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STEM CELL TRANSPLANTATION (R MAZIARZ, SECTION EDITOR)

Clostridium difficile: Deleterious Impact on Hematopoietic Stem Cell Transplantation

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Abstract *C. difficile* infection (CDI), the most common cause of hospital-acquired diarrhea, is very frequent after hematopoietic stem cell transplantation (HSCT). Recent publications suggest it affects between 6 % and 20 % of HSCT recipients during the first year and is more common following allogeneic transplant (allo-HSCT). The best diagnostic strategy remains to be defined, but molecular testing for the toxin genes by polymerase chain reaction (PCR) seems to be replacing the traditional enzyme immunoassays (EIA). The higher sensitivity of the PCR may result in increased measured incidence of disease. *C. difficile* infection typically occurs during the first month after HSCT. Although the course of CDI after HSCT does not seem to be different than in other hospitalized patients, it may result in worsening of bowel graft versus host disease (GVHD) after allo-HSCT. Current evidence suggests a reciprocal effect by which GVHD may increase the risk of CDI and *C. difficile* disease may increase the risk of GVHD. Metronidazole was the treatment most commonly used in all recent series, followed by the combination metronidazole and oral vancomycin. There is minimal information on the use of fidaxomicin in HSCT recipients. Regarding stool transplant, there is one case report of successful use of this modality in an HSCT recipient. These two newer approaches will certainly be investigated in the future.

Keywords *C. difficile* · C difficile infection · CDI · Clostridium difficile-associated disease · Diarrhea · Hematopoietic stem cell transplant · Hematologic malignancies · Immunosuppressed · Epidemiology · Diagnosis · Treatment · Outcomes

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Introduction

C. difficile infection (CDI) is the most common cause of hospital-associated diarrhea and results in high morbidity, mortality and cost [1, 2]. The incidence increased significantly between 2000 and 2008 and only recently seems to be reaching a plateau, at least as measured by diagnosis at hospital discharge [3]. Recent changes in its epidemiology include the apparition of a more virulent strain (BI/NAP1/027) with higher production of toxin and higher resistance to fluroquinolones and the increased recognition of the contribution of nonhospital healthcare-associated (e.g., nursing homes) and community-acquired infection to the overall burden of disease [3].

Most published data suggest CDI is more common in hematopoietic stem cell transplant (HSCT) recipients than in other patients, and more so after allogeneic (allo-HSCT) than after autologous transplant (auto-HSCT). This review will focus on the relevant studies published between January of 2012 and October of 2013. Several papers have advanced our knowledge of CDI in transplant patients, including data on incidence, clinical manifestations, diagnosis and treatment.

The differences between autologous and allogeneic transplantation may be particularly relevant for CDI. Auto-HSCT for the treatment of cancer may be thought of as a form of high-dose chemotherapy with stem cell rescue, whereas allo-HSCT, in addition to variable doses of chemotherapy and radiation, includes an essential immunologic intervention by which the hematopoietic and immunologic systems of the recipient are replaced by the donor's sytems. Not only may allo-HSCT recipients be exposed to more of the classic risk factors for CDI (e.g., antibiotics, proton-pump inhibitors) for longer periods of time, but they are also given immunosuppressive agents, and they may develop graft versus host disease (GVHD), which can cause watery diarrhea. The interaction between CDI and GVHD has been a topic of great interest for a long time, as either of the two problems can be expected to affect the other [4, 5, 6•, 7•].

Of the studies published over the last year, some address auto-HSCT [8•], some allo-HSCT [9••] and some both [6•, 7•, 10••, 11•]. Earlier studies [4, 12, 13••] have been reviewed by Alonso and Marr [14].

Diagnosis of CDI

Guidelines regarding diagnosis and management of CDI have been published by North American [15] and European [16••] professional organizations. The diagnosis of CDI remains problematic [15, 16••]. There are tests that detect the presence of toxigenic *C. difficile* in the stool (but will not differentiate between someone who is colonized and someone who has disease caused by it) and tests that detect the presence of products of *C. difficile* in the stool, mainly the toxin. The most commonly used test is an enzyme immunoassay (EIA) for toxin A and toxin B. Tests for the enzyme Glutamate-dehydrogenase (GDH) are also in use. Several nucleic amplification tests have been approved; these detect the presence of the toxin genes by PCR, and seem to be considerably more sensitive than the EIA. The guidelines stipulate that a diagnosis should require the combination of compatible signs and symptoms with the demonstration of *C. difficile* toxin and the presence of a toxigenic strain of *C. difficile* or histopathology or endoscopic demonstration of pseudomembranes [15, 16••] in the absence of another explanation for the diarrhea. The "best" testing strategy has not been determined, and it may vary depending on the clinical setting and the intended goals (sensitivity, specificity, turnover time and cost are all relevant considerations) [17]. A very large prospective study published in 2013 that compared a variety of commercial methods with the reference standards for cell cytotoxin assay and cytotoxigenic culture showed that the presence of toxin in the stool correlated with outcome, whereas the presence of a toxigenic strain of *C. difficile* did not [18]. The most extreme interpretation of these results suggests that the different tests may be identifying different groups of patients, and attention should be paid to the methods section of the paper to ascertain how the subjects of the study were identified.

The studies herein reviewed used a variety of methods. They frequently used more than one during the time span reported [6 , 8, 11]. Different methods may result in differences in the estimated incidence, making it difficult to compare between institutions, but they may also result in misclassification if (for example) patients with diarrhea caused by GVHD are considered to have CDI because a test finds they carry a toxigenic strain of *C. difficile*.

Epidemiology

All available data support the notion that CDI is more common in HSCT than in oncologic patients in general, and the reported incidence is higher after allo-HSCT.

Kamboj et al., published the results of a survey study performed in 11 cancer centers that found the incidence of hospital-acquired CDI was twice as high in cancer patients than in the general hospital population (15.8 vs 7.4 per 10,000 patient-days) [10••]. This paper is significant because it shows how the diagnostic test used has a significant effect on the estimated rates: PCR (used by six of the 11 centers included in the report) was more sensitive than ELISA (used by four centers) or cytotoxin assay (used by one center) and accordingly resulted in a higher incidence rate (1.72 vs 0.9 per 1000 patient-days). Detailed information in transplant patients was presented only for Memorial Sloan Kettering Cancer Center, 2008–2009, and showed a higher prevalence in allogeneic than in autologous HSCT (27 % vs 9 %).

Other papers on the frequency of CDI in HSCT recipients report similar numbers, and confirm the higher frequency after allo-HSCT: 10.3 % overall at Northwestern Medical Hospital between 2004 and 2008, with 8.5 % after autologous and 10.3 % after allogeneic [7•], 9.2 overall at Johns Hopkins between 2003 and 2008 with 6.5 % in autologous vs 12 % in allogeneic [6•], around 6 % after autologous [8•] and 13 % after allogeneic [9••]. The reason for this difference is not clear. It is possible that increased investigation of diarrhea after allogeneic HSCT may explain part of it (sampling bias), but other possibilities include increased immunosuppression resulting in inability to fight the infection, increased and/or more prolonged use of broad-spectrum antibiotics and the influence of graft versus host disease and its potential effects on bowel microbiota [19].

All the published studies are retrospective. Some investigators have performed case–control studies to try to identify risk factors, and applied a variety of statistical methods to find the significant ones. In one study, with patients of age >60 years, receipt of an allo-HSCT, and VRE colonization were identified as independent risk factors by Cox regression analysis [7•]. The single study that focused on allo-HSCT identified cord blood as the source of stem cells, TBI >12 Gy, and acute GVHD grade ≥2 preceding CDI) [9••]. Alonso identified grade 2 mucositis as the only statistically significant risk factor for CDI after auto-HSCT by multivariate analysis, although the univariate analysis suggested in addition older age and fourth generation cephalosporins [8•]. In Alsonso's study of both auto- and allo-HSCT at Johns Hopkins, she identified that the following risk factors remained significant in the multivariable analysis: receipt of chemotherapy prior to HSCT conditioning, high-risk antibiotics after transplant, acute GVHD and VRE colonization [6•]. Interestingly, the use of proton pump inhibitors seemed to have a protective effect on CDI in this study. Of the antibiotics

commonly used in this group of patients (particularly for the treatment of fever and neutropenia) piperacillin-tazobactam seems to have the lowest risk of CDI [20]. The potential for levofloxacin prophylaxis (commonly used in neutropenic patients) to result in increased rates of CDI has not been adequately studied, but both single studies [21] and one meta-analysis support the notion that the benefits associated with prophylaxis outweigh the risks in neutropenic patients with hematological malignancies [22].

All the studies confirm that CDI tends to occur in the first month after transplant, which has prompted some investigators to suggest prior colonization may play a role in the epidemiology [9••]. The importance of the disruption of the mucosal integrity in the pathogenesis is suggested by the identification of mucositis and TBI as risk factors.

Unfortunately, the nature of the studies, which are retrospective chart reviews over many years during which the diagnostic tests and clinical practices may have changed, make the interpretation of these risk factors difficult. The general concept seems to be that disruptions in the mucosal integrity of the bowel as well as modifications of its microbial flora may predispose to CDI. The connection with GVHD seems to be bidirectional. Two recent studies have confirmed acute GVHD of the bowel as a risk factor for CDI [6•, 9••]. One of them also found data suggesting CDI increases significantly the risk of GVHD [6•], supporting prior observations [5]. Until systematic prospective studies take place, it will be difficult to determine if a more aggressive approach to the treatment of CDI might be justifiable in allo-HSCT to try to decrease the risk of GVHD.

Treatment

Current guidelines for the treatment of CDI do not address HSCT transplant recipients as a special category of patients [15, 16••, 23]. A prominent topic is the severity of CDI and its importance for management. The one randomized trial showed vancomycin to be superior to metronidazole in cases of severe disease based severity on age, body temperature, albumin level and leukocyte count. [24] The American guidelines from the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA) suggest an expert-opinion based clinical classification of the severity of CDI as mild/moderate, severe and severe/complicated based on leucocytosis, renal dysfunction and the presence of hypotension, shock or toxic megacolon [15]. How applicable these criteria would be in the HSCT recipient population is unknown. The new version of the European guidelines explores in great length a variety of potential markers of severity, and suggests that immunodeficiency (which presumably would include HSCT recipients) may be one such marker of severity. This would categorize every episode of CDI in transplant patients as "severe", which does not seem to be borne out by the reported outcomes. Transplant-specific severity criteria have been proposed by Dubberke et al., but they are not in widespread use [25].

Regardless of the concept of severity, the data on treatment from recent papers seem pretty consistent (see Table 1). Metronidazole is the most commonly used treatment, and there is no evidence that vancomycin would be preferable as a first choice simply because the patient has received a transplant. One study that included all patients with hematological malignancies (only a minority had received HSCT) had enough patients who had received metronidazole, vancomycin or a combination to make a comparison, and no difference could be found (although this study suffered from retrospective design, heterogeneous patient population and response rate around 50 % for each treatment). As the Table shows, it is difficult to find evidence to make a recommendation in favor of vancomycin or combination therapy.

Table 1 Results of treatment in recent retrospective case series of *Clostridium difficile* infection in hematopoietic stem cell transplantation patients

Study	Allo or auto	Number of patients with CDI (number of transplants)	Metronidazole only (oral and/or IV)	Vancomycin only	Vanco + metronidazole:	Recurrences
Parmar et al. 2009-2012 [11•]	Both and hem malignancies	73 (27 in HSCT) 390 total patients	74 %	8 %	18 %	20 %
Alonso et al. 2003-2008 [8•]	Auto	53 (873)	69 %	10 %	14 %	15.4 %
Trifilio et al. [7•]	Both	85 (822)	87 %	Vancomycin after intolerance to or failure of metronidazole: 20 %	–	12 %
Willems et al. 2004-2007 [9••]	Allo	53 (407)	90 %	Vancomycin after intolerance to or failure of metronidazole: 10 %	–	10 %
Alonso et al. 2003-2008 [6•]	Both	92 (999)	84 %	2 %	10 %	21.7 %
Chopra et al. 2005 2006 [13••]	Both	51 (361)	84 %	Vancomycin after intolerance to or failure of metronidazole: 16 %	–	4 % 1 (multiple)

Newer treatment modalities include fidaxomicin (a nonabsorbable antibiotic with narrow spectrum of action that has shown to be noninferior to vancomycin) [26, 27••] and fecal transplantation, a modality that attempts to restore the intestinal flora and has shown to be superior to oral vancomycin in a randomized controlled trial [28••]. The 2013 European guidelines state there is not enough evidence to make a recommendation regarding the use of fidaxomicin [16••]. A retrospective single-center study of the use of fidaxomicin in transplant (mainly solid organ) recipients did not find significant differences in outcome among the fifteen patients (including one HSCT recipient) who received fidaxomicin and the 44 who received conventional treatment [29]. The authors emphasize no VRE colonization was observed in the fidaxomicin recipients, although this was not statistically significant. A subgroup analysis of the fidaxomicin trials focusing in cancer patients suggests it may be superior to vancomycin in this population, but by its nature it cannot be considered other than hypothesis-generating (no HSCT recipients seem to have been included) [30]. The first report of successful use of fecal transplantation in an HSCT recipient with severe CDI refractory to medical therapy CDI was published in 2012 [31•]. The patient developed CDI almost a year after HSCT, following chemotherapy for a relapse of the acute lymphoblastic leukemia that had been the indication for transplant, and over the course of three weeks failed treatment with metronidazole, vancomycin, intravenous immunoglobulin, fidaxomicin, rifaximin and tigecycline. She responded promptly to a fecal transplant from her husband, instilled in the upper jejunum by a naso-jejunal tube.

The role of some of possible future chemotherapeutic modalities (including rifaximin, tigecycline, doxycycline, linezolid, nitazoxanide, amixicile LFF571, CB-183 315, and monoclonal antibodies in HSCT recipients has not been explored. Information on these may be found in the review by Ritter and Petri [32].

Recurrences don't seem to be more frequent in transplant recipients than in other patients. The studies report a frequency of recurrences between 10 and 20 %, and only Willems et al., described recalcitrant patients with multiple episodes [9••].

The recent papers do not dwell on the topic of nosocomial transmission. The guidelines for hand hygiene still referenced by the CDC were issued by multiple professional organizations in 2010 [33]. These guidelines recognize that antiseptics in gel solutions and hand-rub preparations are ineffective against the spores of *C. difficile*. They recommend the use of gloves and protective clothing and suggest the potential value of actual hand washing after removing the gloves to mechanically remove spores from the hands, particularly during outbreaks [33.] A detailed evidence-based review of infection control measures to limit the spread of *C. difficile* is available [34] and is referenced by the most recent guidelines [16••].

Conclusion

The diagnosis of CDI continues to be problematic. The increasing use of PCR, a test for products of toxigenic *C. difficile* more sensitive than the previously used EIA will result in increased identification of cases and some degree of misclassification of colonized patients without *C. difficile* associated disease. Operative institutional algorithms for diagnosis may prime sensitivity over turnaround time, and may not be identical to epidemiological surveillance studies.

CDI occurs early after HSCT, and possibly increases the risk of GVHD. Accordingly, it seems reasonable to attempt to diagnose it early and treat it effectively. There are no good comparative studies in HSCT recipients, but the available evidence supports metronidazole as the most reasonable first choice unless there are signs of severe disease. Unfortunately, it is not clear what constitutes severe disease in these immunocompromised patients, but at a minimum, the guidelines-endorsed using the clinical criteria of renal dysfunction, hypotension, shock and/or toxic megacolon [15]. Recurrences seem to happen at approximately the same rate as in the non-HSCT population, and their management should also be the same, although numbers are small and details scant. There is very limited experience with fidaxomicin, but at this point, it seems a perfectly acceptable drug, non-inferior to oral vancomycin although more expensive and perhaps better at preventing recurrences. The role of fecal transplant remains to be defined.

Compliance with Ethics Guidelines

Conflict of Interest Dr. Alejandro Callejas-Díaz and Dr. Juan C. Gea-Banacloche declare no potential conflicts of interest relevant to this article.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of outstanding importance

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