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Infectious Disease

Oral Vancomycin Prophylaxis as Secondary Prevention Against *Clostridioides difficile* Infection in the Hematopoietic Stem Cell Transplantation and Hematologic Malignancy Population

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A B S T R A C T

Clostridioides difficile infection (CDI) is a common complication in the hematopoietic stem cell transplantation (HSCT) and hematologic malignancy (HM) population. CDI is associated with increased hospital length of stay, health care and societal costs, morbidity, and mortality. Identifying strategies for secondary prevention of CDI is of extreme importance in the HSCT/HM population. In this study, our primary objective was to evaluate the effectiveness and safety of an oral vancomycin prophylaxis (OVP) protocol for secondary prevention of CDI in a retrospective cohort of adult autologous/allogeneic HSCT recipients and patients with HM who did not undergo HSCT with a first CDI episode treated with concomitant broad-spectrum antibiotics (BSA). Patients were diagnosed and treated for CDI as inpatients and/or outpatients and were divided into 2 groups based on a preprotocol versus postprotocol analysis: the OVP group, comprising patients who received planned monotherapy with oral vancomycin 125 mg every 6 hours for 14 days for a first episode of CDI and subsequently received OVP posttreatment and a no OVP (NOVP) group, comprising patients who received planned monotherapy with oral vancomycin 125 mg every 6 hours for 14 days for a first episode of CDI and subsequently did not receive OVP posttreatment. OVP was defined as vancomycin 125 mg every 12 hours for up to 7 days after BSA discontinuation. The primary endpoint was recurrent CDI (rCDI), defined as symptoms of loose stools/diarrhea with high clinical suspicion for CDI prompting empiric therapy within 60 days of completion of treatment/prophylaxis for the first CDI episode. The incidence of vancomycin-resistant enterococcal (VRE) infection and 60-day mortality were also compared between the 2 groups. Multivariate logistic regression was created from associated variables to identify independent associations with rCDI. A total of 50 patients were included, 21 in the OVP group (42%) and 29 in the NOVP group (58%). The mean patient age was 58 years, and the cohort was 60% male and 86% Caucasian. HSCT was performed in 60% of the patients, and 76% of CDI cases were diagnosed during hospitalization. The rate of rCDI was significantly lower in the OVP group compared with the NOVP group (5% [1 of 21] versus 35% [10 of 29]; P= .016), with no subsequent increase in VRE infection rate (14% [3 of 21] versus 10% [3 of 29]; P = .686). By multivariable logistic regression, rCDI was inversely associated with OVP (odds ratio [OR], .14; 95% confidence interval [CI], .007 to .994; P = .049) and directly associated with outpatient CDI diagnosis (OR, 8.72; 95% CI, 1.816 to 49.158; P = .007). No between-group differences were found in 60-day mortality (10% [2 of 21] for OVP versus 7% [2 of 29] for NOVP; $P > 0.999$). OVP appears to be safe and effective for secondary prevention of CDI in the HSCT/HM population. Prospective trials are needed to validate the effectiveness of OVP in this vulnerable population to prevent rCDI.

INTRODUCTION

Clostridioides difficile infection (CDI) has been shown to substantially impact patients after hematopoietic stem cell transplant (HSCT) or with hematologic malignancies (HM) and is associated with increased hospital length of stay, health care and societal costs, and risk for morbidity and mortality [1-4].

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In addition, CDI rates have been shown to be 9-fold higher in the HSCT population compared with the general population [5]. Given the increased risk for CDI in the HSCT/HM population, identifying strategies to prevent future occurrences is imperative.

Despite best efforts to effectively treat initial CDI episodes, the risk for 1 or more recurrence(s) has been reported as >20% in the HSCT/HM population [6,7]. In these patients, risk factors that impact the development of an initial CDI episode, such as receipt of chemotherapy, broad-spectrum antibiotic (BSA) use, and graft-versus-host disease (GVHD), continue to impact the risk of CDI recurrence [3,4,6]. Furthermore, the HSCT/HM population remains continually at high risk for CDI due to the frequent use of systemic antimicrobials to prevent life-threatening infections, the use of immunosuppressive therapies, and frequent exposure to healthcare facilities. However, given the paucity and insufficiency of data, the Infectious Diseases Society of America CDI guidelines do not give strong support for medication prophylaxis strategies in patients at high risk for CDI [4].

Recent studies have examined the use of oral vancomycin prophylaxis (OVP) for the prevention of CDI in high-risk populations [8-11]. However, these studies included patients with varying risk factors for CDI and compared OVP at differing dosing regimens against both initial CDI and recurrent CDI (rCDI). OVP has been previously shown to reduce the incidence of rCDI in high-risk patients receiving systemic antimicrobial therapy, but these reports did not focus on HSCT recipients or HM patients [8,9]. A study of allogeneic HSCT recipients showed that primary OVP is effective in preventing initial CDI occurrence [11]; however, information concerning secondary OVP in the HSCT/HM population is limited.

Understanding the role of secondary prevention of CDI with OVP is of extreme importance in the HSCT/HM population due to their continual increased risk of CDI recurrence. In May 2017, our joint working group composed of bone marrow transplantation (BMT) and infectious diseases physician and pharmacists developed and implemented a CDI protocol for the HSCT/HM population that incorporated OVP for secondary prevention (Figure 1). Although numerous institutions may have adopted similar protocols, the number of published studies in the HSCT/HM population is limited. Our primary objective in the present study was to evaluate the effectiveness and safety of OVP for secondary prevention of CDI in the HSCT/HM population at our institution.

METHODS

Patient Selection and Evaluation

The study population was a retrospective cohort of adult patients admitted to our academic health system or seen at the affiliated BMT outpatient clinic between January 2014 and October 2018. Patients age ≥18 years with a history of autologous or allogeneic HSCT and patients with HM who did not undergo HSCT were included. Patients must have been treated for the initial episode of CDI first with planned oral vancomycin monotherapy and must have been receiving a BSA at time of CDI diagnosis and/or during the course of CDI treatment/prophylaxis. Patients who received metronidazole for <48 hours and then switched to vancomycin due to clinician preference (with no evidence of clinical failure) were included in our analysis. Also included were patients with evidence of clinical failure (as judged by the treating physician) throughout the course of primary treatment with oral vancomycin monotherapy who had changes to their treatment regimen.

Patients could have been diagnosed and treated for CDI on an inpatient or an outpatient basis. Only initial CDI episodes and prophylactic regimens using oral vancomycin 125 mg twice daily were included. Reasons for exclusion included incomplete medical record; history of previous CDI; and treatment of the initial CDI episode with metronidazole monotherapy, vancomycin and metronidazole combination therapy (unless metronidazole was added because of possible treatment failure), fidaxomicin monotherapy, supplementation with bezlotoxumab, and regimens using an oral vancomycin taper. Patients in the "postprotocol" period who received vancomycin as initial CDI treatment with no OVP were classified in the NOVP group. *C. difficile* stool sample testing was performed by our institution's molecular laboratory using polymerase chain reaction for the toxin gene (Xpert *C. difficile*; Cepheid, Sunnyvale, CA). Patients were identified through electronic medical record orders for oral vancomycin and positive *C. difficile* toxin polymerase chain reaction results.

Two groups were compared in this analysis: the OVP group, comprising patients who received planned monotherapy with oral vancomycin 125 mg every 6 hours for 14 days for a first episode of CDI and subsequently received OVP post-treatment, and the no OVP (NOVP) group, comprising patients who received planned monotherapy with oral vancomycin 125 mg every 6 hours for 14 days for an initial episode of CDI and subsequently did not receive OVP post-treatment.

Data extracted from the electronic medical record included patient demographic information, comorbidities, and laboratory parameters; hospital length of stay; HM diagnosis; HSCT type and conditioning regimen/intensity (if applicable); presence of GVHD and mucositis; use of probiotics, histamine-2 receptor antagonists, proton pump inhibitors, antibiotics, corticosteroids, or immunosuppressants (not part of chemotherapy) throughout CDI diagnosis/treatment/prophylaxis; antibiotic name; CDI classification; diarrhea severity; recovery of vancomycin-resistant enterococci (VRE) post-CDI treatment/prophylaxis; components of "treatment failure"; CDI recurrence date (if applicable); outpatient BMT clinic visits; 30-day readmission; and in-hospital and 60-day mortality. Once data collection was completed, the database was deidentified for further analysis.

Outcomes and Definitions

The primary outcome was CDI recurrence, defined as symptoms of loose stools/diarrhea with high clinical suspicion for CDI prompting empirical therapy within 60 days of completion of treatment/prophylaxis for the initial CDI episode. Secondary outcomes included the incidence of VRE infections and

Prevention	Patients remaining on *high-risk antibiotics at the end of *C. difficile* treatment, change to prophylactic oral vancomycin 125 mg every 12 hours. Continue prophylactic vancomycin for seven days after high-risk antibiotics are discontinued. Do not use oral vancomycin prophylaxis if bezlotoxumab is given.
*High-risk antibiotics: amoxicillin/clavulanate, ampicillin/sulbactam, piperacillin/tazobactam, ceftriaxone, cefepime, meropenem, imipenem/cilastatin, ertapenem, aztreonam, ciprofloxacin, levofloxacin, moxifloxacin, clindamycin	

Figure 1. Protocol for the prevention of CDI recurrence in the HSCT/HM population.

60-day mortality. Treatment failure, or the inability to achieve initial clinical cure, was also evaluated to further assess potential confounders in our treatment groups before administration of OVP. Components of treatment failure (adapted from a previous definition) included the need for addition of metronidazole, extension of vancomycin dosing duration (>14 days), increase in vancomycin dose, switch to an alternative agent for CDI treatment (eg, metronidazole, fidaxomicin), need for fecal microbiota transplantation, or surgical management [12].

CDI was classified as follows: community-onset (stool collected in an outpatient setting from a patient not discharged from an inpatient location ≤28 days before the current date of specimen collection or stool collected in an inpatient facility within 3 days of admission), community-onset healthcare facility-associated (stool collected in an outpatient or inpatient location from a patient discharged from an inpatient location ≤28 days before the current date of stool specimen collection), or healthcare facility-onset (stool collected from an inpatient location more than 3 days after admission) [13]. Diarrhea severity was classified as mild (<4 episodes per day), moderate (4 to 6 episodes per day), or severe (≥7 episodes per day) [14]. Given the differences between HSCT recipients and HM patients and the general population, severe and complicated CDI episodes were defined based on previous definitions [4,15,16]. Severe CDI episodes were defined as moderate to severe diarrhea, age >60 years, or any of the following within 48 hours of CDI diagnosis: serum creatinine >1.5 mg/dL, white blood cell count >15 or $<.5 \times 10^9$/L, albumin <2.5 g/dL, fever > 38.3°C, and/or colonic thickening or ascites detected on computed tomography scan. Complicated/fulminant CDI was defined as cases with ileus or significant abdominal distension, megacolon, colectomy and/or colonic perforation, lactate >2.2 mmol/L, and/or hypotension (systolic blood pressure <90 mmHg).

Concomitant BSAs included courses of β-lactams (excluding penicillin and antistaphylococcal penicillins), fluoroquinolones, clindamycin, azithromycin, doxycycline, sulfamethoxazole/trimethoprim, and gram-positive agents (eg, vancomycin, daptomycin, linezolid). High-risk antibiotics included β-lactam/β-lactamase inhibitors, cephalosporins, carbapenems, aztreonam, fluoroquinolones, and clindamycin [17,18]. Although only ceftriaxone and cefepime are included as "high-risk" cephalosporins in our CDI secondary prevention protocol (Figure 1), all cephalosporins were evaluated in our analysis.

Statistical Analysis

Nominal variables were evaluated using Fisher's exact test, and continuous variables were analyzed using Student's *t* test for parametric data and the Mann-Whitney *U* test for nonparametric data. We identified univariate associations at a *P*value <.2 between clinical variables and rCDI. A multivariate logistic model was created from these significant variables by forward step methods. Multivariate logistic regression was created from associated variables to identify independent associations with rCDI. All analyses were conducted using SPSS version 23.0 (IBM, Armonk, NY) and JMP version 14.2 (SAS Institute, Cary, NC). All tests were 2-sided with a *P* values <.05 considered statistically significant and 95% confidence intervals (CI) reported.

Ethical Approval

This protocol was reviewed and approved by the Colorado Multiple Institution Review Board as an exempt study.

RESULTS

A total of 50 patients met our inclusion criteria (OVP group, n = 21 [42%]; NOVP group, n = 29 [58%]). Patients in the OVP group were younger (OVP, median 56.0 years [interquartile range (IQR), 43.5 to 61.5 years]; NOVP, median 62.0 years [IQR, 54.0 to 70.5 years]; *P* = .034) and had a greater total body weight (OVP, median 85.5 kg [IQR, 80.1 to 100.1 kg]; NOVP, median 72.8 kg [IQR, 61.1 to 79.8 kg]; *P* = .001). The cohort was predominantly male (60%) and Caucasian (86%). The most common primary HMs were acute myelogenous leukemia (50%) and non-Hodgkin lymphoma (24%). HSCT was performed in 30 of the 50 patients (60%), predominantly allogeneic HSCT (n = 23; 77%). Sixteen of the 23 allogeneic HSCT recipients underwent dual umbilical cord transplantation (69%), 5 received a matched related donor transplant (22%), and 2 received a haploidentical umbilical cord transplant (9%). Other pertinent baseline and disease characteristics are listed in Table 1.

CDI was diagnosed on an outpatient basis in 10% of patients in the OVP group, compared with 35% in the NOVP group (*P* = .051). Among the patients admitted to the hospital during the course of CDI, the median hospital length of stay was 26.0 days (IQR, 21.0 to 34.0 days) in the OVP group and 14.0 days (IQR, 4.0 to 21.0 days) in the NOVP group (*P* = .012). After CDI diagnosis, there was no significant difference in continuation of BSAs between the 2 groups (90% for OVP versus 100% for NOVP); however, high-risk antibiotics were continued for longer after CDI diagnosis in the OVP group (median, 17.5 days [IQR, 14.8 to 31.3 days] versus 11.0 days [IQR, 9.0 to 17.0 days]; *P* = .034). Outpatient BMT follow-up was similar in the 2 groups (95% for OVP versus 86% for NOVP).

Throughout admission and/or during CDI diagnosis/treatment/prophylaxis, no significant differences were detected in the use of probiotics (0% in each group), histamine 2-receptor antagonists (29% for OVP versus 10% for NOVP), proton pump inhibitors (76% for OVP versus 52% for NOVP), calcineurin inhibitors (48% for OVP versus 24% for NOVP), or corticosteroids (38% for OVP versus 35% for NOVP). Immunosuppressant use (not part of a chemotherapy regimen) was higher in the OVP group (33% versus 4%; *P* = .007).

The differences in the incidence of active GVHD being treated (10% for OVP versus 17% for NOVP) and the incidence of mucositis (14% for OVP versus 14% for NOVP) throughout the course of CDI diagnosis/treatment/prophylaxis was nonsignificant between the 2 groups. The lowest median serum albumin level measured within 48 hours of CDI diagnosis was similar in the 2 groups (OVP, 3.15 g/dL [IQR, 2.63 to 3.58 g/dL]; NOVP, 3.20 g/dL [IQR, 2.90 to 3.60 g/dL]). The lowest median absolute neutrophil count within 48 hours of CDI diagnosis was also similar in the 2 groups (OVP, $.90 \times 10^9$/L [IQR, $.25$ to 3.68×10^9/L] versus NOVP, 2.60×10^9/L [IQR, 1.23 to 5.23×10^9/L]). Severe CDI was observed in 86% of patients in both groups, and the incidence of complicated/fulminant CDI was similar in the 2 groups (24% for OVP versus 14% for NOVP). There were significant between-group differences in the incidence of community-onset CDI (10% for OVP versus 41% for NOVP; *P* = .024) and healthcare facility-onset CDI (71% for OVP versus 31% for NOVP; *P* = .009). Other CDI-specific characteristics and BSA use are compared in Tables 2 and 3, respectively.

The rate of rCDI was significantly lower in the OVP group compared with the NOVP group (5% [1 of 21] versus 35% [10 of 29]; *P* = .016), without a subsequent increase in VRE rate (14% [3 of 21] versus 10% [3 of 29]; *P* = .686). On multivariable logistic regression, rCDI was inversely associated with OVP (odds ratio [OR], .14; 95% confidence interval [CI], .007 to .994; *P* = .049) and directly associated with outpatient CDI diagnosis (OR, 8.72; 95% CI, 1.816 to 49.158; *P* = .007) (Table 4). There was no significant between-group difference in 60-day mortality (OVP, 10% [2 of 21] versus NOVP, 7% [2 of 29]; *P* > .999). Treatment failure occurred in 9 of 21 patients (43%) in the OVP group and in 10 of 29 patients (35%) in the NOVP group (*P* = .570). Components of treatment failure observed in each group are listed in Table 5; all differences were nonsignificant, and some patients experienced multiple components of treatment failure.

During the follow-up period, there were no between-group differences in 30-day readmissions (62% for OVP versus 45% f or NOVP). No adverse effects attributed to CDI treatment/prophylaxis were documented. In-hospital mortality occurred in 1 patient in each group.

DISCUSSION

This study documents the effectiveness and safety of OVP for prevention of secondary CDI in our patient cohort with initial CDI. To our knowledge, this is the first study focusing on

Table 1
Baseline and Disease Characteristics

Characteristic	OVP (N = 21)	NOVP (N = 29)	*P* Value
Age, yr, median (IQR)	56.0 (43.5-61.5)	62.0 (54.0-70.5)	**.034**
Weight, kg, median (IQR)	85.5 (80.1-100.1)	72.8 (61.1-79.8)	**.001**
Height, cm, median (IQR)	175.3 (168.8-182.9)	172.2 (163.9-185.4)	.148
Female sex, n (%)	5 (24)	15 (52)	.079
Caucasian race, n (%)	16 (76)	27 (93)	.115
Type 2 diabetes mellitus, n (%)	1 (5)	4 (14)	.383
Chronic kidney disease, n (%)	1 (5)	1 (4)	>.999
Hepatic disease, n (%)	0	1 (4)	>.999
Hematologic malignancy, n (%)	—	—	—
Acute myelogenous leukemia	14 (67)	11 (38)	.085
Chronic lymphoblastic leukemia	0	2 (7)	.503
Myelodysplastic syndrome	2 (10)	1 (4)	.565
Hodgkin lymphoma	0	1 (4)	>.999
Non-Hodgkin lymphoma	3 (14)	9 (31)	.201
Multiple myeloma	2 (10)	3 (10)	>.999
Other	0	2 (7)	.503
HSCT, n (%)*	12 (57)	18 (62)	.776
Autologous	1 (8)	6 (33)	.193
Allogeneic	11 (92)	12 (67)	.193
Matched related donor	4 (33)	1 (6)	.128
Dual cord blood	6 (50)	10 (56)	>.999
Haploidentical cord blood	1 (8)	1 (6)	>.999
Conditioning regimen	12 (100)	18 (100)	>.999
Myeloablative	4 (33)	5 (28)	>.999
Reduced intensity	8 (67)	9 (50)	.465
Nonmyeloablative	0	2 (11)	.503
Unknown	0	2 (11)	.503

Significant *P* values are in bold type.
* All data described for OVP and NOVP used a total of 12 and 18 patients, respectively.

OVP as a prevention measure for rCDI in both the inpatient and outpatient HSCT/HM populations.

Previous studies in the HSCT/HM population have described leading risk factors for CDI as receipt of chemotherapy before conditioning for HSCT, BSA use for infection prevention of s, use of myeloablative conditioning regimens for those undergoing HSCT, and acute GVHD [3,6]. All of these risk factors may play roles by disrupting gastrointestinal mucosa and/or intestinal microbiota diversity [19,20]. Because these are unavoidable risk factors in this patient population, our key focus needs to be on strategies for preventing CDI and rCDI.

Previously reported studies have shown that OVP has promise for prevention of CDI. In a retrospective study, Van Hise et al [8] found a significantly lower incidence of rCDI in patients receiving OVP. In 2016, Carignan et al [9] reported that the use of OVP reduced the risk of rCDI in patients experiencing relapsed CDI [9]. Ganetsky et al published the first evaluation of OVP in the HSCT population (largely primary prevention), reporting a CDI incidence of 0% in the OVP group versus 20% in the NOVP group ($P < 0.001$) [11]. The potential disadvantages of primary prophylaxis with oral vancomycin for all HSCT/HM patients are increased costs and adverse events, gut microbiota disruption, and resistance pressure over time [21,22].

Our data add to the sparse studies in the HSCT/HM population suggesting that OVP may be effective in secondary prevention of CDI at a dose of 125 mg twice daily. Furthermore, our evaluation highlights key differences from the currently available literature analyzing OVP. Our study cohort included not only autologous and allogeneic HSCT recipients (including dual umbilical cord and haploidentical cord transplants), but also patients with HMs who did not undergo HSCT, who are similarly at increased risk of rCDI. Important to highlight, there were no significant differences between the 2 cohorts in type

Table 2
CDI-Specific Characteristics During the Initial Episode

Characteristic	OVP (N = 21), n (%)	NOVP (N = 29), n (%)	*P* Value
CO CDI	2 (10)	12 (41)	**.024**
CO-HCFA CDI	4 (19)	8 (28)	.526
HO CDI	15 (71)	9 (31)	**.009**
Mild diarrhea	10 (48)	15 (52)	>.999
Moderate diarrhea	7 (33)	5 (17)	.315
Severe diarrhea	4 (19)	9 (31)	.515

Significant *P* values are in bold type.
CO indicates community onset; CO-HCFA, community-onset; HO, healthcare facility onset.

Table 3
Broad-Spectrum Antibiotics Received During CDI Diagnosis and/or Treatment/Prophylactic Course with Oral Vancomycin

Antibiotic	OVP (N = 21)	NOVP (N = 29)	*P* Value
Aminopenicillins, n (%)	1 (5)	2 (7)	>.999
BL/BLI, n (%)	3 (14)	4 (14)	>.999
Third/fourth-generation cephalosporins, n (%)	20 (95)	27 (93)	>.999
Other cephalosporins, n (%)	4 (19)	7 (24)	.741
Carbapenems, n (%)	12 (57)	8 (28)	**.045**
Fluoroquinolones, n (%)	17 (81)	14 (48)	**.037**
Gram-positive antibiotics, n (%)	13 (62)	12 (41)	.160
SMX/TMP, n (%)	9 (43)	13 (45)	>.999
Doxycycline, n (%)	1 (5)	0	.420
Duration of high-risk antibiotics after CDI diagnosis, d, median (IQR)	17.5 (14.8-31.3)	11.0 (9.0-17.0)	.034

Significant *P* values are in bold type.
BL/BLI indicates beta-lactam/beta-lactamase inhibitor; SMX/TMP, sulfamethoxazole/ trimethoprim.
Aminopenicillins included amoxicillin and ampicillin. BL/BLI included piperacillin/tazobactam and ampicillin/sulbactam. Third/fourth-generation cephalosporins included ceftriaxone and cefepime. Carbapenems included meropenem and ertapenem. Fluoroquinolones included levofloxacin and moxifloxacin. Gram-positive antibiotics included vancomycin, daptomycin, and linezolid. No patient received amoxicillin/clavulanate, imipenem/cilastatin, ciprofloxacin, or clindamycin.

Table 4
Variables Directly or Inversely Associated with rCDI Infection after Multivariable Logistic Regression

Variable	OR (95% CI)	*P* Value
OVP	.14 (.007-.994)	**.049**
Outpatient CDI diagnosis	8.72 (1.816-49.158)	**.007**

Significant *P* values are in bold type.

of HSCT or HM, or the intensity of the conditioning regimens used for HSCT (Table 1). Our study also included patients with similar risk factors, no previous history of CDI (until diagnosed in the study period), OVP at a regimen consistent for all patients evaluated, and a high proportion of umbilical cord transplants. Although patients in the OVP group were younger, there were many notable differences between the 2 groups that would not be expected to decrease the incidence of rCDI in the OVP group, including increased use of fluoroquinolones, carbapenems, and immunosuppressants (not part of chemotherapy); longer hospital length of stay and duration of high-risk antibiotic use, and a higher incidence of HO CDI infections.

Historically, CDI has been considered a nosocomial infection, but has been emerging in the community in patients previously considered low risk [23]. One interesting finding in our study is the high incidence of rCDI in the outpatient setting (OR, 8.72; 95% CI, 1.816 to 49.158; *P* = .007), which indicates a potential nidus, warranting heightened infection prevention in ambulatory care settings. In ambulatory care settings, common areas and restrooms are shared among high-risk patients, and hygiene and contact precautions may be more relaxed compared with those in acute care settings. Because most of the available research on CDI and rCDI has focused on the inpatient setting, our data should place precedence for clinicians to place emphasis on CDI research in the ambulatory sector.

The incidence and promotion of VRE infections are of much concern with prolonged oral vancomycin courses, because oral vancomycin has been shown to promote colonization by VRE [21,22]. Although our data showing no differences in subsequent VRE infections is reassuring, further research is needed to analyze the long-term effects of prolonged courses of OVP and the incidence of new VRE colonization and infections.

Of note, there were differences between the 2 groups in outpatient CDI diagnosis (trending toward significance), hospital length of stay, and community-onset and healthcare facility-onset CDI. Regarding the numerically observed increased outpatient CDI diagnosis in the NOVP group, there is no obvious explanation for these occurrences, but a possible explanation could be the increased attention on and awareness of CDI by outpatient nursing staff. This higher rate of outpatient CDI diagnosis in the NOVP group could further explain the increased incidence of community-onset CDI in this group. Although not significant, there were numerically more allogeneic HSCTs performed in the OVP group and more autologous HSCTs performed in the NOVP group. Because allogeneic HSCTs generally take longer to engraft, most allogeneic HSCT recipients will remain in the hospital longer than autologous HSCT recipients, which could have contributed to the observed differences in hospital length of stay. The longer hospital length of stay observed in the OVP group could also explain the higher incidence of healthcare facility-onset CDI seen in this group.

Table 5
Primary and Secondary Study Endpoints

Endpoint	OVP (N = 21), n (%)	NOVP (N = 29), n (%)	*P* Value
Recurrent CDI	1 (5)	10 (35)	**.016**
VRE infection	3 (14)	3 (10)	.686
60-d mortality	2 (10)	2 (7)	>.999
Treatment failure*	9 (43)	10 (35)	.570
Addition of metronidazole	6 (29)	4 (14)	.286
Extending duration of vancomycin (>14 d)	3 (14)	6 (21)	.716
Increase in vancomycin dose	2 (10)	3 (10)	>.999
Switch to an alternative agent	0	2 (7)	.503

Significant *P* values are in bold type.
* No patient received a fecal microbiota transplant or surgical management.

Limitations of this study include the retrospective design, lack of long-term follow-up in a small number of cases, and the inability to account for readmissions to other healthcare systems. One important limitation of the study is that the optimal duration of treatment for CDI in immunocompromised patients, particularly those continued on high- risk antibiotics after completion of standard CDI treatment, is controversial. Some centers may continue standard oral vancomycin treatment regimens throughout the period of overlapping high-risk antibiotics, whereas others may treat for a defined period, then reduce the vancomycin interval for prevention of rCDI when continued exposure to high-risk antibiotics are needed. However, a retrospective review found no differences in rCDI in patients receiving regular CDI treatment (10 to 14 days) versus those receiving extended CDI treatment (>14 days) and concomitant antibiotics [24]. For the development of our institutional protocol, we decided that CDI treatment would be 14 days, and patients continued on high-risk antibiotics after this point we would continue twice daily OVP. The lower dosing interval used for prophylaxis appeared to effectively prevent rCDI in our cohort and may have implications for lowering costs, preventing resistance, and/or improving tolerability. Furthermore, the components of treatment failure could have skewed the risk for recurrence (eg, addition of metronidazole, extension of treatment duration); however, there were no significant between-group differences in these components (Table 4).

Of note, there were some changes to cleaning and infection prevention practices throughout the preprotocol and postprotocol periods in an effort to reduce healthcare facility-onset CDI rates at our institution. These changes in practice could have influenced the rate of initial CDI episode in our population, although this is unlikely to have made a significant impact on the rate of rCDI in the 2 time frames. Because patients had been diagnosed with an initial episode in both the preintervention and postintervention periods, the majority would remain colonized after initial CDI treatment and remain at high risk for recurrence, given the continued exposure to BSAs and overall state of immunosuppression, regardless of cleaning practices. In addition, the increased attention to and awareness of CDI by nursing staff in the outpatient areas between the 2 study periods could have led to improved hygiene and use of special precautions for those known to be colonized with *C. difficile*. This may have contributed in some way to the observed differences in outpatient CDI diagnoses between the OVP and NOVP groups.

Despite these limitations, some strengths of our report should be noted. CDI recurrence was evaluated 60 days after treatment/prophylaxis was completed, and not 60 days after initial diagnosis. The Infectious Diseases Society of America CDI guidelines define rCDI as an episode of symptoms and a positive CDI assay following an episode with positive assay result in the previous 14 to 56 days [4]. Furthermore, because the majority of CDI episodes recur within 30 days, and because most patients in each group received outpatient BMT follow-up, this expanded duration should accurately encompass all true CDI recurrences [25]. Furthermore, the OVP regimen was consistent throughout our study period, we excluded patients that were discharged on an oral vancomycin taper, and also excluded patients receiving other available CDI treatment regimens/medications as initial treatment that could have confounded our results.

Of interest is the difference in rCDI between OVP and fidaxomicin, as fidaxomicin at differing dosing schemes has been shown to reduce CDI recurrence when compared to oral vancomycin [26,27]. Further research is also needed to determine the optimal dosing regimen for OVP and duration of OVP after BSA discontinuation, the promotion and incidence of VRE infections following prolonged oral vancomycin courses, and differences in rCDI between OVP and probiotics.

OVP appears to be an effective and safe method for secondary prevention of CDI in the HSCT/HM population. Prospective studies are needed to validate the effect of OVP in this immunosuppressed population with increased risk of rCDI.

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