**Clostridium Difficile Infection after Allogeneic Hematopoietic Stem Cell Transplant: Strain Diversity and Outcomes Associated with NAP1/027**

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**Article history:**
Received 25 March 2014
Accepted 16 June 2014

**Key Words:**
Clostridium difficile infection
Allogeneic hematopoietic stem cell transplantation
NAP1/027 strain
Immunocompromised host

**ABSTRACT**
Allogeneic hematopoietic stem cell transplantation (HSCT) recipients are at high risk for developing *Clostridium difficile* infection (CDI). We studied the incidence, risk factors, NAP1/027 prevalence, and clinical outcomes, including acute lower gastrointestinal graft-versus-host disease (GI GVHD), associated with early CDI in this population. A retrospective review was conducted of patients who underwent allogeneic HSCT at Memorial Sloan Kettering Cancer Center from January 1, 2005 to September 30, 2010. Early CDI was defined as infection occurring from day 0 to day 40 from stem cell infusion. Among 793 patients who received allogeneic HSCTs, early CDI occurred in 11.9%; 56% cases were between day 5 and day 60. Overall incidence was 25.2 cases/10,000 at-risk days. There was a high prevalence of NAP1/027 strains during peak incidence (61% in 2008). NAP1/027 was the most common strain in both adult and pediatric cases (24% and 23%, respectively). CDI was clinically mild, including those due to NAP1/027. Metronidazole was the primary treatment for 91 of 94 patients, 7 of 8 cases refractory to metronidazole had no response to vancomycin, and none was due to NAP1/027. Relapse of CDI was common (31%). The cumulative incidence of GI GVHD in patients with and without early CDI was 6.8% and 8%, respectively (P = .5). Most cases of CDI occurred during conditioning or immediately after transplant. Despite high prevalence of NAP1/027, we found only mild disease. Most patients were treated successfully with metronidazole, irrespective of NAP1/027 status. There was no significant association between early CDI and subsequent development of GI GVHD. This study demonstrates the high incidence of CDI early after allogeneic HSCT with wide diversity among infecting strains. Despite the high prevalence of NAP1/027, the disease is mild but relapses are common. No association was found between CDI and subsequent development of GI GVHD.

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**INTRODUCTION**
Patients undergoing hematopoietic stem cell transplantation (HSCT) are particularly at risk for *Clostridium difficile* infection (CDI) because of the extended length of stay for transplant, frequent antibiotic use, and an immunocompromised state. *C. difficile* rates as high as 12.5% to 27% have been described in allogeneic HSCT recipients, a risk 15 to 20 times greater than other hospitalized patients [1-6], including solid organ transplant recipients.

Despite the rising incidence of CDI since the emergence of the NAP1/027 strain, the prevalence and impact of infection with this particular strain among allogeneic HSCT recipients has never been examined [7,8]. Although the frequency of CDI is much higher among allogeneic HSCT recipients when compared with autologous stem cell and solid organ transplantation recipients, the disease is reported to be mild in allogeneic HSCT recipients [2,9-12]. Despite this, immunocompromising conditions have been associated with severe CDI. As a consequence, some experts recommend vancomycin as first-line therapy for CDI because of the inability to accurately apply clinical scoring systems that measure severity of CDI in this population [13,14]. CDI has also been implicated in the development of acute gastrointestinal graft-versus-host disease (GI GVHD), postulated to be
triggered by disruption of mucosal barriers and release of proinflammatory cytokines. However, no conclusive evidence has supported this hypothesis [1,12,15].

We examined the incidence, molecular epidemiology, and clinical characteristics of early CDI, especially in relation to occurrence of the NAP1/027 strain. We also explored the potential relationship between early CDI and subsequent development of GVHD, with a focus on grade II or higher acute lower GI GVHD, in a large cohort of allogeneic HSCT recipients. The study population included patients that had received conventional T-cell–depleted and cord blood allografts.

**METHODS**

**Study Design and Patient Population**

This is a retrospective review of 793 adult and pediatric patients who underwent allogeneic HSCT for hematologic malignancies at Memorial Sloan Kettering Cancer Center (MSKCC) from January 1, 2005 until September 30, 2010. During this time, MSKCC was a 432-bed tertiary care facility in New York City with 19,000 annual admissions and 140,000 patient days. The adult bone marrow transplant unit at MSKCC is composed of a 28-bed unit, whereas the pediatric inpatient unit has 39 beds. All allogeneic HSCT patients are admitted to a private room and routinely placed under protective isolation (mask and gloves).

All demographic, clinical, and laboratory information were obtained from the institutional Clinical Research Database. Additional information not available in this database was obtained by MD chart review. The MSKCC Institutional Review Board reviewed the study and granted a HIPAA waiver of authorization.

**Antibacterial Prophylaxis**

Patients received antibacterial prophylaxis starting from day \(-2\) of allogeneic HSCT until development of febrile neutropenia, overt infection, or engraftment, whichever occurred first. The choice of agent was levofloxacin for patients receiving a nonmyeloablative conditioning regimen regardless of stem cell source. Ciprofloxacin was used for cord blood recipients who underwent myeloablative or reduced-intensity conditioning. Vancomycin prophylaxis was used for recipients of peripheral blood or bone marrow allografts who received a myeloablative or reduced-intensity conditioning regimen. Engraftment was defined as the first of 3 consecutive days with an absolute neutrophil count \(>500\) cells/\(\mu L\). Fever was defined as a temperature \(\geq 38.0\) °C.

**Graft-versus-Host Disease**

GVHD was monitored and managed as per MSKCC guidelines and was graded according to the International Bone Marrow Transplant Registry classification [16]. Acute lower GI GVHD was defined as GVHD that was diagnosed within the first 100 days after transplant.

**Clostridium difficile Infection**

**Case definition**

A case of CDI was defined by clinical history compatible with CDI and a positive test. “Early” CDI was an infection that occurred from day \(-10\) until day \(-40\) of transplant. This timeline was derived from the median length of stay for first transplants during the study period. Complicated CDI was defined by severe disease characterized by any of the following: systemic sepsis, intensive care unit admission, endoscopic evidence of pseudomembranous colitis, or toxic megacolon.

**Diagnostic methods**

From January 2005 until September 2008, diagnosis of CDI at MSKCC was performed by the cytotoxin neutralization assay. After September 2008, a 3-step testing algorithm was implemented that included a first-step glutamate dehydrogenase assay followed by the cytotoxin neutralization assay for all glutamate dehydrogenase–positive samples. C. difficile isolates were routinely stored for typing only after January 2008. PCR ribotyping and multilocus sequence typing (MLST) of isolates was performed as previously described [17,18].

**Treatment for CDI**

First-line treatment was metronidazole 500 mg p.o. (or i.v. for patients unable to tolerate oral medications) every 8 hours for a total of 14 days or discontinuation of broad-spectrum antibiotics, whichever was longer. Second-line treatment was oral vancomycin 125 mg p.o. 4 times daily at the discretion of the treating physician.

**Statistical Analysis**

Incidence rates were calculated by using the number of events divided by the total number of patient-days at risk. All second transplants were removed from the numerator and denominator when calculating incidence. Categorical variables were compared using the chi-square test, and continuous variables were compared using the Mann-Whitney rank sum test for the baseline characteristics of early CDI. Simple logistic regression was used for the univariate analysis of risk factors of early CDI. Multiple logistic regression was used for multivariate analysis of risk factors of early CDI among adult patients.

**RESULTS**

A total of 793 allogeneic HSCTs were performed during the study period, comprising 598 adult patients and 195 pediatric patients. Overall, 169 patients (21.3%) had at least 1 episode of CDI in the first year after transplant. Early CDI occurred in 94 transplant recipients (11.9%), including 25 patients younger than 21 years. Overall, the incidence of early CDI was 25.2 cases per 10,000 patient-days at risk. The highest percentage of cases were observed in the years 2007 and 2008 (14.3 and 16.3%, respectively) and declined subsequently to 9.1% in 2010 (\(P = .38\)). No outbreaks were reported during the study period (Figure 1).

**C. difficile Characteristics and Outcome**

Ninety-four patients had early CDI, and 56% of infections occurred from day \(-5\) to day \(+5\) (Figure 2). Table 1 shows the baseline characteristics of the study cohort, and Supplementary Table 1 shows clinical characteristics of patients with early CDI. Diarrhea was mild (grade 1) in most cases (76.1%). Forty-four percent of patients were neutropenic, and none developed acute renal failure at the time of CDI. Fourteen patients had imaging with abdominal x-ray series or computed tomographic scanning; 3 among these had evidence of colitis and none had ileus, toxic megacolon, or evidence of perforation. There were no deaths attributed to CDI.

Most patients received metronidazole (91/94) at a dose of 500 mg 3 times daily for 10 to 14 days or until an alternate agent was used. For 8 of 91 patients, treatment was changed to vancomycin because of persistent diarrhea (median time to treatment switch, 5.5 days; range, 3 to 8 days). The time of onset of CDI for all but 1 case with refractory diarrhea was between day \(-7\) and day 0. Seven of these patients had persistent diarrhea despite changing to vancomycin, and antimotility agents were eventually used for symptom relief. In 4 of 7 cases, retesting for CDI was done before initiating antimotility agents and was negative in all cases. For 1 patient, diarrhea resolved after changing to vancomycin without concomitant use of antimotility agents. Molecular typing was done on isolates retrieved from 7 of 8 patients; none was infected with the NAP1/027 strain.

Concomitant antibacterial agents for fever and neutropenia prophylaxis or management of concurrent infection were used in 89% of patients during CDI treatment (Table 2). Twenty-nine patients (31%) had relapse of CDI. The median time to relapse was 79 days. Nine patients (9.6%) had early relapse within 8 weeks after the index episode.
Strain Characteristics by PCR Ribotyping and MLST

Isolates from 42 of 58 infections that occurred after January 2008 were available for analysis by MLST and PCR ribotyping (Figure 3, Supplementary Figure 1). Storage of samples was random and not determined by clinical severity of disease. The overall prevalence of NAP1/027 among the typed isolates from the study years 2008 to 2010 was 24%. The highest frequency of infections by NAP1/027 correlated with the peak incidence of CDI in 2008, when 61% (8/13) of all typed isolates were NAP1/027. The percentage of NAP1/027 in the study in 2009 and 2010 were 6.2% and 7.6%, respectively.

There was concordance between the MLST and ribotyping results; all 10 isolates identified as 027 in our study were identified as ST-1 by the MLST scheme. The 32 non-NAP1 strains were characterized by MLST: the most common among these was ST-2 (n = 5) followed by ST-3 and -42 (n = 3 each), followed by ST-8, -10, -11, -43, -44, and -58 (2 each) and isolated strains belonging to ST types 4, 16, 34, 41, 46, 54, 103, 123, and 191. Although most NAP1 infections were detected in the second half of 2008, none of these or other patients diagnosed with common strains overlapped in time or space, suggesting that hospital-based transmission did not occur during the time of transplant (Figure 3).

The 42 typed isolated included 13 of 16 infections (81%) from pediatric transplant recipients and 29 of 42 infections (69%) diagnosed from adult transplant recipients during this time period. NAP1/027 strains accounted for approximately one fourth of infections in both populations (23% in pediatric and 24% in adult patients). Univariate analysis did not reveal any significant differences in clinical severity or outcomes associated with CDI infection due to the NAP1/027 strain when compared with non-NAP1/027 strains (Table 2). The only notable finding was the higher relapse rate among NAP1/027 infections; however, this did not reach statistical significance.

Relationship Between CDI and Acute Lower GI GVHD

To explore the relationship between early CDI and subsequent development of lower GI GVHD, we examined the
probability of developing acute lower GI GVHD (grade ≥ II in the first 100 days) in patients with and without early CDI. We only evaluated patients in whom CDI preceded the development of GI GVHD. Overall, 46 study patients were diagnosed with acute lower GI GVHD in the first 100 days after transplant, and 4 of these patients had early CDI. The cumulative incidence of acute lower GI GVHD in patients with early CDI was 6.8% compared with 8% in patients without early CDI ($P = .5$) (Figure 4A). The incidence of acute lower GI GVHD was highest in patients undergoing conventional transplantation who did not have early CDI, although the difference did not reach statistical significance (Figure 4B).

### Transplant Characteristics and Related Risk Factors

We compared the characteristics of 94 cases of early CDI with the 699 allogeneic HSCT recipients without early CDI to identify risk factors for early CDI (Table 3). No statistically significant associations were found between CDI and demographic characteristics such as age and sex or transplant variables such as underlying disease, HLA matching status, conditioning intensity, use of total body irradiation (TBI)-containing conditioning regimens, or nonmyeloablative conditioning regimen. The lack of significant association persisted in the adjusted logistic regression model for CDI. Antibiotic prophylaxis with fluoroquinolones and vancomycin was examined, and no associated risk of CDI was identified.
DISCUSSION

Allogeneic HSCT recipients are among the most susceptible hosts for CDI [1,3,12,15]. Our study demonstrates that most CDIs occur around the time of conditioning and in the first week after stem cell infusion. We report early CDI rates over a wide peritransplant period (day −10 to day +40) and a slightly higher rate than previous studies from major transplant centers that have examined rates of CDI in the first month after allogeneic HSCT (5.6% to 8.35% in the study by Alonso et al. [1]) and in Europe (6.4% in study by Willems et al. [6]). Differences in study population, antimicrobial prophylaxis, and testing practices (eg, varying policies regarding rejection of formed stools for testing) may account at least in part for the difference in rates. MSKCC is a referral center, and about 50% of patients who undergo transplant have received pretransplant care elsewhere. Often, prior history of CDI in the pretransplant phase of illness cannot be ascertained. Most patients (>90%) undergoing allogeneic HSCT at MSKCC are tested for *C. difficile* irrespective of stool consistency, leading to ascertainment bias.

Although NAP1 was the most commonly isolated strain in our cohort, no epidemiologic evidence of patient-to-patient transmission was found and no outbreaks occurred during the study period. Overall, 19 ST types were found among the typed isolates, with NAP 1/027 being the most common strain. However, the prevalence of this strain varied over time, and overall during the study period, wide diversity of infecting strains was encountered. This finding, along with the timing of infection, suggests that most CDI seen early after transplant occurs in previously colonized patients and establishment of colonization likely occurs before transplant. Prospective studies using PCR for screening at MSKCC have identified colonization rates as high as 39% in this population, with detection mostly early after transplant. Approximately 70% of patients who developed early CDI in this cohort were previously colonized with tcdB- strains of *C. difficile* [19]. Further evidence supporting this notion comes from a recent study done at Karmanos Cancer Center where allogeneic HSCT recipients were screened for *C. difficile* upon admission and at weekly
intervals thereafter. Fourteen percent of patients were found to be colonized with *C. difficile* on initial screening, and *C. difficile* accounted for most patients who developed infection subsequently. Only 8 of 107 patients who tested negative on initial screen were later suspected to have nosocomial acquisition of *C. difficile* [20].

The NAP1/027 strain first appeared in the United States and North America almost a decade ago [7,21]. Infection due to this strain has been associated with a higher incidence and severity of infection. The strain is a hypertoxin producer that has been associated with the increased severity of illness observed with NAP1/027 infection [22]. The impact of infection due to this particular strain has not been described in previous studies of allogeneic HSCT recipients, except in the study by Willems et al. [6] in which no cases were attributed to it. At MSKCC, we observed a doubling of the rate of CDI between the years 2006 and 2007 (Figure 1), without any substantial change in the number of transplants performed or the testing method for CDI. Although strains from these study years (2006 and 2007) were not examined by molecular typing, the NAP1/027 prevalence among tested strains during peak *C. difficile* incidence in our cohort was 61%. This suggests that the high rates observed from 2007 to 2009 were likely driven by high prevalence of this strain, which was endemic at many medical centers across the United States during these years.

The disease observed in our cohort was uniformly mild, irrespective of the infecting strain type, and no poor outcomes were associated with NAP1/027 infection except for higher relapse rates; however, the number of cases was too small to reach statistical significance. Although most cases of CDI had resolution of diarrhea with metronidazole, nonresponse was noted in 8 patients in whom treatment was changed to vancomycin. Diarrhea persisted, however, and antimotility agents were used for symptom relief in 7 of these patients. Diarrhea in the peritransplant period can occur because of a variety of factors, and physician knowledge about the epidemic NAP1/027 strain may have influenced decisions regarding treatment change. Among 7 patients in whom treatment failure with metronidazole was suspected and strain typing could be performed, none had infection with the NAP1/027 strain. These cases were not deemed to be metronidazole failures. They occurred during conditioning or stem cell infusion, and the persistent symptoms were attributed to the regimens rather than refractory CDI. Vancomycin was used as first-line therapy in only 3 cases. Comparison of vancomycin with metronidazole for symptom resolution and relapse therefore could not be made due to the small number of patients in the former group. Similar to other studies of allogeneic HSCT recipients, relapse of CDI was common and occurred in 31% of patients.

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OR indicates odds ratio; CI, confidence interval; AOR, adjusted odds ratio; REF, reference group; BM, bone marrow; PBSC, peripheral blood stem cell; NA, not applicable; RIC, reduced-intensity conditioning; FQ, Fluoroquinolone.

* Low TBI < 200 Gy.
Our study has several other important findings. First, risk factor analysis for early CDI suggested that patients with acute myeloid leukemia and those who received cord blood grafts had a higher risk of CDI, but the association did not persist in multivariate analysis. Although studies have postulated mucosal injury resulting from the conditioning regimen, especially TBI, as a risk factor for CDI, we did not find a significant association even with full-dose TBI [6]. Second, the development of acute lower GI GVHD after CDI has led some to speculate a causal relationship between the 2 conditions. However, we found the cumulative frequency of acute lower GI GVHD in our cohort was not significantly different in the group of patients with and without early CDI. The association, if any, may not have become overt due to the use of T cell depletion and the lower incidence of GVHD at our center. No difference was observed when examined by transplant type, including in persons receiving cord blood transplants and TBI-containing conditioning regimens, although only a small number of patients were diagnosed with acute lower GI GVHD in these groups (Figure 4B). The reverse association of acute lower GI GVHD as a risk factor for CDI evaluated in other reports [2,12,15] should be interpreted cautiously. Testing bias in this population and pitfalls of current diagnostic methodologies, especially molecular-based testing, which detects the toxin gene rather than the toxin, can contribute to overestimates of clinically significant infection.

The limitations of this study are its retrospective design, the lack of strain typing of all 94 cases of CDI, and the fact that pretransplant history of CDI could not be ascertained for approximately half of the patients in our cohort who received pretransplant care elsewhere. Antibiotics used for treatment during transplantation were not evaluated as an independent variable, because >90% of patients received antibiotic prophylaxis or treatment of infections in the first 40 days after transplant. Diarrhea occurs relatively commonly in the early transplant period because of the effects of conditioning regimens, and thus the patients are tested for enteric pathogens frequently. It is possible that some patients who were carriers of C. difficile had the diarrheal illness ascribed to CDI when in fact the conditioning regimen caused the symptoms, leading to an overestimation of rates.

Our findings are especially relevant because of the widespread implementation of molecular-based testing methods by most transplant centers. Recently, PCR-based screening using serial stool samples from patients undergoing allogeneic HCT at our center identified 37 patients with toxigenic C. difficile, among which only 16 were clinically suspected to have CDI [19]. When used for diagnosis of CDI, molecular methods offer many advantages over widely used enzyme immunoassays and cytotoxin neutralization assays, including higher sensitivity and rapid turnaround time, and detection of colonization is much higher with these assays that detect the toxin gene. With doubling of C. difficile detection rates reported by many centers after implementation of PCR [3,23], interpretation of a positive test in this population will have to be carefully evaluated in prospective studies that use screening strategies and rigorously implemented clinical scoring systems to overcome the diagnostic challenge of distinguishing between active infection and colonization [3].

Notably, this study found very mild CDI disease, in contrast to the severe infections reported in solid organ transplant recipients. Even the NAP1/027 strain, which accounted for most infections in our cohort, was not associated with severe illness in this population, perhaps demonstrating the importance of host factors in the development of severe disease. Although conventional C. difficile severity scoring systems are not applicable in our cohort, metronidazole appears to be safe and effective in this population, despite widespread use of concomitant antibacterial agents. The impact of treatment choice on reducing relapse of C. difficile disease needs to be formally investigated in prospective studies. Unlike previous reports, we found no association between early CDI and subsequent development of acute lower GI GVHD in our cohort [11,12,15].

Acknowledgments

Financial disclosure: Supported by National Institutes of Health/National Institute of Allergy and Infectious Diseases career development award to M.K. (K23 AI083880).

Conflict of interest statement: There are no conflicts of interest to report.

Authorship statement: A.A.J. and G.P. both contributed equally to this article.

Supplementary Data

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.bbmt.2014.06.025.

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