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Clostridium difficile infection among hematopoietic stem cell transplant recipients: beyond colitis

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Abstract

Purpose of review—To review the most recent data regarding the epidemiology, risks factors, and outcomes among hematopoietic stem cell transplant recipients with *Clostridium difficile* infection (CDI).

Recent findings—With the emergence of an epidemic strain of *C. difficile* known as NAP1 in the early 2000s, rates of this infection have escalated globally. Hematopoietic stem cell transplant recipients appear to be one of the most vulnerable populations for the development of CDI. Traditional risk factors for CDI including antimicrobial exposure and older age are likely only a piece of the overall risk profile, with recent study results also emphasizing other factors such as transplant type, conditioning regimen, and graft-versus-host disease (GVHD). The relationship between CDI and subsequent development of GVHD, particularly of the gastrointestinal tract, is of specific interest. A bidirectional relationship of association has been highlighted in a number of recent studies and underscores the need for further prospective studies to address the potential indirect effects of alloreactivity induced by CDI.

Summary—CDI has emerged as one of the most common infections in the early transplant period. Recent studies have begun to address the epidemiology of disease, risk factors for, and outcomes after infection in the stem cell transplant. However, more research is needed to unravel the observed relationship between CDI and GVHD.

Keywords

Clostridium difficile; colitis; graft-versus-host disease; hematopoietic stem cell transplant

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Conflicts of interest

C.D.A. reports no conflicts of interest.

INTRODUCTION

Clostridium difficile infection (CDI) is the leading cause of infectious diarrhea among hospitalized patients estimated to be responsible for more than 300 000 cases of infectious diarrhea and more than 14 000 deaths in the United States each year [1–4]. It is a predominately nosocomial infection that causes a spectrum of clinical disease ranging from mild diarrhea to fulminant colitis. Patients undergoing hematopoietic stem cell transplantation (HSCT) appear to be one of the highest risk populations for this infection, with rates of CDI exceeding 25% in some studies [5▪]. In the last decade, rates of infection have escalated globally. These epidemiologic changes have been linked to an epidemic strain of the pathogen known as NAP1/BI/027, which has been associated with increased frequency and severity of disease [6,7]. Of particular concern to immunocompromised hosts is its association with enhanced toxin production and high-level resistance to fluoroquinolone antibiotics, commonly used for prophylaxis and treatment during the transplant course. Why HSCT recipients are at an elevated risk for CDI compared with the general hospitalized population is an area of intense debate, but is likely to be a combination of factors including nosocomial exposures (i.e. prolonged hospital stays and antimicrobial exposure) in addition to host factors such as degree of immune impairment and inability to mount a humoral response to *C. difficile*-specific toxins [8,9]. Furthermore, the infection appears to have several downstream effects specific to this population including a noteworthy association with subsequent development of gastrointestinal tract graft-versus-host disease (GVHD). This article serves to review the most current data regarding epidemiology, risk factors, and clinical outcomes, including the association with GVHD, among recipients of HSCT with CDI.

EPIDEMIOLOGY OF *C. DIFFICILE* INFECTION AFTER HEMATOPOIETIC STEM CELL TRANSPLANTATION

C. difficile has been established as an important cause of infectious diarrhea among HSCT recipients since the early 1980s [10]. From 1994 to 1999, rates of infection were reported to be between 2 and 18% among a heterogeneous population of HSCT recipients [11–15]. In the early 2000s, a number of publications noted escalating rates of infection among HSCT recipients corresponding with the emergence of the NAP1 strain globally [16–22]. However, few provided detailed host risk factor analysis. Since 2010, larger studies over greater time periods have allowed us to better explore the epidemiology in this population [5▪,23–28,29▪] (Table 1). The most recent literature suggests that rates of infection are in the range of 6–8% within the first year of autologous HSCT (auto-HSCT) [26,28,29▪]. Rates among allogeneic HSCTs (allo-HSCTs) rates have been significantly higher, ranging from 12 to 27% [5▪,26–28,29▪]. Unfortunately, there has been tremendous variability between rate calculations among centers over the last decade. Guidelines [30] now suggest standardizing case definitions to reflect cases per 10 000 patient-days for improved comparability among centers.

PATHOGENESIS OF INFECTION

The pathogenesis of infection relies upon disruption of the normal colonic flora leading to colonization by a pathogenic strain of *C. difficile*. Traditionally, antibiotic exposure has been the leading driver of disruption of the endogenous flora, particularly receipt of broad-spectrum penicillins, cephalosporins, clindamycin, and fluoroquinolones. In the HSCT recipients, other factors such as receipt of cytotoxic chemotherapy may cause dysregulation of the colonic flora leading to colonization. In a report by Loo *et al.* [31], prior chemotherapy increased the risk for *C. difficile* colonization more than two-fold. Colonization with nonpathogenic strains of the bacterium may provide some protection from CDI in some individuals, possibly by inhabiting the microbial space that toxigenic strains need to infect the patient [32].

Once colonization with a toxigenic strain occurs, the bacterium elaborates two toxins: toxin A (the enterotoxin) and toxin B (the cytotoxin). These toxins cause damage to the host by inactivating GTPases on Rho/Ras families leading to cytoskeletal changes in the colonic cell, disruption in tight junctions, and a cytokine cascade that draws neutrophils to the site of infection [33]. Colonic ulceration and subsequent accumulation of proteins, mucus, and inflammatory cells result in the development of pseudomembranous colitis, a finding that has been considered virtually pathognomonic for CDI.

CLINICAL PRESENTATION AND DISEASE SEVERITY: CAN WE USE TRADITIONAL MARKERS OF SEVERITY IN THIS POPULATION?

Anecdotal data suggests that the pathogenesis of this infection may be different in immunosuppressed patients, with an absence of pseudomembranes seen in one small report of eight ‘immunosuppressed’ patients who underwent endoscopy at the time of diagnosis of CDI [34]. These observations are supported by the recent publications which have noted few markers of severe disease and low rates of recurrent disease in most cases [26,28,29▪]. It is possible that immunosuppression may attenuate the disease. Alternatively, we may be underestimating the burden and severity of disease in this population by relying on the severity scores which rely heavily upon white blood cell (WBC) and creatinine elevation [30]. Wang *et al.* [35] observed that patients with hematologic malignancies had overall lower creatinine levels and lower WBC counts at the time of CDI diagnosis, an observation that was also noted in cases in the study by Alonso *et al.*

In 2007, Dubberke *et al.* [36] proposed a CDI severity of illness score for allo-HSCT recipients using a modified version of the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0 (CTCAE) and presenting clinical symptoms, although to date this has not been adopted universally. Alternatively, it is possible that published studies may be overestimating the burden of disease by including patients with *C. difficile* colonization who have diarrhea related to other causes [37]. Further research in this field will hinge upon standardizing testing methods and severity of illness scores, and clearly delineating CDI from *C. difficile* colonization.

MAJOR RECENT ARTICLES ADDRESSING THE RATES AND RISK FACTORS

Chopra *et al.* [26] retrospectively examined the rates of CDI among 361 HSCT recipients from 2005 to 2006 in Detroit, Michigan, USA, and found an overall rate of CDI of 14%, with greater rates of infection among allo-HSCT recipients (18%) compared with auto-HSCT recipients (8%). The study defined CDI cases as patients with diarrhea and a positive laboratory assay test for *C. difficile* toxin in the stool, and endoscopic or histopathologic evidence of pseudomembranous colitis. Detection of *C. difficile* toxin in the stool was performed by the enzyme immunoassay for toxin A and toxin B. Rates/patient-days were calculated using the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA) guidelines. CDI rate per 10 000 patient-days was 24.0 per 10 000 patient-days among HSCT recipients, compared with 16.8 per 10 000 patient-days for oncology patients and 2.6 per 10 000 patient-days for general hospitalized patients. A total of 71% of cases were identified in the first 30 days of HSCT. All patients with CDI responded to therapy and there was only one case of severe CDI (8%), low rates of recurrent CDI (5% among allo-HSCT recipients and 0% among auto-HSCT recipients), and no deaths attributable to the infection.

Willems *et al.* [27] retrospectively reviewed 414 allo-HSCT recipients at Saint-Louis Hospital (Paris, France) from 2004 to 2007. CDI was defined according to the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines [38]. Cases were defined as diarrhea without evidence of another pathogen causing diarrhea and the presence of toxigenic *C. difficile* in the stool. All cases were identified in the first year of HSCT. A total of 50% of cases occurred within the first month of HSCT with a median time to infection of 25 days after HSCT. A total of 53 cases were compared to 354 controls without CDI. In the time-dependent risk factor analysis, factors associated with increased risk for CDI included cord blood as the source of stem cells [hazard ratio 2, 95% confidence interval (CI) 1–3.8, $P = 0.04$]; total body irradiation (TBI) at least 12Gy (associated with early CDI: hazard ratio 2.3, 95% CI 1.2–4.5, $P = 0.01$); and acute GVHD grade 2 or higher (associated with late CDI: hazard ratio 27.2, 95% CI 3.5–210.4, $P = 0.002$).

Alonso *et al.* [28] retrospectively reviewed 999 autologous and allogeneic HSCT recipients at Johns Hopkins Hospital (Baltimore, Maryland, USA) from 2003 to 2008. CDI was defined as diarrhea plus a positive stool assay for toxigenic *C. difficile*. Overall CDI rate was 9.2%. CDI rate was 6.5% among auto-HSCT recipients and 12.5% among allo-HSCT recipients. Timing curves revealed that disease occurred at a median of 6.5 days for auto-HSCT recipients and at a median of 33 days for allo-HSCT recipients. A case–control analysis was performed to identify the risk factors for CDI among allo-HSCT recipients. In that analysis, factors associated with increased risk for CDI included receipt of chemotherapy prior to conditioning for HSCT, broad-spectrum antimicrobial use, acute GHVD [adjusted odds ratio (aOR) 4.45, 95% CI 1.54–12.84, $P = 0.006$], and vancomycin-resistant *Enterococci* (VRE) colonization (aOR 5.87, 95% CI 1.97–17.47, $P = 0.002$). Recurrent CDI was observed in 21.7% of cases. A risk factor analysis found that acute gastrointestinal GVHD was the strongest risk for recurrent CDI (aOR 4.23, 95% CI 1.20–

14.86, $P = 0.02$). The early timing of CDI and the risks associated with prior chemotherapy also raised the possibility that a proportion of patients may be colonized with *C. difficile* preconditioning.

Trifilio *et al.* [29▪] retrospectively reviewed 822 autologous and allogeneic HSCT recipients at Northwestern Memorial Hospital (Chicago, Illinois, USA) from 2004 to 2008. CDI was defined as diarrhea plus positive stool assay for *C. difficile* toxin A or B or a culture positive for toxigenic *C. difficile*. Overall rate of CDI was 10.3%, with higher rates among allo-HSCT recipients (14.5%) compared with auto-HSCT recipients (8.5%). Cox regression analysis identified the following factors to be independently associated with CDI: age greater than 60 years, receipt of an allo-HSCT, and VRE colonization (all $P < 0.001$). A risk stratification model was developed. This found that patients who had all three factors had the highest risk for CDI with an incidence of greater than 20%.

INDIRECT EFFECTS OF *C. DIFFICILE* INFECTION: IS THERE AN ASSOCIATION BETWEEN *C. DIFFICILE* INFECTION AND GRAFT-VERSUS-HOST DISEASE?

The intestinal microbiome undergoes dramatic shifts during the transplant course with reduced bacterial diversity likely related to factors such as antimicrobial exposure, chemotherapeutic agents, and radiation [39▪▪]. Alterations in the gastrointestinal microbiome may influence the risk for transplant complications such as bacteremic episodes [39▪▪] and development of GVHD [40▪▪]. Our current understanding of GVHD involves a multiple step process that starts with the activation of host antigen-presenting cells followed by donor T-cell activation and proliferation. The final step involves induction of cellular mediators leading to tissue damage [41]. It is believed that certain microbes may trigger the first step of this process culminating in immune dysregulation and the development of GVHD.

To date, there have been four publications that have suggested an association between CDI and the subsequent development of GVHD among allo-HSCT recipients [17,25,28,29▪]. The earliest observation was made by Chakarbarti *et al.* who found that CDI was associated with severe GVHD (grade 3–4) (OR 9.8, 95% CI 2.1–43) in a retrospective analysis of 75 allo-HSCT recipients. Isolation of *C. difficile* in the stool appeared to be temporally associated with the development or worsening of GVHD in 60% of case patients. The temporal relationship between CDI and subsequent GVHD was also observed by Dubberke *et al.* who found that patients with CDI were more likely to develop new-onset GVHD ($P < 0.001$), new-onset severe GVHD ($P < 0.001$), or new-onset gut GVHD ($P = 0.007$). A similar observation was noted by Alonso *et al.* who found that CDI diagnosis preceded GVHD diagnosis in 85.7% of patients who developed biopsy-proven gut GVHD and by Trifilio *et al.* who noted that CDI patients were more likely to develop severe GVHD at day 60 and day 100 after HSCT.

With these observations, there appears to be mounting evidence for an association between CDI and GVHD. More clinical and experimental data are needed to tease out whether there is a true cause-and-effect relationship between CDI and GVHD development or whether

GVHD in and of itself provides risk for the infection, or represents sampling bias with diarrheal episodes. Either way, this association could have great significance given our current approach to treatment and prevention of infection and GVHD.

WHAT IS THE BEST FORM OF TREATMENT FOR *C. DIFFICILE* INFECTION AFTER HEMATOPOIETIC STEM CELL TRANSPLANTATION AND CAN INFECTION BE PREVENTED?

There are no randomized clinical trials to date that have focused on the best form of treatment for CDI among HSCT recipients. Current treatment guidelines proposed by both the American and European Infectious Diseases Societies [30,38] suggest treatment with oral metronidazole for mild and moderate cases of CDI. Oral vancomycin is suggested for the treatment of severe cases. Both guidelines hinge on traditional severity of illness scores utilizing WBC count and changes in serumcreatinine, which have not been validated in immunocompromised hosts and which can provide spurious conclusions for obvious reasons within the neutropenic population in particular.

Metronidazole has been used as primary treatment for mild-to-moderate CDI for years with observational data to suggest that it is likely effective in this population [26,28]. However, its use in stem cell transplant recipients may be limited by drug toxicity such as metallic taste, nausea, and dose-dependent peripheral neuropathy, all of which may have overlap with toxicity from systemic chemotherapeutic agents. Toxicity, coupled with a concern over clinical failure reported with metronidazole use [42,43] in observational studies during the 2000s, has prompted many centers to move toward up-front therapy with oral vancomycin for CDI in immunosuppressed patients.

Recently, fidaxomicin was approved for the treatment of CDI. In a post hoc analysis of two randomized controlled trials comparing fidaxomicin versus oral vancomycin for the treatment of CDI, Cornely *et al.* [44] identified 183 patients with cancer (67.8% solid tumor, 20.2% hematologic malignancy, and 12.0% solid tumor and hematologic malignancy) and found that patients with cancer had lower overall cure rates, but similar rates of recurrent CDI when compared to patients without cancer. HSCT recipients were not explicitly defined in this study. Among cancer patients, overall cure rates were 97.3% in the fidaxomicin group and 87.5% in the vancomycin group for patients who had received greater than 8 days of treatment (OR 5.07, 95% CI 1.07–23.98, $P = 0.04$). The median time to resolution of diarrhea was longer in cancer patients (100 h) compared with patients without cancer (55 h; $P = 0.0003$). In that analysis, fidaxomicin appeared to be superior to vancomycin for initial cure, recurrence, and sustained clinical response in patients who had cancer.

Currently, the mainstays of CDI prevention include antimicrobial stewardship and infection control practices such as barrier precautions and environmental cleaning [45]. Despite the implementation of these measures in most centers, rates continue to remain high and therefore alternative strategies for prevention, including prophylactic agents against *C.difficile*, have been under investigation. The Safety and Efficacy of Fidaxomicin Versus Placebo for Prophylaxis Against Clostridium Difficile-Associated Diarrhea in Adults

Undergoing Hematopoietic Stem Cell Transplantation (DEFLECT-1) trial recently opened for enrollment in the USA [46] and is poised to be the first study to address the possibility of prevention of CDI in HSCT recipients. This study is a phase 3b, multicenter, randomized controlled trial comparing the safety and efficacy of fidaxomicin versus placebo in HSCT recipients receiving fluoroquinolone antibiotics in the first 30 days after HSCT. Enrollment is expected to be completed in 2014.

CONCLUSION

Patients undergoing HSCT appear to have significant risks for the development of CDI in the first year of transplant. It is likely that this risk is a combination of modifiable factors as well as host factors. To date, research in this field has been limited by variable *C. difficile* testing methods, inconsistent case definitions, and highly heterogeneous patient populations between centers. From the available literature, it appears that the infection is more than just a ‘nuisance’ bug. Patients and providers should be aware of the potential downstream complications from the infection such as a possible link between CDI and subsequent development of gut GVHD. Further research in this field hinges upon standardizing the case definitions of CDI. Larger, multicenter, prospective studies are also needed to evaluate the basic pathogenesis of disease, best treatments, and consequences of CDI in specific, unique patients such as those who receive allo-HSCTs.

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 390).

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KEY POINTS

- *Clostridium difficile* infection is a common, predominately early, complication of hematopoietic stem cell transplant.
- Hematopoietic stem cell transplant recipients represent a high-risk population for *C. difficile* infection in recent studies.
- *C. difficile* infection appears to have several possible downstream effects including an observed bidirectional relationship of association with graft-versus-host disease.

Table 1

Studies evaluating CDI in HSCT recipients, 2010 to present

Author (year)	Study period	HSCT type	Patients	Rate of CDI (%)
Leung (2010) [23]	2003–2007	Allo	26	26.9 (Allo)
Therriault (2010) [24]	2003–2008	Allo	231	3.5 (Allo)
Dubberke (2010) [25]	2001–2003	Allo	104	Not specified
Chopra (2011) [26]	2005–2006	Both	361	14.1 (Both); 18.1 (Allo); 8.3 (Auto)
Willems (2012) [27]	2004–2007	Allo	414	12.8 (Allo)
Alonso (2012) [28]	2003–2008	Both	999	9.2 (Both); 6.5 (Auto); 12.5 (Allo)
Kamboj[a] (2012) [5▪]	2008–2009	Both	597	18.4 (Both); 9.0 (Auto); 27.0 (Allo)
Trifilio (2012) [29▪]	2004–2008	Both	822	10.3 (Both); 8.5 (Auto); 14.5 (Allo)

[a]Data represent a subset of patients noted in the study from Memorial Sloan Kettering Cancer Center, 2008–2009. Overall rate of hospital-onset (HO)-CDI was 15.8 per 10 000 patient-days among patients with cancer across 11 U.S. centers.