Risk for Clostridium difficile Infection After Allogeneic Hematopoietic Cell Transplant Remains Elevated in the Postengraftment Period

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Background. Clostridium difficile infection (CDI) is a frequent cause of diarrhea among allogeneic hematopoietic cell transplant (HCT) recipients. It is unknown whether risk factors for CDI vary by time posttransplant. Methods. We performed a 3-year prospective cohort study of CDI in allogeneic HCT recipients. Participants were enrolled during their transplant hospitalizations. Clinical assessments were performed weekly during hospitalizations and for 12 weeks posttransplant, and monthly for 30 months thereafter. Data were collected through patient interviews and chart review, and included CDI diagnosis, demographics, transplant characteristics, medications, infections, and outcomes. CDI cases were included if they occurred within 1 year of HCT and were stratified by time from transplant. Multivariable logistic regression was used to determine risk factors for CDI. Results. One hundred eighty-seven allogeneic HCT recipients were enrolled, including 63 (34%) patients who developed CDI. 38 (60%) CDI cases occurred during the preengraftment period (days 0-30 post-HCT) and 25 (40%) postengraftment (day >30). Lack of any preexisting comorbid disease was significantly associated with lower risk of CDI preengraftment (odds ratio [OR], 0.3; 95% confidence interval [CI], 0.1-0.9). Relapsed underlying disease (OR, 6.7; 95% CI, 1.3-33.1), receipt of any high-risk antimicrobials (OR, 11.8; 95% CI, 2.9-47.8), and graft-versus-host disease (OR, 7.8; 95% CI, 2.0-30.2) were significant independent risk factors for CDI postengraftment. Conclusions. A large portion of CDI cases occurred during the postengraftment period in allogeneic HCT recipients, suggesting that surveillance for CDI should continue beyond the transplant hospitalization and preengraftment period. Patients with continued high underlying severity of illness were at increased risk of CDI postengraftment.

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Clostridium difficile infection (CDI) is a common infectious complication of allogeneic hematopoietic cell transplantation (HCT), but the epidemiology, risk factors, and outcomes of CDI in these patients are poorly understood.

Estimates of CDI incidence among allogeneic HCT recipients vary widely, with an upper range of approximately 30%.1-9

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The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of CDC.

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Many studies of CDI in this patient population are limited to autologous HCT recipients; other studies combine allogeneic and autologous HCT recipients and such combined study results may not be applicable to allogeneic HCT recipients alone. Incidence rates and time from transplant to CDI may be different between autologous and allogeneic transplant recipients, possibly because of differences in immnosuppression, underlying severity of illness, or antimicrobial exposures between these 2 transplant populations.

Risk factors for CDI specific to HCT patients have proven difficult to identify, likely because of study design limitations and the ubiquity of traditional CDI risk factors among allogeneic HCT recipients. Several prior studies have evaluated and the ubiquity of traditional CDI risk factors among allogeneic and autologous HCT recipients and such comparisons, stratified by time from transplant.

Study Design

This cohort study was conducted at Siteman Cancer Center, the NCI designated comprehensive Cancer Center of BJH, a 1250-bed, tertiary care facility in St. Louis, Missouri. The study was performed in conjunction with the Organ Transplant Infection Prevention and Detection Project (OTIP) of the Centers for Disease Control and Prevention. OTIP was a prospective cohort study of infections in patients undergoing allogeneic HCT or lung transplant. At BJH, only allogeneic HCT recipients were enrolled in the OTIP study, and specific additional data related to CDI were collected at BJH, as described below. The study dates were April 2007 to March 2010. During the study period, the HCT ward at BJH did not have a required neutropenic fever prophylaxis protocol, and cefepime was the preferred agent for neutropenic fever. Study participants were approached to participate after admission for their allogeneic HCT hospitalization. An assessment of each participant was performed at enrollment and weekly during each hospitalization. After discharge, participants were contacted by phone weekly for up to 12 weeks posttransplant. After 12 weeks, participants were contacted monthly for 30 months post-HCT. If participants were readmitted to the hospital, they were followed up weekly until discharge. Seven participants had >1 HCT during the study period; for these participants, only the first HCT was included in analyses. The Washington University Human Research Protection Office approved this study and written informed consent was obtained from all participants.

Data Collection

Demographic data collected at study enrollment included age, sex, race, underlying disease status at the time of transplant, comorbid diseases, type of allogeneic HCT conditioning, prior chemotherapy/immunosuppressive therapies, and transplant history. Comorbid diseases were defined as one for which the patient was receiving treatment or medical consultation. Other data collected at the time of transplantation included transplant date and time, ongoing immunosuppressive medications received, and laboratory culture and/or test results. The weekly inpatient and outpatient assessments included patient status (home, inpatient, ICU, deceased), mechanical ventilation, current medications, and symptoms of infection. All infections were reviewed by an infectious diseases physician (E.R.D.) to determine whether the infection was probable, confirmed, or neither. Infections were defined according to National Nosocomial Infections Surveillance (NNIS) criteria (now National Healthcare Safety Network). Graft-versus-host disease (GVHD) was scored according to the Glucksberg criteria. In addition to interviews, clinical data were collected prospectively from medical records when participants were hospitalized and as available from outpatient clinic records.

CDI-Specific Data Collection

CDI was defined as a positive toxin assay for C. difficile plus clinical symptoms consistent with CDI. Positive C. difficile toxin assay results from the BJH laboratory were collected as part of the ongoing assessments. The BJH laboratory used a toxin CDI test for CDI diagnosis during the study period (Remel Xpect C. difficile Toxin A/B, Lenexa, KS). CDI-specific data included: CDI onset date, method of diagnosis (toxin, endoscopy, CT scan), presence of CDI symptoms (diarrhea, abdominal pain or distension, ileus, peritoneal signs, fever, hypothenmia, blood in stool, toxic megacolon), outcomes (duration of illness, colectomy or other surgery for CDI, death due to CDI), and type of, duration of, and response to CDI therapy. Antimicrobial exposures before, during, and after CDI were collected. Prospectively collected medication data were supplemented with data collected electronically from the hospital’s Medical Informatics database. CDI cases were classified by severity (mild, moderate, severe) according to modified Common Terminology Criteria for Adverse Events (CTCAE) criteria; details of this classification system have been published elsewhere.

Data Analysis

Participants were excluded from analyses if they had a history of CDI within the previous 60 days and/or were still receiving antimicrobial treatment for CDI at the time of their allogeneic HCT (n = 9). For CDI cases, the CDI diagnosis date was considered the index date. For controls (all allogeneic HCT recipients who did not develop CDI), an index date was randomly selected such that the distribution of time from...
CDI severity

| Variable | N = 63 with CDI n (%) |
|----------|-----------------------|
| CDI severity<sup>a</sup> | Mild | 32 (51) |
| | Moderate | 14 (22) |
| | Severe | 17 (27) |
| Time from transplant to CDI (median days [range]) | 23 (0-365) |
| CDI 0-30 d posttransplant (preengraftment) | 38 (60) |
| CDI 31-99 d posttransplant (postengraftment) | 11 (18) |
| CDI 100-365 d posttransplant (postengraftment) | 14 (22) |
| Diagnosis method | Toxic assay | 63 (100) |
| | Endoscopy | 1 (2) |
| | CT scan | 3 (5) |
| Setting onset of CDI | Inpatient | 54 (86) |
| | Outpatient | 9 (14) |
| | If outpatient, admitted for CDI? | 9 (100) |
| Classification<sup>B</sup> | Healthcare onset, healthcare facility-associated | 50 (79) |
| | Community onset, healthcare facility-associated | 9 (14) |
| | Indeterminate | 4 (6) |
| Symptoms | Diarrhea severity grade (maximum during illness)<sup>c</sup> | 1 | 26 (41) |
| | | 2 | 19 (30) |
| | | 3 | 11 (18) |
| | | 4 | 7 (11) |
| | Abdominal tenderness during CDI | 0 |
| | Abdominal tenderness within 48 h of CDI diagnosis | 0 |
| | Peritoneal signs | 0 |
| | Peritoneal signs within 48 h of CDI diagnosis | 0 |
| | Abdominal distension during CDI | 0 |
| | Abdominal distension within 48 h of CDI diagnosis | 0 |
| | Fever during CDI | 34 (54) |
| | Fever within 48 h of CDI diagnosis | 27 (43) |
| | Hypothermia during CDI | 13 (21) |
| | Hypothermia within 48 h of CDI diagnosis | 4 (6) |
| | Blood in stool during CDI | 0 |
| | Blood in stool within 48 h of CDI diagnosis | 0 |
| | Toxic megacolon | 0 |
| | Surgery for CDI | 0 |
| | Response to CDI therapy | Responded | 61 (97) |
| | | Did not respond | 1 (2) |
| | | Unknown | 1 (2) |
| | Duration of CDI (median days from symptom onset to resolution of diarrhea [range]) | 6 (1-51) |
| | Days from symptom onset to response to therapy (median [range]) | 5 (1-51) |
| | Days from symptom onset to diarrhea improvement (median [range]) | 4 (1-51) |
| | Duration of CDI antimicrobial treatment (median [range]) | 17 (3-83) |
| | Oral antimicrobial treatment | Oral metronidazole alone | 37 (59) |

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TABLE 1. (Continued)

| Variable | N = 63 with CDI n (%) |
|----------|-----------------------|
| Oral and IV metronidazole | 6 (10) |
| Oral vancomycin alone | 2 (3) |
| Oral vancomycin and oral metronidazole | 5 (8) |
| Oral vancomycin and IV metronidazole | 3 (5) |
| Oral metronidazole, IV metronidazole, and oral vancomycin | 9 (14) |
| Oral metronidazole, IV metronidazole, oral vancomycin, and intravenous immunoglobulin | 1 (2) |

<sup>a</sup>Health care onset, healthcare facility associated = CDI diagnosis ≥48 hours after hospital admission; Community onset, healthcare facility associated = CDI diagnosis as outpatient or <48 hours after admission with a discharge from a healthcare facility in the previous 4 weeks; Indeterminate = CDI diagnosis as outpatient or <48 hours after admission with a discharge from a healthcare facility in the previous 4–12 weeks.<sup>d</sup>

<sup>b</sup>Toxin assay performed with Per modified CTCAE criteria.<sup>19,22</sup>

<sup>c</sup>Log-rank P = 0.91; 38% of mild CDI died vs. 43% of moderate CDI and 26% of severe CDI.

<sup>d</sup>Log-rank P = 0.75; 39% of preengraftment CDI died vs. 40% of postengraftment CDI.

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allogeneic HCT to the index date was comparable between cases and controls. Data analyses were stratified by time from transplant to index date: 0 to 30 days posttransplant (preengraftment), and 31 to 365 days posttransplant (postengraftment). Only 2 CDI cases occurred more than 365 days posttransplant; these were considered outliers and were excluded from analyses. Antimicrobials were classified into high risk and low risk categories based on risk of causing CDI and our prior analysis. High risk antimicrobials included aminopenicillins/penicillins, cephalosporins, 8-methoxyfluoroquinolones, and clindamycin<sup>2,3</sup>; all other antimicrobials were considered low risk. Data such as medications were included if they occurred within the 30 days before index date, including pretransplant exposures when applicable. Neutropenia within 48 hours before index date was included. Risk factors for CDI were evaluated using chi-square/Fischer exact tests or univariate logistic regression, and logistic regression was used for multivariable analyses. Because of small sample sizes, priority for inclusion of variables into the models was based on clinical/biological plausibility, sufficient sample size within the variable, and univariate analyses. Variables with zero cells on univariate analyses were excluded from multivariable models. Due to the small sample size in the postengraftment analyses, at most 3 variables could be included at a time in multivariable models to avoid over specification. Death within 180 days of CDI was compared by CDI severity and time from transplant using the log-rank test. Analyses were performed with SPSS, version 21.0 (IBM Corp, Armonk, NY) and SAS version 9.2 (SAS, Cary, NC).

RESULTS

Two hundred fifty-four allogeneic HCT patients were approached to participate in the study; 199 consented to participate (78%), and 187 (74%) were included in analyses. Of the 187 patients, 63 (34%) developed CDI within 1 year...
of HCT and 124 (66%) did not. CDI symptoms and antimicrobial treatment are described in Table 1. Nine (14%) cases were diagnosed as outpatients. No participants required surgery for CDI. Ninety-seven percent of participants responded to antimicrobial therapy, and the median time to resolution of symptoms was 6 days. The majority of the CDI cases were classified as mild (51%), followed by moderate (22%) and severe (27%) according to the modified CTCAE criteria. There were no significant differences in death within 180 days post-CDI between mild, moderate, and severe CDI or between preengraftment (n = 38) and postengraftment CDI (n = 25) (Table 1; P > 0.05 for all).

Thirty-eight (60% of total) cases of CDI were diagnosed in the preengraftment period and 81 controls had their

### TABLE 2.

Risk factors for CDI preengraftment (0-30 days after transplant) (N = 119): univariate analysis and multivariable logistic regression model

| Variables                                | CDI cases n = 38 (n [%]) | Controls n = 81 (n [%]) | uOR (95% CI) | P     | aOR (95% CI) | P     |
|-------------------------------------------|--------------------------|--------------------------|--------------|-------|--------------|-------|
| Age, y                                    |                          |                          |              |       |              |       |
| 18-39                                     | 9 (24)                   | 20 (25)                  | Reference    |       |              |       |
| 40-65                                     | 27 (71)                  | 60 (74)                  | 1.0 (0.4-2.5) | 1.00  |              |       |
| >65                                       | 2 (5)                    | 1 (1)                    | 4.4 (0.4-55.6) | 0.25  |              |       |
| Female                                    | 14 (37)                  | 33 (41)                  | 0.8 (0.4-1.9) | 0.69  |              |       |
| Comorbidities                             |                          |                          |              |       |              |       |
| Cardiovascular disease                    | 15 (40)                  | 19 (24)                  | 2.1 (0.9-4.9) | 0.07  |              |       |
| Pulmonary disease                         | 5 (13)                   | 6 (7)                    | 1.9 (0.5-6.6) | 0.33  |              |       |
| GI disease                                | 6 (16)                   | 6 (7)                    | 2.3 (0.7-7.8) | 0.16  |              |       |
| Renal disease                             | 0 (0)                    | 3 (4)                    | Undefined    | 0.55  |              |       |
| Previous splenectomy                      | 2 (5)                    | 1 (1)                    | 4.4 (0.4-50.6) | 0.24  |              |       |
| Diabetes                                  | 5 (13)                   | 9 (11)                   | 1.2 (0.4-3.9) | 0.77  |              |       |
| Autoimmune disease                        | 0                        | 0                        |              |       |              |       |
| HIV, HCV, HBV                             | 2 (5)                    | 4 (5)                    | 1.1 (0.2-6.1) | 1.00  |              |       |
| Other comorbid disease                    | 13 (34)                  | 27 (33)                  | 1.0 (0.5-2.3) | 0.93  |              |       |
| No comorbid disease                       | 7 (18)                   | 31 (38)                  | 0.4 (0.1-0.9) | 0.03  | 0.3 (0.1-0.9) | 0.02 |
| Neutropenic within 48 h of index date     | 26 (68)                  | 47 (58)                  | 1.6 (0.7-3.5) | 0.28  |              |       |
| Myeloblastic conditioning                  | 28 (74)                  | 49 (61)                  | 1.8 (0.8-4.3) | 0.16  | 2.1 (0.9-5.0) | 0.10 |
| Related donor                             | 13 (34)                  | 25 (31)                  | 1.2 (0.5-2.6) | 0.72  |              |       |
| Matched donor                             | 37 (97)                  | 78 (96)                  | 1.4 (0.1-14.1) | 1.00  |              |       |
| Relapsed underlying disease²              | 12 (32)                  | 18 (22)                  | 1.6 (0.7-3.8) | 0.27  |              |       |
| Hospitalized at index date                | 37 (98)                  | 72 (89)                  | 4.6 (0.6-37.9) | 0.17  |              |       |
| Medications in 30 d before index date³    |                          |                          |              |       |              |       |
| Any antimicrobials                         | 35 (92)                  | 65 (80)                  | 2.9 (0.8-10.5) | 0.12  | 3.2 (0.8-12.0) | 0.09 |
| Any high risk antimicrobials              | 27 (71)                  | 50 (62)                  | 1.5 (0.7-3.5) | 0.32  |              |       |
| Any low risk antimicrobials               | 27 (71)                  | 55 (68)                  | 1.2 (0.5-2.7) | 0.73  |              |       |
| Growth factors                            | 17 (45)                  | 34 (42)                  | 1.1 (0.5-2.4) | 0.78  |              |       |
| Gastric acid suppressor                   | 36 (97)                  | 80 (99)                  | 0.5 (0.03-7.6) | 0.54  |              |       |
| PPI                                        | 16 (42)                  | 36 (44)                  | 0.9 (0.4-2.0) | 0.81  |              |       |
| H2 blocker                                | 35 (92)                  | 76 (94)                  | 0.8 (0.2-3.4) | 0.71  |              |       |
| Chemotherapy or total body irradiation    | 36 (95)                  | 79 (98)                  | 0.5 (0.1-3.4) | 0.59  |              |       |
| Narcotics                                  | 20 (53)                  | 42 (52)                  | 1.0 (0.5-2.2) | 0.94  |              |       |
| Insulin                                    | 7 (18)                   | 16 (20)                  | 0.9 (0.3-2.5) | 0.86  |              |       |
| Immunosuppressive/steroid                 | 38 (100)                 | 81 (100)                 |              |       |              |       |
| Infections within 30 d before index date ⁴ |                          |                          |              |       |              |       |
| Any infection                             | 14 (37)                  | 34 (42)                  | 0.8 (0.4-1.8) | 0.60  |              |       |
| BSI²                                      | 3 (8)                    | 9 (11)                   | 0.7 (0.2-2.7) | 0.75  |              |       |
| Pneumonia                                 | 2 (5)                    | 3 (4)                    | 1.4 (0.2-9.0) | 0.65  |              |       |
| Fungal infection                          | 1 (3)                    | 0 (0)                    | Undefined    | 0.32  |              |       |
| Viral infection                           | 7 (18)                   | 7 (9)                    | 2.4 (0.8-7.4) | 0.12  |              |       |
| GVHD                                      |                          |                          |              |       |              |       |
| Any GVHD before index date                | 1 (3)                    | 1 (1)                    | 2.2 (0.1-35.5) | 0.54  |              |       |
| Any GVHD within 7 d before index date     | 1 (3)                    | 1 (1)                    | 2.2 (0.1-35.5) | 0.54  |              |       |
| Gut GVHD within 7 d before index date     | 0                        | 0                        |              |       |              |       |

² Relapsed disease status at the time of transplant.
³ Pretransplant medication exposures were included when applicable.
⁴ ≥ all met NNIS criteria.
aOR, adjusted OR; uOR, unadjusted OR; 95% CI, 95% confidence interval.
randomly selected index date in this time period. Only lack of any underlying comorbid disease was significantly associated with CDI in univariable analysis (protective effect: odds ratio [OR], 0.4; Table 2). Cardiovascular disease was marginally associated with increased risk of CDI in univariable analysis (Table 2). In multivariable analysis, only lack of any underlying comorbid disease was significantly associated with lower risk of CDI (OR, 0.3), although there was a trend for myeloablative conditioning and receipt of any antimicrobials in the previous 30 days to be associated with increased risk of CDI (Table 2).

There were 25 CDI cases in the postengraftment period, and 43 controls had their randomly selected index date during that time (Table 3). Numerous risk factors for CDI were identified in univariable analysis: neutropenia within 48 hours before CDI/index, myeloablative conditioning, admitted at index date, receipt of any antimicrobials, high risk antimicrobials, low risk antimicrobials, gastric acid suppressor, proton pump inhibitor (PPI), and the presence of GVHD (Table 3).

### Table 3

Risk factors for CDI postengraftment (>30 days posttransplant) (N = 68): univariate analysis and multivariable logistic regression model

| Variable                                      | CDI cases n = 25 (n [%]) | Controls n = 43 (n [%]) | uOR (95% CI) | P-value | aOR (95% CI) | P    |
|-----------------------------------------------|--------------------------|--------------------------|--------------|---------|--------------|------|
| Age, y                                        |                          |                          |              |         |              |      |
| 18-39                                         | 5 (20)                   | 12 (28)                  | Reference    |         |              |      |
| 40-65                                         | 19 (76)                  | 24 (56)                  | 1.9 (0.6-6.3) | 0.30    |              |      |
| >65                                           | 1 (4)                    | 7 (16)                   | 0.3 (0.03-3.6) | 0.37    |              |      |
| Female                                        | 10 (40)                  | 17 (40)                  | 1.0 (0.4-2.8) | 0.97    |              |      |
| Comorbidities                                 |                          |                          |              |         |              |      |
| Cardiovascular disease                        | 10 (40)                  | 7 (16)                   | 3.4 (1.1-10.7) | 0.03    |              |      |
| Pulmonary disease                             | 1 (4)                    | 2 (9)                    | 0.9 (0.1-9.9) | 1.00    |              |      |
| GI disease                                    | 3 (12)                   | 7 (16)                   | 0.7 (0.2-3.0) | 0.74    |              |      |
| Renal disease                                 | 0                        | 0                        |              |         |              |      |
| Splenectomy                                   | 1 (4)                    | 1 (2)                    | 1.8 (0.1-29.3) | 1.00    |              |      |
| Diabetes                                      | 4 (16)                   | 4 (9)                    | 1.9 (0.4-8.2) | 0.45    |              |      |
| Autoimmune disease                            | 1 (4)                    | 0 (0)                    | Undefined    | 0.37    |              |      |
| HIV, HCV, HBV                                 | 0 (0)                    | 1 (2)                    | Undefined    | 1.00    |              |      |
| Other comorbid disease                        | 6 (24)                   | 17 (40)                  | 0.5 (0.2-1.5) | 0.19    |              |      |
| No comorbid disease                           | 8 (32)                   | 21 (49)                  | 0.5 (0.2-1.4) | 0.18    |              |      |
| Neutropenic within 48 h of index date         | 11 (44)                  | 0 (0)                    | Undefined    | <0.01   |              |      |
| Myeloablative conditioning                    | 23 (92)                  | 30 (70)                  | 5.0 (1.0-24.3) | 0.04    |              |      |
| Related donor                                 | 10 (40)                  | 15 (35)                  | 1.2 (0.5-3.4) | 0.67    |              |      |
| Matched donor                                 | 25 (100)                 | 41 (95)                  | Undefined    | 0.53    |              |      |
| Relapsed diseasea                             | 9 (36)                   | 7 (16)                   | 2.9 (0.9-9.1) | 0.07    | 6.7 (1.3-33.1) | 0.02 |
| Admitted at index date                        | 22 (88)                  | 4 (9)                    | 71.5 (14.6-349.1) | <0.01 |
| Medications in 30 d before index date         |                          |                          |              |         |              |      |
| Any antimicrobials                            | 25 (100)                 | 32 (74)                  | Undefined    | <0.01   |              |      |
| Any high-risk antimicrobials                  | 20 (90)                  | 14 (33)                  | 8.3 (2.6-26.7) | <0.01  | 11.8 (2.9-47.8) | <0.01 |
| Any low-risk antimicrobials                   | 25 (100)                 | 31 (72)                  | Undefined    | <0.01   |              |      |
| Growth factors                                | 12 (48)                  | 10 (23)                  | 3.0 (1.1-8.8) | 0.04    |              |      |
| Gastric acid suppressor                       | 22 (88)                  | 20 (47)                  | 8.4 (2.2-32.4) | <0.01   |              |      |
| PPI                                           | 13 (52)                  | 11 (26)                  | 3.2 (1.1-8.8) | 0.03    |              |      |
| H2 blocker                                    | 11 (44)                  | 15 (35)                  | 1.5 (0.5-4.0) | 0.46    |              |      |
| Chemotherapy or total body irradiation        | 10 (40)                  | 10 (23)                  | 2.2 (0.8-6.4) | 0.14    |              |      |
| Narcotic                                      | 11 (44)                  | 11 (26)                  | 2.3 (0.8-6.5) | 0.12    |              |      |
| Insulin                                       | 9 (36)                   | 5 (12)                   | 4.3 (1.2-14.8) | 0.03   |              |      |
| Immunosuppressive/steroid                     | 23 (92)                  | 41 (95)                  | 0.6 (0.1-4.3) | 0.62    |              |      |
| Infections in 30 d before index date          |                          |                          |              |         |              |      |
| Any infection                                 | 10 (40)                  | 9 (21)                   | 2.5 (0.9-7.5) | 0.09    |              |      |
| BSIb                                          | 5 (20)                   | 2 (5)                    | 5.1 (0.9-28.8) | 0.09    |              |      |
| Pneumonia                                     | 2 (8)                    | 3 (7)                    | 1.2 (0.2-7.5) | 1.00    |              |      |
| Fungal infection                              | 2 (8)                    | 1 (2)                    | 3.7 (0.3-42.5) | 0.55    |              |      |
| Viral infection                               | 2 (8)                    | 4 (9)                    | 0.8 (0.1-5.0) | 1.00    |              |      |
| GVHD                                          |                          |                          |              |         |              |      |
| Any GVHD before index date                    | 17 (68)                  | 13 (30)                  | 4.9 (1.7-14.2) | <0.01  | 7.8 (2.0-30.2) | <0.01 |
| Any GVHD within 7 d before index date         | 8 (32)                   | 2 (5)                    | 9.6 (1.9-50.2) | <0.01  |              |      |
| Gut GVHD within 7 d before index date         | 3 (12)                   | 0 (0)                    | Undefined    | 0.05    |              |      |

aData Relapsed disease status at the time of transplant.

bAll met NNIS criteria.
that the majority of CDI cases occurred within a few days be-
Chakrabarti and Alonso1,3 found median times to CDI of
of allogeneic transplant patients was 25 days after HCT.
apy and immunosuppressive or steroid use, were also
pose to CDI due to immune disruption, such as chemother-
80% of noncases received an antimicrobial in the previous
engraftment period. Antimicrobial exposure is
engraftment period, as suggested by our risk factor analysis
have been identified previously. This may be due to the uni-
30 days to 1 year.1,3,6,9-15,17,18,24 Kinnebrew et al6 found
that the majority of CDI cases occurred within a few days be-
before or after HCT; however, the maximum follow-up time was
was 35 days after transplant. Alonso et al19 found 81% of
CDI cases occurred within 30 days of autologous HCT. By
contrast, Willems et al,25 who evaluated CDI up to a year
post-HCT, found that the median time to CDI in their cohort
of allogeneic transplant patients was 25 days after HCT.
Chakrabarti and Alonso1,3 found median times to CDI of
38 and 33 days in their allogeneic HCT populations, respec-
Similarly, we found that 60% of the CDI cases oc-
curred within 30 days of HCT, 18% occurred between days
31 and 99, and 22% of CDI cases occurred 100 or more days
after transplant. These results, along with those of previous
investigators, indicate CDI may be more common during the
late posttransplant period than has previously been rec-
ognized.1,3,9 Post-HCT surveillance for CDI should continue
beyond 30 days to fully understand the epidemiology of CDI
in HCT patients, and to facilitate interventions to prevent
CDI at different times posttransplant.
Few specific risk factors for CDI after allogeneic HCT
have been identified previously. This may be due to the uni-
versality of common risk factors for CDI in the pre-
engraftment period, as suggested by our risk factor analysis
in the preengraftment period. Antimicrobial exposure is
widely considered the primary risk factor for CDI, but anti-
microbial use in the preengraftment period was ubiquitous
in our allogeneic HCT population; 92% of CDI cases and
80% of noncases received an antimicrobial in the previous
30 days. Other medications or procedures that could predis-
pose to CDI due to immune disruption, such as chemother-
apy and immunosuppressive or steroid use, were also
nearly universal in this allogeneic HCT population. It is likely
these variables do increase patients’ risk of CDI, but all allo-
genetic HCT patients are exposed to these types of medica-
tions. Instead, our results indicate patients’ underlying
health status pretransplant may be the primary determinant
of individual risk for CDI in the preengraftment period.
The only independent predictor of CDI in the preengraftment
period we identified was having no underlying comorbid dis-
ase, which was protective of CDI. Although underlying
health status is not a modifiable risk factor, the presence of
any comorbidity in allogeneic HCT recipients could be used
to target CDI prevention efforts. Receipt of myeloablative
conditioning pretransplant was marginally associated with
increased risk of CDI during the preengraftment period.
Kinnebrew et al6 also found that myeloablative conditioning
increased the risk of CDI. Myeloablative conditioning leads
to greater neutropenia and damage to the mucosa than
nonmyeloablative conditioning,25 resulting in increased suscep-
tibility to other infections (leading to antimicrobial exposures)
and thus increased risk of CDI. Conversely, the mucositis caused
by myeloablative conditioning with resultant diarrhea may lead
to increased testing for C. difficile and detection of asymp-
tomatic carriage in people with diarrhea from other causes.26
In contrast, we identified numerous risk factors for CDI
during the postengraftment period. The results of univariable
and multivariable analyses indicate the patients at highest
risk for CDI in the postengraftment period were those pa-
ients with prolonged immune disruption, as indicated by
prior infections, antimicrobial use, GVHD, and neutropenia.
Reducing these patients’ exposure to the inpatient healthcare
environment may decrease their risk of CDI.27 When this
approach is impossible, careful assessment of the need for and
selection of antimicrobials and gastric acid suppressants
should be performed. That a much larger proportion of pa-
tients received antimicrobials than had an infection does indi-
cate it may be possible to safely reduce or narrow the
spectrum of antimicrobial prescriptions for these patients.
These approaches have been somewhat successful at reduc-
ing rates of CDI in the general hospital population,28 al-
though CDI remains a significant problem overall.29
The relationship between GVHD and CDI is complex and
deserves additional study. Available data suggest GVHD may
be both a risk factor and/or an outcome of CDI. In our study,
GVHD of any kind was associated with significantly in-
creased risk of CDI in the postengraftment population. Gut
GVHD was marginally associated with increased risk of
CDI in univariable analysis, but the number of individuals
with gut GVHD was too small for the variable to be included
in the multivariable model. We have noted this relationship
between GVHD and increased risk of CDI previously at
our institution,19 as have Alonso et al and Chakrabarti
et al.1,3 Alonso found that CDI preceded GVHD in 86% of
patients, suggesting that GVHD may be an outcome of
CDI. In our analyses, we specifically examined GVHD with
onset before CDI and found GVHD to be a risk factor for
CDI in the postengraftment period. This apparent contradic-
tion can be explained by the high degree of colinearity be-
 tween the conditions, particularly in the case of gut GVHD
and CDI.25 Both gut GVHD and CDI may arise from loss
of a healthy gut microbiome. Jenq et al30 reported the loss
of gastrointestinal species diversity post-HCT in patients
with GVHD, both in a mouse model and in humans. This
loss of the normal gut microbiome has serious consequences
for patients. Taur et al31 reported increased post-HCT mor-
tality in patients with low bacterial diversity in the gut
microbiome. The growing list of conditions and/or negative
patient outcomes arising from the disrupted microbiome
should give further impetus to efforts aimed at protecting pa-
tients’ normal flora, particularly through the judicious and
responsible use of antimicrobials.
Previous estimates of CDI incidence in the allogeneic HCT
population range from 12% to 30%.1,3-7,9 Our observed
CDI incidence of 34% is slightly higher than previously published estimates, but this may be related to differences in study design. Kinnebrew et al reported an incidence of 17% within 35 days posttransplant; our CDI incidence within 30 days of transplant was comparable at 20%. In addition, because of our prospective study design and frequent follow-up with participants, we were able to capture outpatient CDI cases among the allogeneic transplant population that may have been missed if only inpatient data were used. It is also possible that awareness of CDI among transplant physicians has increased in recent years. In a previous analysis of CDI in allogeneic HCT recipients at our facility, 43% of CDI cases were classified as having mild to moderate CDI and 57% as having severe CDI. In the current study, using the same modified CTCAE criteria for grading CDI severity, 73% of cases were classified as mild/moderate and only 27% as severe. Heightened awareness of CDI may lead to increased diagnosis of mild CDI cases that would previously have been underdetected or earlier detection of CDI that would have become severe if diagnosis was delayed; however, transplant patients are particularly prone to diarrhea due to multiple other causes (side effects of chemotherapy, radiation, or other medications, GVHD, and so on), and the increase in mild/moderate cases of CDI also may have led to increased false-positive rates. Throughout the duration of the current study and our previously published study, our clinical microbiology laboratory used toxin enzyme immunoassay assays for C. difficile detection. Compared to PCR-based C. difficile detection, toxin enzyme immunoassay assays are less likely to detect asymptomatic colonization, so detection of asymptptomatically colonized participants with diarrhea due to unrelated causes should have been minimized. Analyses of CDI incidence and outcomes in allogeneic transplant patients over time should take into consideration the diagnostic tests used and how they may impact our understanding of CDI epidemiology.

There are several limitations to this study. We did not obtain stool samples from participants, so we were unable to determine whether preexisting colonization was a risk factor for CDI or may have led to detection of asymptomatic carriage in subjects with diarrhea due to other causes. Data on asymptomatic colonization preallogeneic HCT combined with detailed, prospective clinical data could resolve the question of whether some participants with mild CDI are in fact asymptptomatically colonized and experiencing diarrhea due to other causes. Finally, as with many studies of risk factors for CDI among allogeneic transplant recipients, our multivariable models were limited by small sample size. Allogeneic HCT recipients are a fairly small patient population, and larger, multicenter studies are needed to alleviate this problem. Despite these limitations, ours is one of the larger analyses of risk factors for CDI after allogeneic HCT. In addition, due to differences in patient risk factors for infection during the pre versus postengraftment period, we believe it is more appropriate to separate the pre and postengraftment periods to identify risk factors for CDI.

Although most previous studies have focused on CDI in the immediate posttransplant period, our study indicates that surveil lance for CDI should continue into the postengraftment period as CDI continues to impact allogeneic HCT recipients’ health postengraftment. Clinicians should carefully weigh patients’ needs for antimicrobials with the potential long-term consequences of extensive antimicrobial use. Future studies, particularly larger, multicenter studies, will help further elucidate the epidemiology of CDI in allogeneic HCT recipients and may reveal novel strategies for CDI prevention in this challenging patient population.

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