and IgA Multiple Myeloma. (26)

Studies have reported conflicting results on risk factors associated with the development of CDI in HSCT patients. In a retrospective review of 781 HSCT patients (both allogeneic and autologous) Aldrete *et al.*(30) reported a CDI incidence of 11%. They found the following risk factors to be significantly associated with the development of CDI; hospitalization in previous 60 days, the use of specific chemotherapy regimens [Bortezomib, dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, etoposide (VDT-PACE), ifosfamide, etoposide, carboplatin (ICE)] 60 days before index admission and prior cephalosporin

administration. Age, race, transplant type, underlying disease, mucositis, GVHD and prior antibiotics did not differ statistically between cases and controls. Lavalley *et al.* (31) studied the epidemiology and risk factors associated with the development of CDI in allogeneic HSCT patients exclusively in Quebec, Canada and reported an incidence of 8.6% (n= 760). The following risk factors were found to be associated with the development of CDI; development of mucositis, reactivation of CMV, and other Herpesviridae viruses. GVHD and high-risk antibiotics (clindamycin, carbapenems, fluoroquinolones, antipseudomonal penicillins, third- and fourth-generation cephalosporins) were not found to be associated with CDI. (31)

The main aim of our analysis is to report on the local experience and to study published literature for risk factors associated with the development of CDI in HSCT recipients. Our secondary aims are to determine the incidence and outcomes of CDI in our patient population.

PATIENTS AND METHODS

Study Design and Patient Population

We performed a retrospective review of electronic medical records of all patients (with and without *C. difficile* toxin-positive stool samples) who underwent HSCT. The study population was divided into two groups of adult patients who underwent HSCT. The treatment group consisted of patients who underwent HSCT and developed CDI post-transplant whereas control group comprised of patients who underwent HSCT but did not develop subsequent CDI. All included patients were admitted to the bone marrow transplant (BMT) unit for HSCT from November of 2013 to May of 2016 at Banner University Medical Center, a tertiary care, an academic center in Tucson, Arizona. The study was approved by the institutional review board of the University of Arizona. Key variables related to each patient's HSCT and CDI were recorded in a REDCap database. CDI cases were identified and included in our database in accordance with the Infectious Diseases Society of America (IDSA) definitions. Specifically, we included cases that manifested diarrhea with a positive *C. difficile* stool assay or otherwise detected a toxigenic *C. difficile* strain. Based on the same definitions, symptomatic patients with diarrhea and histopathologic or endoscopic evidence of pseudomembranous colitis were also included. (32) To compare our results with other studies, we searched for relevant studies through PubMed using the following keywords: "*Clostridium difficile* infection" and "HSCT patients".

Data Extraction

The following variables were collected: age, gender, diabetes diagnosis, underlying malignancy, type of transplant, stem cell source, myeloablative vs. non-myeloablative conditioning regimen, presence and type of acute graft versus host disease (GVHD), presence of mucositis by grading scale, need for nutritional support via total parental nutrition (TPN) or enteral tube feedings, number of documented infections, duration and number of antibiotics (NOA) used, length of stay (LOS) in hospital, PPI use prior to and during hospitalization for HSCT, and vancomycin- resistant enterococci (VRE) colonization.

For the diagnosis of CDI, variables were collected relative to the onset of HSCT (i.e. 30 days prior, during HSCT, or 6 months after HSCT) (Table 1, 2). The following additional data were collected: duration of diarrhea, bowel movement frequency, treatment regimen, treatment duration, and pertinent laboratory data including neutrophil count, white cell count, and serum creatinine.

Institutional Transplant Practices

All patients received prophylaxis against gram-negative bacteria, *Pneumocystis jiroveci*, fungi, and herpes simplex virus infections using ciprofloxacin, intravenous pentamidine, fluconazole, and acyclovir, respectively. Upon development of neutropenic fever, empiric broad-spectrum antipseudomonal antibiotic therapy was initiated with cefepime until a specific source of infection was established using microbiologic and imaging studies. Use of additional empiric antibiotics or antifungal therapy was determined based on drug allergies, focal symptoms, and infectious disease history. Patients with diarrhea at any point during HSCT had stool samples sent for *C. difficile* testing.

C. difficile Testing

Stool samples were tested with a PCR for *C. difficile* (The Xpert® *C. difficile*/Epi made by Cepheid) and rapid membrane enzyme immunoassay (EIA) lateral flow for glutamate dehydrogenase (GDH) antigen. Patients who were positive for GDH were tested for toxins A and B by *C. difficile* QUIK CHEK COMPLETE® test by Abbot. A tissue culture cytotoxin assay was performed on antigen-positive, rapid toxin negative specimens. We included newly diagnosed as well as primary and relapse/recurrent CDI cases in our review.

Infection Control Practices

Patients were placed in private rooms with high-efficiency particulate air (HEPA) filters upon admission. Isolation precautions were implemented as per guidelines and hand hygiene was monitored.

Statistical Analysis

The primary outcome was to observe the association of risk factors that were differentially present among patients who developed CDI post HSCT as compared to the comparable population of patients who underwent HSCT but did not develop CDI. Patients were followed until the development of CDI or discharge from the hospital. Patient characteristics were described using means, standard deviations, medians, and ranges. To compare the differences between categorical patient variables, Wald chi-square, and Fischer's exact test was used. When the variances were not equal, Satterthwaite method was used for comparison and p-values were reported. A p value of less than 0.05 was considered statistically significant. Binary logit regression model was used to assess the risk factors associated with CDI post-HSCT patients and respective odds ratios were calculated. Only the risk factors found to be significant in univariate model were considered for further analysis by multivariate linear regression model. Statistical analyses were performed using statistical software (SAS version 9.3, SAS Institute, Cary, NC).

RESULTS

Patient Characteristics

During the study period (2013–2016), a total of 180 adult patients were admitted for HSCT. The overall incidence of CDI in HSCT patients at our center during this study period was 9.4% (17 patients). The incidence of CDI was higher in allogeneic HSCT (20%, 11 CDI cases out of total 55 Allo-SCT recipients) versus autologous HSCT (4.8%, 6 CDI cases out of 125 Auto-SCT recipients). Baseline patient characteristics are shown in Table 3. In our HSCT population, the most common underlying malignancy was multiple myeloma (35%) followed by lymphoma (24%) and acute leukemia (15%). Three out of 17 patients with CDI (17.6%) were diagnosed with NAP 1 positive *C. difficile* strains.

Comparison of Patients with and without CDI

There were no statistically significant differences in age, gender, cancer type, transplant type across both groups of patients. However, patients with CDI were found to have a longer LOS and NOA compared to those without CDI (p-values of 0.0476 and 0.002 respectively). This held true across different HSCT categories (i.e. prior to HSCT and during HSCT). The mean NOA in patients who developed CDI was 4 (range 1–10) compared to the mean NOA of 2.5 (p-value of 0.02) in patients without CDI. The average LOS was 25 days (range 17–54) in patients with CDI and 19 days (p-value of 0.0476) in patients without CDI. Univariate analysis revealed that the odds of CDI were less with allogeneic HSCT as compared to autologous HSCT (OR= 0.20, 95% C.I = 0.07 – 0.58, p-value <0.001). Other than that, there was no difference in the association of risk factors among post HSCT patients who did and did not develop CDI: NOA (OR = 1 (95% C.I = <1 – >99, p-value = 0.97), age (OR= 0.99, 95% C.I = 0.96 – 1.02, p-value = 0.001), gender (OR= 0.56, 95% C.I = 0.22 – 1.61, p-value <0.001), MM vs others (OR= 3.33, 95% C.I = 0.75 – 14.89, p-value = 0.99)) etc.

Treatment and Outcomes of CDI Cases

All patients with CDI in our cohort were treated with either metronidazole, oral vancomycin, or fidaxomicin. The most commonly used antibiotic regimen was oral vancomycin 125 mg, four times per day (n=8) followed by oral metronidazole 500 mg every 8 hours (n=4) and oral vancomycin 250 mg four times per day (n=4). Only one patient was treated with fidaxomicin. (Table 4) Antibiotics were given for an average duration of 17.94 days (range: 8–30) which is until resolution of symptoms. Patients were followed over a period of six months following the transplant. Five patients developed CDI during the 6-months period preceding HSCT. Only two of 17 patients (11.8%) with CDI experienced a recurrence of CDI after HSCT. No patient suffered from toxic megacolon or ileus and no patient underwent colectomy. There was no mortality associated with CDI at our center. Univariate analysis revealed no significant association of any antibiotic as increased risk of CDI post HSCT in both groups at risk who received the treatment.

DISCUSSION

Due to the multiple unique challenges, HSCT recipients face increased risk and have a high incidence of CDI. Our single-center study showed a higher incidence of CDI 20% (11 cases)

among allo-HSCT recipients as compared to 4.8% in auto-HSCT recipients (6 cases), a finding which is similar to the reported literature. (9, 33),(13, 24, 34, 35) Our analysis did not find any statistically significant association of factors such as patients' age, gender, cancer type, allogeneic donor source, and transplant type with the development of CDI. However, small patient population size is a limitation of our study. A meta-analysis by Fekety *et al.* reported a recurrence rate of up to 20% in patients who were treated with either metronidazole or vancomycin.(36) The unique findings at our hospital are the low recurrence rate (11.8%) of CDI and lack of mortality associated with CDI. These findings are in contrast with a few previous studies.(24, 33) This difference could be due to the prompt diagnosis and treatment of patients with CDI at our hospital. Our analysis found the longer LOS and greater than four lines of antibiotics used prior to and during HSCT was significantly higher in patients with CDI compared to those without CDI. Prior studies have shown LOS, ICU stay,(6, 21) duration and type of antibiotics used (6, 7, 9, 22) as independent risk factors for the development of CDI.

Many post-HSCT CDI cases are a result of re-activation due to pre-transplantation *Clostridium difficile* colonization (CDC). In such cases, CDI occurs very early after transplantation.(9) It is suggested that defects in humoral immunity specific to *C. difficile* toxins may lead to primary as well as recurrent CDI.(7, 37, 38) Bruminhet *et al*(19) reported that patients who had CDC prior to HSCT, developed CDI sooner compared to uncolonized. Others reported asymptomatic CDC does not increase the risk of symptomatic CDI, and may even reduce the risk.(39, 40) We do not have data on pre-transplantation colonization in our retrospective study.

Most of our cases with CDI were successfully treated with oral vancomycin. Less than 25% of patients were treated with metronidazole and only one patient required fidaxomicin. The preference of vancomycin over metronidazole at our center is in contrast with other studies (12, 13, 34, 41, 42) but its use is supported by Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA) guidelines.(32) Fidaxomicin was approved by the FDA for the treatment of CDI, based on the study by Louie *et al* (43) which reported a higher rate of diarrhea resolution and decreased recurrence with fidaxomicin use. In clinical practice, the trend has shifted towards the frontline use of fidaxomicin or oral vancomycin. Intravenous metronidazole still has a role for the treatment of patients with fulminant CDI and ileus. Guidelines from IDSA and SHEA strongly recommend a 10-day course of vancomycin or fidaxomicin instead of metronidazole as the first-line treatment for severe or non-severe CDI.(32) Definition of severe CDI includes white blood cell (WBC) count > 15000 cells/mL and/or serum creatinine > 1.5 mg/dL. However, using these criteria in the peritransplant period, it is almost impossible to classify HSCT patients into severe or non-severe category due to low or undetectable white blood cell counts, poor baseline nutritional status, and regimen related nephrotoxicity. Moreover, routine use of calcineurin inhibitors for graft versus host disease (GVHD) prophylaxis after HSCT can alter serum creatinine values.(32, 44, 45) Alternative criteria for severity in HSCT have been proposed by Dubberke *et al.* utilizing the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) to classify CDI as mild (grade I diarrhea/colitis), moderate (grade 2 diarrhea/colitis), and severe (grade 3 or higher diarrhea/colitis) based upon symptoms noted at 48 hours before or after CDI diagnosis.(46)

Although these alternative criteria did identify patients who were more likely to have persistent symptoms, required a switch in therapy due to lack of response, or developed bloodstream infections but their use has not been widely adopted. Further prospective research is needed to establish criteria in the HSCT patient to determine the severity of disease and appropriate first line and second line therapeutic intervention.(47)

It is difficult to differentiate diarrhea due to CDI and diarrhea due to regimen-related toxicity.(19) *C. difficile* toxin can be easily detected using modern laboratory techniques but differentiating CDI from colonization remains an important diagnostic challenge. PCR is widely used across the nation for diagnostic purposes. However, it has potential to over diagnose by misdiagnosing colonization as CDI. To enforce good diagnostic stewardship practices, our institution switched from PCR to GDH testing a year ago. Because of limited data on optimal testing strategy for CDI, IDSA and SHEA provide weak guidelines on this subject.(32) A multistep approach that incorporates GDH assay and toxin testing is recommended with reflex to PCR.(32)

Most of the risk factors associated with the development of CDI in HSCT recipients (especially allogeneic-HSCT recipients) are non-modifiable. The recurrence rate of CDI after initial antibiotic therapy is about 35%.(48, 49) So, there is need for treatment strategies for recurrent CDI. In 2017, IDSA and SHEA guidelines on CDI were updated.(32) Various recommended options are; (1) Tapered course of vancomycin or a 10-day course of fidaxomicin after initial treatment of CDI, (2) Probiotics, which are a safe and cost-effective option but definitive data on their efficacy to prevent recurrent CDI is lacking, (3) For patients with recurrent CDI, FMT should be considered, however, there are safety concerns about its use in transplant patients. Also, antimicrobial and proton pump inhibitors stewardship strategies, contact isolation measures, and hand hygiene compliance are recommended measures for the prevention of CDI.(15, 50)

A systematic review by Drekonja *et al* (51) found that fidaxomicin and oral vancomycin did not differ for the initial treatment outcomes but recurrence was less frequent with fidaxomicin use. Louie *et al.* (43) showed that fidaxomicin use resulted in significantly higher rates of diarrhea resolution and lower rates of recurrence when compared with vancomycin. Fidaxomicin may have limited efficacy against the NAP1–027 strain, which is associated with health care facility onset CDI.(52)

Studies have shown that asymptomatic carriers of *C. difficile* have a high titer of anti-toxin A IgG and hence they have a lower risk of recurrent CDI. This has led to the development of a novel bivalent candidate vaccine composed of a highly purified preparation of toxin A and B. The vaccine is delivered via intramuscular route. The dose of the vaccine is 0.5 ml.(53) In a phase I clinical trial, 50 adults (18–55 years) and 48 elderly (>65 years) volunteers were randomized to receive either the candidate *C. difficile* toxoid vaccine (2ug, 10ug, or 50ug) or placebo. The vaccine was administered on days 0, 8 and 56. By the day 56, a 4-fold rise in anti-toxin A antibody titer was observed in 100% of the adult patients in all dose groups with a mean anti-toxin A IgG of 59.2, 57.4 and 141.4 Elisa units (EU), respectively. In elderly patients, a 4-fold rise in anti-toxin A antibody titer was seen in 50%, 89% and 100% of the patients receiving 2ug, 10ug and 50ug dose, with a mean anti-toxin A IgG of 8.7, 22.8

and 22.9 EU, respectively. At day 36, the antibody titers remained elevated in adult patients while the titers declined in elderly population. Patients receiving 50 µg dose of the vaccine showed the quickest response. The seroconversion rate was lower for toxin B compared to toxin A in adult patients while in the elderly population, the rate was higher compared to toxin-A.(54) In another study, 3 patients with recurrent CDI received toxoid vaccine. Two out of 3 patients showed a 3 fold and a 4-fold rise in anti-toxin A antibody titer while a 52 fold and a 20-fold rise in anti-toxin B antibody titers, respectively. All 3 patients, who were previously on continuous vancomycin for recurrent CDI, were able to discontinue the treatment without the disease recurrence.(55) A total of six phase I clinical trials involving more than 200 participants have been completed and have demonstrated that *C. difficile* vaccine is well tolerated and has an excellent immunogenic effect in young adults as well as in elderly patients.(53)

The limitations of our current study include small population size, lack of a control group, and a retrospective review study design. Since our study design did not take into account the timing of exposure and we did not incorporate the measures of transmission and pre-transplant colonization rate, we could not draw inferences about causality. Also, there is a chance that some patients with CDC had been misclassified as CDI cases. Most patients lacked data on VRE colonization. Finally, it was not possible for us to evaluate and compare with other studies the potential risk factors that were not recorded in the medical records of our patients.

CONCLUSION

This single-center study demonstrates that CDI has an incidence rate of 9.4% in HSCT recipients. Established risk factors for the development of CDI including age, gender, cancer type, and transplant type were not identified as risk factors in our population. However, longer LOS and use of greater than four lines of antibiotics were observed among those with CDI compared to those without CDI. Data on CDI prophylaxis in these patients is emerging and randomized prospective trials are needed.

Acknowledgments

Funding Source:

This work was supported in part by grant P30 CA023074 from the National Cancer Institute, National Institutes of Health, Bethesda, MD.

REFERENCES

1. Rupnik M, Wilcox MH, Gerding DN. Clostridium difficile infection: new developments in epidemiology and pathogenesis. Nat Rev Microbiol. 2009;7(7):526. [PubMed: 19528959]
2. Magill SS, Edwards JR, Bamberg W, et al. Multistate point-prevalence survey of health care-associated infections. N Engl J Med. 2014;370(13):1198–208. [PubMed: 24670166]
3. Lessa FC, Winston LG, McDonald LC, Emerging Infections Program CdST. Burden of Clostridium difficile infection in the United States. N Engl J Med. 2015;372(24):2369–70. [PubMed: 26061850]
4. Vehreschild MJ, Weitershausen D, Biehl LM, 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(6):823–8. [PubMed: 24607558]

5. Bruminhent J, Wang Z-X, Hu C, et al. Clostridium difficile colonization and disease in patients undergoing hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant*. 2014;20(9):1329–34. [PubMed: 24792871]
6. Spadão F, Gerhardt J, Guimarães T, et al. Incidence of diarrhea by Clostridium difficile in hematologic patients and hematopoietic stem cell transplantation patients: Risk factors for severe forms and death. *Rev Inst Med Trop Sao Paulo*. 2014;56(4):325–31. [PubMed: 25076434]
7. Alonso CD, Dufresne SF, Hanna DB, et al. Clostridium difficile infection after adult autologous stem cell transplantation: a multicenter study of epidemiology and risk factors. *Biology of blood and marrow transplantation : Biol Blood Marrow Transplant*. 2013;19(10):1502–8.
8. Boyle NM, Magaret A, Stednick Z, et al. Evaluating risk factors for Clostridium difficile infection in adult and pediatric hematopoietic cell transplant recipients. *Antimicrob Resist and Infect Control*. 2015;4(1).
9. Alonso CD, Treadway SB, Hanna DB, et al. Epidemiology and outcomes of Clostridium difficile infections in hematopoietic stem cell transplant recipients. *Clin Infect Dis*. 2012;54(8):1053–63. [PubMed: 22412059]
10. Kinnebrew MA, Lee YJ, Jenq RR, et al. Early Clostridium difficile infection during allogeneic hematopoietic stem cell transplantation. *PLoS One*. 2014;9(3):e90158. [PubMed: 24662889]
11. Kamboj M, Xiao K, Kaltsas A, et al. Clostridium difficile infection after allogeneic hematopoietic stem cell transplant: strain diversity and outcomes associated with NAP1/027. *Biol Blood Marrow Transplant*. 2014;20(10):1626–33. [PubMed: 24973628]
12. Willems L, Porcher R, Lafaurie M, et al. Clostridium difficile infection after allogeneic hematopoietic stem cell transplantation: incidence, risk factors, and outcome. *Biol Blood Marrow Transplant*. 2012;18(8):1295–301. [PubMed: 22387347]
13. Trifilio SM, Pi J, Mehta J. Changing epidemiology of Clostridium difficile-associated disease during stem cell transplantation. *Biol Blood Marrow Transplant*. 2013;19(3):405–9. [PubMed: 23219779]
14. Chopra T, Chandrasekar P, Salimnia H, et al. Recent epidemiology of Clostridium difficile infection during hematopoietic stem cell transplantation. *Clin Transplant*. 2011;25(1).
15. Cohen SH, Gerding DN, Johnson S, et al. Clinical practice guidelines for Clostridium difficile infection in adults: 2010 update by the society for healthcare epidemiology of America (SHEA) and the infectious diseases society of America (IDSA). *Infect Control Hosp Epidemiol*. 2010;31(5):431–55. [PubMed: 20307191]
16. Gu SL, Chen YB, Lv T, et al. Risk factors, outcomes and epidemiology associated with Clostridium difficile infection in patients with haematological malignancies in a tertiary care hospital in China. *J Med Microbiol*. 2015;64(Pt 3):209–16. [PubMed: 25596117]
17. Chakrabarti S, Lees A, Jones S, et al. Clostridium difficile infection in allogeneic stem cell transplant recipients is associated with severe graft-versus-host disease and non-relapse mortality. *Bone Marrow Transplant*. 2000;26(8):871. [PubMed: 11081387]
18. Dubberke ER, Reske KA, Srivastava A, et al. Clostridium difficile-associated disease in allogeneic hematopoietic stem-cell transplant recipients: risk associations, protective associations, and outcomes. *Clin Transplant*. 2010;24(2):192–8. [PubMed: 19624693]
19. Akahoshi Y, Kimura S, Nakano H, et al. Significance of a positive Clostridium difficile toxin test after hematopoietic stem cell transplantation. *Clin Transplant*. 2016;30(6):703–8. [PubMed: 27019071]
20. Schuster MG, Cleveland AA, Dubberke ER, et al. Infections in Hematopoietic Cell Transplant Recipients: Results From the Organ Transplant Infection Project, a Multicenter, Prospective, Cohort Study. *Open Forum Infect Dis*. 2017;4(2):ofx050. [PubMed: 28491889]
21. Shah NN, McClellan W, Flowers CR, et al. Evaluating Risk Factors for Clostridium difficile Infection In Stem Cell Transplant Recipients: A National Study. *Infect Control Hosp Epidemiol*. 2017;38(6):651–7. [PubMed: 28330512]
22. Cózar-Llistó A, Ramos-Martínez A, Cobo J. Clostridium difficile Infection in Special High-Risk Populations. *Infect Dis Ther*. 2016;5(3):253–69. [PubMed: 27515721]

23. Tschudin-Sutter S, Carroll KC, Tamma PD, et al. Impact of toxigenic clostridium difficile colonization on the risk of subsequent C. difficile infection in intensive care unit patients. *Infect Control Hosp Epidemiol.* 2015;36(11):1324–9. [PubMed: 26223207]
24. Willems L, Porcher R, Lafaurie M, et al. Clostridium difficile infection after allogeneic hematopoietic stem cell transplantation: incidence, risk factors, and outcome. *Biol Blood Marrow Transplant.* 2012;18(8):1295–301. [PubMed: 22387347]
25. Raza S, Baig MA, Russell H, et al. Clostridium difficile infection following chemotherapy. *Recent Pat Anti-infect Drug Discov.* 2010;5(1):1–9.
26. Krishna SG, Zhao W, Apewokin SK, et al. Risk factors, preemptive therapy, and antiperistaltic agents for Clostridium difficile infection in cancer patients. *Transpl Infect Dis : an official journal of the Transplantation Society.* 2013;15(5):493–501.
27. Garey K, Dao-Tran T, Jiang Z, et al. A clinical risk index for Clostridium difficile infection in hospitalised patients receiving broad-spectrum antibiotics. *J Hosp Infect.* 2008;70(2):142–7. [PubMed: 18723249]
28. Bauer MP, Notermans DW, Van Benthem BH, et al. Clostridium difficile infection in Europe: a hospital-based survey. *Lancet.* 2011;377(9759):63–73. [PubMed: 21084111]
29. Lee YJ, Arguello ES, Jenq RR, et al. Protective Factors in the Intestinal Microbiome Against Clostridium difficile Infection in Recipients of Allogeneic Hematopoietic Stem Cell Transplantation. *Journal Infect Dis.* 2017;215(7):1117–23. [PubMed: 28498996]
30. Aldrete SD, Kraft CS, Magee MJ, et al. Risk factors and epidemiology of Clostridium difficile infection in hematopoietic stem cell transplant recipients during the peritransplant period. *Transpl Infect Dis.* 2017;19(1).
31. Lavallee C, Labbe AC, Talbot JD, et al. Risk factors for the development of Clostridium difficile infection in adult allogeneic hematopoietic stem cell transplant recipients: A single-center study in Quebec, Canada. *Transpl Infect Dis.* 2017;19(1).
32. McDonald LC, Gerding DN, Johnson S, et al. Clinical practice guidelines for Clostridium difficile infection in adults and children: 2017 update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). *Clin Infect Dis.* 2018;66(7):e1–e48. [PubMed: 29462280]
33. Pilcante J, Rojas P, Ernst D, et al. Clostridium difficile infection in Chilean patients submitted to hematopoietic stem cell transplantation. *Rev Bras Hematol Hemoter.* 2015;37(6):388–94. [PubMed: 26670401]
34. Bilgrami S, Feingold J, Dorsky D, et al. Incidence and outcome of Clostridium difficile infection following autologous peripheral blood stem cell transplantation. *Bone Marrow Transplant.* 1999;23(10):1039. [PubMed: 10373070]
35. Avery R, Pohlman B, Adal K, et al. High prevalence of diarrhea but infrequency of documented Clostridium difficile in autologous peripheral blood progenitor cell transplant recipients. *Bone Marrow Transplant.* 2000;25(1):67. [PubMed: 10654017]
36. Fekety R, McFarland LV, Surawicz CM, et al. Recurrent Clostridium difficile diarrhea: characteristics of and risk factors for patients enrolled in a prospective, randomized, double-blinded trial. *Clin Infect Dis.* 1997;24(3):324–33. [PubMed: 9114180]
37. Kyne L, Warny M, Qamar A, et al. Asymptomatic carriage of Clostridium difficile and serum levels of IgG antibody against toxin A. *N Engl J Med.* 2000;342(6):390–7. [PubMed: 10666429]
38. Kyne L, Warny M, Qamar A, et al. Association between antibody response to toxin A and protection against recurrent Clostridium difficile diarrhoea. *Lancet.* 2001;357(9251):189–93. [PubMed: 11213096]
39. Samore MH, DeGirolami PC, Tluczo A, et al. Clostridium difficile colonization and diarrhea at a tertiary care hospital. *Clin Infectious Dis.* 1994;18(2):181–7.
40. Shim JK, Johnson S, Samore MH, et al. Primary symptomless colonisation by Clostridium difficile and decreased risk of subsequent diarrhoea. *Lancet.* 1998;351(9103):633–6. [PubMed: 9500319]
41. Arango JI, Restrepo A, Schneider DL, et al. Incidence of Clostridium difficile-associated diarrhea before and after autologous peripheral blood stem cell transplantation for lymphoma and multiple myeloma. *Bone Marrow Transplant.* 2006;37(5):517–21. [PubMed: 16435018]

42. Scardina TL, Kang Martinez E, Balasubramanian N, et al. Evaluation of Risk Factors for Clostridium difficile Infection in Hematopoietic Stem Cell Transplant Recipients. *Pharmacotherapy*. 2017;37(4):420–8. [PubMed: 28226419]
43. Louie TJ, Miller MA, Mullane KM, et al. Fidaxomicin versus vancomycin for Clostridium difficile infection. *N Engl J Med*. 2011;364(5):422–31. [PubMed: 21288078]
44. Debast S, Bauer M, Kuijper E. European Society of Clinical Microbiology and Infectious Diseases. European Society of Clinical Microbiology and Infectious Diseases: update of the treatment guidance document for Clostridium difficile infection. *Clin Microbiol Infect*. 2014;20(Suppl 2):1–26.
45. Miller MA, Louie T, Mullane K, et al. Derivation and validation of a simple clinical bedside score (ATLAS) for Clostridium difficile infection which predicts response to therapy. *BMC Infect Dis*. 2013;13(1):148. [PubMed: 23530807]
46. Dubberke ER, Sadhu J, Gatti R, et al. Severity of Clostridium difficile-associated disease (CDAD) in allogeneic stem cell transplant recipients: evaluation of a CDAD severity grading system. *Infect Control Hosp Epidemiol*. 2007;28(2):208–11. [PubMed: 17265405]
47. Zar FA, Bakkanagari SR, Moorthi K, et al. A comparison of vancomycin and metronidazole for the treatment of Clostridium difficile-associated diarrhea, stratified by disease severity. *Clin Infect Dis*. 2007;45(3):302–7. [PubMed: 17599306]
48. Kelly CP, LaMont JT. Clostridium difficile—more difficult than ever. *N Engl J Med*. 2008;359(18):1932–40. [PubMed: 18971494]
49. Wilcox MH, Gerding DN, Poxton IR, et al. Bezlotoxumab for Prevention of Recurrent Clostridium difficile Infection. *N Engl J Med*. 2017;376(4):305–17. [PubMed: 28121498]
50. Hsu J, Abad C, Dinh M, et al. Prevention of endemic healthcare-associated Clostridium difficile infection: reviewing the evidence (Structured abstract). *Am J Gastroenterol*. 2010; 105(11):[2327–39 pp.]. [PubMed: 20606676]
51. Drekonja D, Butler M, MacDonald R, et al. Comparative effectiveness of Clostridium difficile treatments: a systematic review (Structured abstract). *Ann Intern Med*. 2011; 155(12):[839–47 pp.]. [PubMed: 22184691]
52. Lessa FC, Mu Y, Bamberg WM, et al. Burden of Clostridium difficile infection in the United States. *New Engl J Med*. 2015;372(9):825–34. [PubMed: 25714160]
53. Foglia G, Shah S, Luxemburger C, et al. Clostridium difficile: development of a novel candidate vaccine. *Vaccine*. 2012;30(29):4307–9. [PubMed: 22682287]
54. Greenberg RN, Marbury TC, Foglia G, et al. Phase I dose finding studies of an adjuvanted Clostridium difficile toxoid vaccine. *Vaccine*. 2012;30(13):2245–9. [PubMed: 22306375]
55. Sougioultzis S, Kyne L, Drudy D, et al. Clostridium difficile toxoid vaccine in recurrent C. difficile-associated diarrhea. *Gastroenterology*. 2005;128(3):764–70. [PubMed: 15765411]

Table. 1

Myeloablative regimens and stem cell source for transplantation

<u>Myeloablative Regimen</u>	Melphalan	59 (70.2%),
	BEAM	12 (14.3%),
	BuCyEtop	2 (2.4%)
	CarboEtop	3 (3.6%)
	Cy/TBI	4 (4.8%)
	Flu/Mel	3 (3.6%),
	TBI/Flu	1 (1.2%)
<u>Stem Cell Source</u>	Peripheral Blood	170 (93.9%)
	Bone Marrow	11 (6.1%)

Abbreviations: Bu, busulfan; Cy, cyclophosphamide; Etop, etoposide; Carbo, carboplatin; TBI, total body irradiation; Flu, flucytosine; Mel, melphalan; BEAM, carmustine, etoposide, cytarabine and melphalan.

Table. 2

Complications like GVHD, mucositis, VRE colonization, PPI use, TPN use, PEG/NG tube feeding among HSCT recipients

	Characteristics	All patients N (%)
<u>Acute GVHD</u>	Yes	9 (16.4%)
	No	46 (83.6%)
<u>Mucositis</u>	Yes	124 (68.5%)
	No	57 (31.5%)
	Grade I	50 (40.3%)
	Grade II	19 (15.3%)
	Grade III	13 (10.5%)
	Grade IV	20 (16.1%)
	Not documented	22 (17.7%)
<u>VRE colonization</u>	Yes	11 (6.4%)
	No	48 (27.7%)
	Not documented	114 (65.9%)
<u>PPI use during hospital admission for HSCT</u>	Yes	49 (27.2%),
	No	131 (72.8%)
<u>TPN needed in mucositis</u>	Yes	22 (12.2%),
	No	159 (87.8%)
<u>PEG/NG tube feeding in grade IV mucositis</u>	Yes	7 (3.9%),
	No	174 (96.1%)

Abbreviations: GVHD, graft versus host disease; HSCT, hematopoietic stem cell transplant; N, number of patients; *NG*, nasogastric; PEG, percutaneous endoscopic *gastrostomy*; PPI, proton pump inhibitor; VRE, vancomycin resistant enterococci.

Table. 3

Comparison of demographic and transplantation data and outcomes for patients with or without *Clostridium difficile* infection

Characteristics	N (%)	CDI n (%)	NO CDI n (%)	p - value
Total number of patients	180			
CDI before transplant	5 (3%)			
<u>Difference in sex</u>				
Male	116 (64.4%)	9 (5%)	107 (59%)	0.229
Female	64 (35.6%)	8 (4.4%)	56 (31%)	N.S
<u>Mean Age (years)</u>	180	52.7 (44.8 – 60.6)	51 (48.8 – 53.2)	0.63
<u>Cancer type</u>				
MM	63 (35%)	3 (1.6%)	60 (33%)	N.S
NHL	29 (16%)	2 (1%)	27 (15%)	N.S
ALL	16 (9%)	3 (1.6%)	13 (7%)	N.S
HL	17 (9.5%)	0	14 (8%)	0.1772
AML	12 (6.7%)	2 (1%)	10 (5.5%)	N.S
MDS	6 (3.3%)	1 (0.5%)	5 (2.8%)	N.S
CML	5 (2.8%)	1 (0.5%)	4 (2.2%)	N.S
Others [‡]	35 (19%)	5 (2.8%)	30 (17%)	N.S
<u>Transplant type</u>				
Autologous	125 (69%)	6 (4.8%)	119 (95.2%)	N.S
Allogeneic	55 (31%)	11 (20%)	44 (80%)	N.S
MUD	29 (53%)	7 (13%)	22 (40%)	N.S
MRD	15 (27%)	2 (3.6%)	13 (23.6%)	N.S
Haploidentical	8 (14.5%)	1 (2%)	7 (4%)	0.6022
MMUD	2 (3.6%)	1 (2%)	1 (2%)	N.S
MMRD	1 (2%)	0	1 (2%)	N.S
<u>LOS (days)</u>	180	25.6 (20.9 – 30.4)	19.6 (15.9 – 23.4)	0.0476
<u>Mean number of antibiotics used prior to and during HSCT</u>	180	4 (2.7 – 5.2)	2.6 (1.99–3.2)	0.02

[‡] B cell lymphoma, Burkitts lymphoma, Diffuse Large B Cell Lymphoma, Ewing's Sarcoma, Mantel Cell lymphoma.

Abbreviations: AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; CML, chronic myeloid leukemia; CDI, *Clostridium difficile* infection; HL, hodgkin's lymphoma; HSCT, hematopoietic stem cell transplant; MM, multiple myeloma; MDS, myelodysplastic syndrome; MRD, matched related donor; MUD, matched unrelated donor; MMUD, mismatched unrelated donor; MMRD, mismatched related donor; N, number of patients; NHL, non-hodgkin's lymphoma; LOS, length of stay.

Table. 4*Clostridium difficile* infection treatment regimen to hematopoietic stem cell transplant patients

Antibiotic used	Number of patients (%)
Vancomycin 125 mg QID	8 (53%)
Vancomycin 250 mg QID	4 (23.5%)
Metronidazole 500mg Q8H	4 (23.5%)
Fidaxomicin 200 mg BID	1 (6%)

Abbreviations: BID, twice a day; QID, four times a day; Q8H, every eight hourly.