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RESEARCH ARTICLE

Clostridium difficile in Autologous Hematopoietic Stem Cell Transplant Patients

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Abstract

Diarrhea is a common complication of hematopoietic stem cell transplant (HSCT) due to multiple etiologies, including toxicity from the conditioning regimen and *Clostridium difficile* (*C. difficile*) infection. We hypothesized that *C. difficile* infection is uncommon in recipients of autologous HSCT (auto-HSCT) and testing for *C. difficile* is over utilized at our institution. We performed a retrospective, single center analysis of the use of polymerase chain reaction (PCR) testing for *C. difficile* among adult auto-HSCT recipients in the first 45 days post-procedure. Patients were identified by cross referencing the existing list of patients who had an auto-HSCT between May 2011 and May 2014 with the Premier SafetySurveillor® list of *C. difficile* PCR tests conducted in patients during the same time period. Among the 160 patients identified, the incidence of *C. difficile* infection was 5.0% with nearly three-quarters of auto-HSCT patients being tested. We further reviewed *C. difficile* PCR positive patients for risk factors according to Infectious Diseases Society of America (IDSA) guidelines for *C. difficile* infection. Based upon assessment of risk factors in patients who tested positive for *C. difficile* infection, we recommend additional study to evaluate for the need for antimicrobial prophylaxis with fluoroquinolones during the neutropenic post-transplant period as well as proton pump inhibitor (PPI) therapy in this patient population. Limiting the use of these agents could be a method to decrease *C. difficile* risk factors; therefore, potentially decreasing PCR testing and *C. difficile* infection.

Keywords

Autologous, Transplant, *Clostridium difficile*

Abbreviations

C difficile: Clostridium difficile; IDSA: Infectious Diseases Society of America; PPI: Proton Pump Inhibitor; HSCT: Hematopoietic Stem Cell Transplant; IRB: Institutional Review Board; BEAM: Carmustine, Etoposide, Cytarabine, Melphalan

Introduction

Clostridium difficile (*C. difficile*) is a gram-positive anaerobic infection of the gastrointestinal tract causing infectious diarrhea. *C. difficile* represents a leading cause of infectious diarrhea in hospitalized patients with an increasing incidence and associated mortality [1]. The IDSA (Infectious Diseases Society of America) recognizes several risk factors for *C. difficile* infection including age ≥ 65 years, proton pump inhibitor (PPI) therapy, broad spectrum antibiotic use, being immunocompromised, receiving cancer chemotherapy, as well as previous *C. difficile* infection. These risk factors make hematopoietic stem cell transplant (HSCT) patients particularly susceptible to developing infections with *C. difficile*. Studies at other institutions have revealed a *C. difficile* infection rate of 5.7-6.2% within the first year post-autologous HSCT [2]. In addition, HSCT recipients have been reported to be at a 9-fold higher risk for *C. difficile* infection than the general population due to the presence of several risk factors [3].

Patients undergoing an auto-HSCT receive various

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conditioning regimens that are known to cause diarrhea, making it difficult to differentiate between infectious and treatment related diarrhea. The observation of diarrhea often triggers testing for *C. difficile* even if the timing and intensity are compatible with expected toxicity from the conditioning regimen, creating a cost burden and triggering contact isolation precautions. Therefore, we set out to do a retrospective analysis on the utilization of PCR testing and incidence of *C. difficile* infection during the first 45 days post auto-HSCT, with focus on results within the first 14 days when diarrhea is expected from conditioning.

Methods

Patient population and data collection

Following institutional review board (IRB) approval, we identified all patients who received auto-HSCTs between May 2011 and May 2014 using an established institutional transplant data registry. This was then cross-referenced with a list obtained from Premier SafetySurveillor®, which is an automated, web-based infection tracking and antimicrobial utilization tool, used to help prevent hospital acquired infections, to identify which transplant patients had received *C. difficile* PCR testing and which of those were positive. Existing electronic medical records were then accessed for the patients who had a positive *C. difficile* PCR test conducted within the first 45 days after their transplant. All data collected included patient age, gender, antibiotic use post-transplant, *C. difficile* PCR testing result, time to positivity, history of previous *C. difficile* infection, malignancy requiring transplantation, and conditioning regimen received. Of note, our institutional specific practice is to administer prophylaxis for bacterial infections using ciprofloxacin (Cipro®) from day 0 until engraftment.

Not all transplant patients were included in our final analysis. Patients not receiving BEAM (carmustine, etoposide, cytarabine, melphalan; employed in the treatment of lymphomas) or melphalan (employed in the treatment of multiple myeloma) conditioning for autologous HSCT were excluded from our study due to small sample size and to reduce heterogeneity. Any positive *C. difficile* result after day + 45 was not recorded.

C. difficile PCR testing

Testing for *C. difficile* via PCR is the preferred method of analysis at our institution, as well as many institutions throughout the country. Focus Diagnostics® supplies our PCR test utilized to detect *C. difficile.* This assay uses bi-functional fluorescent probe-primers with reverse primers to target a sequence in the well conserved region of the *C. difficile* toxin B gene. Toxigenic *C. difficile* strains are able to produce virulence factors; toxin A (enterotoxin) and toxin B (cytotoxin), yet these are rarely produced concurrently. PCR testing provided by Focus Diagnostics® assesses for the presence of toxin B in the stool. PCR assays have been compared to several previous testing methods, and extensively studied, revealing sensitivities of up to 100% and specificities of 99.2% [4,5]. However, a meta-analysis found sensitivities of 90% with specificities of 96% [6]. Due to the rapid turn-around time (1 hour) with high sensitivity and specificity, PCR testing has largely replaced cytotoxicity, toxigenic, and EIA (enzyme immunoassay) methods of testing. Another benefit of PCR is the small amount of stool needed to test for *C. difficile*.

Additionally, repeat *C. difficile* testing after a negative initial result within 7 days appears to be of little to no benefit in detecting potentially initial false negative results [7]. In fact, repeat testing within the first 7 days of *C. difficile* PCR is now restricted at many institutions, including ours. After a positive PCR is reported, repeat PCR can still reveal a positive result in as many as 50% of patients for up to 10-14 days. Repeat PCR testing after treatment also is not recommended. Clinical symptoms after treatment are more consistent with resolution of *C. difficile* infection and should be used to assess efficacy of treatment [7,8].

Results

A total of 160 patients were included in the analysis. The overall incidence of *C. difficile* infection was 5.0%, which is in line with results reported in other studies of patients undergoing autologous HSCT. Table 1 describes our experience with PCR testing and characterizes the patients with a positive *C. difficile* result.

Patients who underwent more than one *C. difficile* PCR test in the 45 days after transplant were further analyzed. For patients who received BEAM conditioning, only 3 patients were tested twice. The average day of initial testing was conducted on day + 3.7 post-transplant, and the average day of repeat testing was day + 20 post-transplant. The average time between tests was 16 days, with only 1 in 3 patients' repeat test having a positive result (on day + 33). For patients

Table 1: Demographic Information.

	BEAM Conditioning		**Melphalan Conditioning**
	Hodgkin Lymphoma (N = 13)	**Non-Hodgkin Lymphoma (N = 33)**	**Multiple Myeloma (N = 114)**
Age Median (Range)	39 (56, 19)	58 (73, 28)	60 (74, 29)
Men (%)	38	64	55
Patients Tested N (%)	24 (72)	7 (54)	83 (73)
PCR-Confirmed Infection N (%)	1 (7.7)	2 (6.0)	5 (4.4)

who received melphalan as their conditioning regimen, 13 patients received more than one *C. difficile* PCR; 1 patient had 3 tests, 2 patients had 4 tests, all others had 2 tests conducted in the 45 day period post-transplant. The average day of initial testing for melphalan patients was day + 8 and the average day of repeat testing was day + 17.8. Of note, only 1 in 13 patients was positive upon repeat *C. difficile* testing in this group (on day + 24). The average time between tests was 5.5 days. All additional tests performed remained negative with no positive testing observed within 7 days of the last negative PCR.

Finally, our analysis concluded by evaluating if patients had additional risk factors based on IDSA risk factors mentioned previously. Since all patients included in the analysis received ciprofloxacin prophylaxis and a PPI it is impossible to determine whether these exposures increased the risk for *C. difficile* colitis. Average age for all patients, regardless of cancer type or conditioning regimen, was 57-years-old. No patients who tested positive had a previous *C. difficile* PCR positive result prior to transplant. All patients were receiving chemotherapy and considered immunocompromised at the time of study.

Discussion

The results of our study reveal that the incidence of *C. difficile* infection is low in auto-HSCT patients within the first 45 days after transplant. This incidence likely remains unchanged if extended to one-year post-transplant, as an autologous transplant patient's risk for *C. difficile* is highest during neutropenic periods experienced postconditioning regimen and prior to engraftment. Our *C. difficile* infection rate is overall comparable to other published results. To identify 1 positive result, 14.3 patients were tested, regardless of conditioning regimen; 10.3 patients for BEAM conditioning, 16.6 patients for melphalan conditioning. In the majority of melphalan treated patients, most PCR tests were conducted on day + 9 to + 11 post-transplant while BEAM treated patients had the majority of tests conducted on days + 5 to + 7, with the average day of positive result for either regimen being day + 12 (median of day + 8). Diarrhea related to conditioning regimens is expected to occur during these time points, confirming our hypothesis that excessive testing was performed, representing potential unnecessary additional costs to the institution and patient. However, during the acute post-transplant period, day 0-14, 6 of 114 (5.3%) patients had a positive test result.

Excess cost arises not only from collecting a sample for *C. difficile* PCR testing, but also from infectious precautions the patient is subsequently placed under requiring the use of gowning, gloving, and hand washing for every individual who enters the patient's room. In addition, based on assessment of IDSA risk factors for *C. difficile* in this study, use of PPIs and broad spectrum antibiotics represent the two potentially modifiable areas for decreasing a patient's risk of developing *C. difficile*. Future studies are warranted to compare patients who receive PPI therapy and antimicrobial prophylaxis to those who do not to assess for potential decreases in the incidence of *C. difficile* infections.

Limitations to our study include small sample size, particularly in patients undergoing BEAM conditioning. Additional limitations to this study include its single center design and being retrospective in nature. Patients receiving melphalan conditioning for multiple myeloma consisted of a relatively large proportion of patients in our study compared to previously published studies. The incidence of *C. difficile* in this patient population was 4.4%, which is slightly lower than the average reported incidence.

Despite patients having several risk factors for the development of *C. difficile* infection, PCR positivity is low in the first 14 days post-transplant. During this time period of expected gastrointestinal toxicity from conditioning regimens, judicious use of PCR testing should be employed. The practice of universally administering fluoroquinolone prophylaxis and PPIs to autologous HSCT patients also requires discussion and investigation. This is an area to pursue to decrease health care costs as well as morbidity and mortality associated with the development of *C. difficile* in this unique patient population.

Acknowledgement

We have no acknowledgements to make at this time.

Ethical Statement

This study was submitted, reviewed and accepted by the institutional review board at the Medical University of South Carolina.

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