Antimicrobial Stewardship & Healthcare Epidemiology (2024), **4**, e107, 1–7
doi:10.1017/ash.2024.90

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Original Article

Effectiveness of oral vancomycin as prophylaxis against *Clostridioides difficile* infection in hematopoietic stem cell transplant patients

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Abstract

Objective: Patients receiving hematopoietic stem cell transplants (HSCT) are at increased risk for *Clostridioides difficile* infection (CDI). The purpose of this study was to assess the effectiveness of oral vancomycin prophylaxis (OVP) for CDI in HSCT patients.

Design: Single-center, retrospective cohort.

Setting: Tertiary care academic medical center in New Jersey.

Patients: Patients ≥18 years old during admission for the HSCT were included. Patients who were admitted <72 hours or who had an active CDI prior to HSCT day 0 were excluded.

Methods: Medical records of patients admitted between January 2015 and August 2022 to undergo an allogeneic or autologous HSCT were reviewed. The primary end point was the incidence of in-hospital CDI. Secondary end points included the incidence of vancomycin-resistant enterococci (VRE) bloodstream infections, VRE isolated from any clinical culture, gram-negative bloodstream infections, hospital survival, and hospital length of stay. Exploratory end points, including 1-year survival, relapse, and incidence of graft-versus-host disease, were also collected.

Results: A total of 156 HSCT patients were included. There was 1 case of CDI (1 of 81, 1.23%) in the OVP group compared to 8 CDI cases (8 of 75, 10.67%) in the no OVP group ($P = .0147$). There were no significant ($P > .05$) between-group differences in incidence of gram-negative bloodstream infections, hospital survival, and length of stay. There were zero clinical cultures positive for VRE.

Conclusions: In-hospital incidence of CDI in HSCT patients was significantly decreased with OVP. Randomized controlled trials are needed in this high-risk population to assess the efficacy and risks of OVP for CDI.

(Received 27 February 2024; accepted 23 April 2024)

Introduction

Clostridioides difficile infection (CDI) is one of the most common infections after hematopoietic stem cell transplantation (HSCT).[1] Up to 33% of HSCT patients are affected by CDI, which is a ninefold increase in incidence compared with the general population. CDI most commonly occurs in the first few weeks posttransplant but can also occur in the late posttransplant stage.[1] Major risk factors for CDI include antibiotic exposure, recent stay in a healthcare facility, 65 years or older, immunocompromised states, proton pump inhibitor use, and previous CDI.[2–4] Due to their disease state and treatment, patients receiving HSCT have enhanced CDI risk factors. These patients will likely have multiple hospitalizations, increased exposure to broad-spectrum antibiotics and chemotherapy, decreased immune function, and alterations in gut microbiome from their treatment.[1,5,6]

HSCT patients are at high risk for CDI; however, there are limited data on the role of CDI prophylaxis in this population. Previous retrospective studies in this patient population have identified oral vancomycin as a potentially effective option for

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Previous presentations: Presented in part as a poster presentation at IDWeek 2023, Boston, MA, USA

Cite this article: Reitmeyer KM, Rana B, Awad D, *et al.* Effectiveness of oral vancomycin as prophylaxis against *Clostridioides difficile* infection in hematopoietic stem cell transplant patients. *Antimicrob Steward Healthc Epidemiol* 2024. doi: 10.1017/ash.2024.90

primary and secondary CDI prophylaxis, but more information is needed.[5,6] Therefore, the objective of this study was to evaluate the effectiveness of oral vancomycin as CDI prophylaxis for patients admitted for allogeneic or autologous stem cell transplants.

Methods

Study design

This was a single-center, retrospective cohort study of patients treated with HSCT. The study site was Robert Wood Johnson University Hospital (RWJUH) in New Brunswick, a 620-bed tertiary academic medical center affiliated with Rutgers Cancer Institute of New Jersey, the state's only National Cancer Institute-designated Comprehensive Cancer Center. Approximately 150 autologous and allogeneic HSCTs are performed each year. The data were collected through electronic medical record reviews of patient encounters for HSCT. The study protocol was reviewed and approved by the Rutgers University Institutional Review Board.

Oral vancomycin prophylaxis

In December 2019, the bone marrow transplant (BMT) team at RWJUH New Brunswick implemented a protocol for universal oral vancomycin prophylaxis (OVP) as part of standard clinical practice. This protocol required OVP at a dose of 125 mg by mouth twice daily from admission to discharge for all patients admitted for HSCT. Prior to this, the decision for OVP was made by the provider and was not routinely used at this institution. The study cohort was stratified as pre- and postuniversal OVP implementation.

Inclusion and exclusion

Patients ≥18 years old at the time of admission for the HSCT were included. Patients who were admitted <72 hours or who were being treated for an active CDI prior to day 0 of HSCT were excluded.

Clostridioides difficile diagnostics and study end points

The primary end point was the incidence of in-hospital CDI. CDI positivity was defined as a toxin/glutamate dehydrogenase (GDH) positive test or polymerase chain reaction (PCR) positive test. Stool samples were analyzed by the RWJUH New Brunswick on-site microbiology laboratory. The clinical testing algorithm in the laboratory was as follows: toxin/GDH assay was conducted first, and CDI was diagnosed if both the toxin and GDH assays were positive. If the results of the toxin assay and GDH assay were inconsistent, the test would reflex to a PCR test to confirm the diagnosis. If PCR-positive, the patient was diagnosed as having CDI. The RWJUH clinical microbiology laboratory only performed CDI testing on liquid stools for the full duration of the study period.

Secondary end points included the incidence of gram-negative bloodstream infections, hospital survival, and hospital length of stay. The incidence of vancomycin-resistant enterococci (VRE) bloodstream infections and VRE isolated from any clinical culture were also secondary outcomes. Exploratory end points included 1-year survival, 1-year relapse, and 1-year non-relapse mortality. In the subset of patients receiving allogeneic transplants, 1-year graft-versus-host disease (GVHD) diagnosis (clinical diagnosis from BMT team documentation), and 1-year GVHD-free, relapse-free survival was analyzed as an exploratory end point as some studies suggest that CDI after allogeneic HSCT may increase the risk of this immunologic complication.[5] GVHD data were collected based on documentation of clinical diagnosis by the BMT team.

Data collection

A list of patients who received an HSCT between January 1, 2015, and August 31, 2022, was obtained using International Classifications of Diseases, 10th Revision (ICD-10) diagnosis codes related to allogeneic and autologous HSCT. Patients were screened for eligibility. First, patients were chosen consecutively before and after December 2019, and then for data abstraction feasibility, a random number generator was used to include patients that represented the entire study period until the targeted sample size was achieved. Variables collected included demographics, past medical history and comorbidities, disease characteristics, transplant characteristics, medication history, inpatient antibiotic use, laboratory and microbiological data, and data relating to length of stay, survival, relapse, and GVHD.

Statistical analysis

Statistical analysis was conducted using SAS software version 9.4 (SAS Institute, Cary, NC, USA). Baseline characteristics, disease characteristics, antibiotics exposure during hospital stay, and outcomes variables were stratified by the primary predictor, pre- and postuniversal OVP implementation. Inferential statistics were performed. The median and interquartile range were reported for continuous variables based on the normality of distribution, whereas categorical variables were summarized using frequencies and percentages. The χ^2 or Fisher's exact test was used to analyze statistically significant differences in categorical variables. Student t test or Wilcoxon test (nonparametric) was used to compare continuous variables. P-values > .05 were not considered statistically significant. The target sample size was a total of 156 to have 80% power to detect an effect size of 11% (12% in control vs 1% in intervention) with an alpha of 0.05 and beta of 0.2. The effect size was determined by a review of prior studies[5,6] and what would be determined to be clinically relevant.

Results

Study population

A total of 160 patients who received HSCT between January 1, 2015, and August 31, 2023, were screened, and 156 patients met the inclusion criteria and were analyzed (Figure 1). There was a total of 75 patients in the preuniversal prophylaxis era (no OVP) and 81 patients in the postuniversal prophylaxis era (OVP). No patients in the preuniversal prophylaxis era received OVP. Baseline characteristics are listed in Table 1. Most patients were males (69%). The most common comorbidities were hypertension (41%) and hyperlipidemia (27%). The median age was 58 years in the no OVP group and 56 years in the OVP group. 71% of patients received autologous transplants. The most common indications for transplant were multiple myeloma, acute myeloid leukemia, and Hodgkin lymphoma. Of the conditioning regimens used, high-dose melphalan was the most common. Disease characteristics are listed in Table 2. Patients in the OVP group had more days of antibiotics during admission (median 12 vs 11 days, $P = .0305$), and a higher proportion received levofloxacin (88.9% vs 69.3%, $P = .0025$) compared with the no OVP group (Table 3).

https://doi.org/10.1017/ash.2024.90 Published online by Cambridge University Press

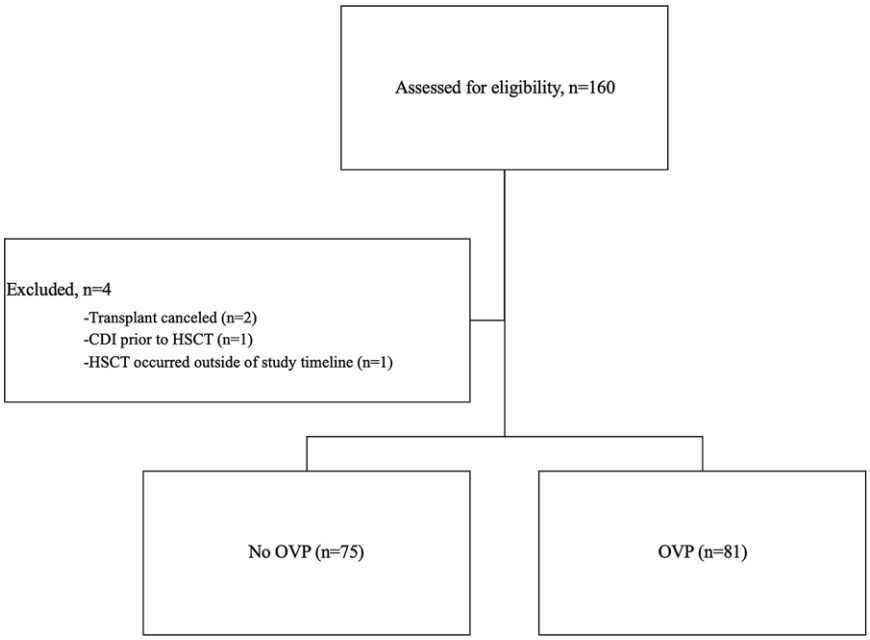

Figure 1. Flow chart of patient inclusion. CDI, *Clostridioides difficile* infection; HSCT, hematopoietic stem cell transplants; OVP, oral vancomycin prophylaxis.

End points

There was 1 case of CDI (1 of 81, 1.23%) in the OVP group compared to 8 CDI cases (8 of 75, 10.67%) in the no prophylaxis group ($P = .0147$). In the OVP group, the CDI was given a diagnosis of a PCR test. Of the positive CDIs in the no prophylaxis group, 3 were given a diagnosis of the toxin/GDH assay, and 5 were given a diagnosis of a PCR test. There were no significant between-group differences in the incidence of gram-negative bloodstream infections, hospital survival, and length of stay. The median length of hospital stay was 20 days in the no prophylaxis group and 21 days in the OVP group. All but 1 patient in each group survived the hospital admission. There were zero clinical cultures positive for VRE in either group during the transplant admission. There were no statistically significant between-group differences in any of the exploratory end points (Table 4).

Discussion

This study demonstrated that OVP in HSCT patients was effective at preventing in-hospital CDI compared with no prophylaxis. Only 1 patient who received OVP tested positive for CDI compared to 8 patients who did not receive OVP. There were no between-group differences in secondary outcomes including those specified as proxy measures for consequences of disruption to the gut microbiota (gram-negative bloodstream infection and incidence of VRE infection/colonization) as a result of OVP administration.

Our study is consistent with the findings of previously reported observational data. A recent retrospective study of OVP in allogeneic HSCT patients conducted by Ganetsky et al.[5] found that CDI occurred in 0 of 90 patients (0%) in the OVP group compared to 11 of 55 patients (20%) who did not receive oral vancomycin ($P < .001$). They found that oral vancomycin was effective at preventing CDI without increasing the risk of other complications such as VRE, GVHD, bloodstream infections, or relapse. The investigators also analyzed the incidence of GVHD due to a suspected association between early CDI and GVHD. They did not find an association between OVP and GVHD of any grade. In the subset of patients in our study who underwent allogeneic HSCT, there was no difference in rates of GVHD diagnosis; however, there were too few subjects to interpret meaningful significance to this finding. Future studies that are adequately powered for this end point are needed to determine the risk of transplant-related complications. Morrisette and colleagues conducted a retrospective analysis to assess the effectiveness of OVP as secondary CDI prophylaxis in patients undergoing HSCT and patients with hematologic malignancies.[6] Their study also demonstrated the effectiveness of OVP at preventing recurrent CDI with infections occurring in 1 of 21 (5%) in the OVP group compared with 10 of 29 (35%) in the non-OVP group ($P = .016$). The results of our study are in concordance with these findings. Lastly, a recent study by Altemeier and colleagues observed similar findings to our study among allogeneic HSCT patients (11% vs 2%, $P = .018$) for no OVP versus OVP.[7]

Although results from this study are optimistic, there are still concerns with utilizing OVP in this patient population. The implications of using OVP for CDI on HSCT patients' enteric microbiota are not well-defined. Some data in healthy males demonstrate that oral vancomycin induces changes in the relative abundance of gut bacterial microbiota and fecal metabolites, but its effect in the HSCT population requires further study.[8] The long-term risks of this practice in HSCT patients cannot be fully understood with the currently available data, and more research is needed. Disruptions to the microbiome by early administration of systemic antibiotics active against commensals around the time of HSCT have been associated with transplant-related mortality.[9] We observed no difference in transplant-related outcomes, but these were exploratory end points, as our study was not powered or designed specifically to assess these outcomes.

The use of oral and intravenous vancomycin has been associated with an increased risk of VRE colonization.[10] There were zero clinical cultures positive for VRE in either group during the transplant admission. The lack of association of VRE infection with OVP is consistent with prior studies, though none have been powered to detect VRE infection as a primary outcome. The lack of observed association may be due to the very high fecal levels of vancomycin achieved with typical enteric vancomycin dosing

https://doi.org/10.1017/ash.2024.90 Published online by Cambridge University Press

Table 1. Baseline clinical and demographic characteristics

Characteristic	No OVP (n = 75)	OVP (n = 81)	P-value
Age in years, median (IQR)	58 (53–63)	56 (48–62)	.1849
Sex, *n* (%)			.7085
Female	22 (29.33)	26 (32.10)	
Male	53 (70.67)	55 (67.90)	
Race, *n* (%)			.7792
African American	14 (18.67)	19 (23.46)	
White	36 (48.00)	35 (43.21)	
Asian	5 (6.67)	5 (6.17)	
Other	20 (26.67)	22 (27.16)	
BMI, median (IQR)	26.6 (23.2–30.0)	29.5 (25.4–33.6)	.0030
Comorbidities, *n* (%)			
Hypertension	32 (42.67)	32 (39.51)	.6884
Diabetes mellitus	9 (12.00)	10 (12.35)	.9474
CKD	3 (4.00)	5 (6.17)	.7210
Hyperlipidemia	18 (24.00)	24 (29.63)	.4283
CAD	3 (4.00)	3 (3.70)	1.0000
DVT/PE	8 (10.67)	8 (9.88)	.8709
HIV/AIDS	3 (4.00)	1 (1.23)	.3517
COPD	2 (2.67)	1 (1.23)	.6085
PUD/GERD	7 (9.33)	2 (2.47)	.0889
Liver disease	7 (9.33)	8 (9.88)	.9085
Asthma	3 (4.00)	6 (7.41)	.4978
History of CDI in last year, *n* (%)	1 (1.33)	5 (6.17)	.2117
History of bezlotuxumab, *n* (%)	0 (0.00)	1 (1.23)	1.0000
Vancomycin allergy, *n* (%)	2 (2.67)	0 (0.00)	.2295
Serum creatinine on admission, median (IQR)	0.8 (0.6–1.0)	0.8 (0.7–1.0)	.7925
Received inpatient proton pump inhibitor, n (%)	73 (97.33)	79 (97.53)	1.0000
Hospital admission 90 days prior to transplant, *n* (%)			.8708
Yes	25 (33.33)	28 (34.57)	
No	50 (66.67)	53 (65.47)	

Note. OVP, oral vancomycin prophylaxis; IQR, interquartile range; BMI, body mass index; CKD, chronic kidney disease; HD, hemodialysis; CAD, coronary artery disease; DVT, deep vein thrombosis; PE, pulmonary embolism; HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome; PUD, peptic ulcer disease; GERD, gastroesophageal reflux disease; CDI, *Clostridioides difficile* infection.

(900–8700 μg/g), which we postulate could inhibit VRE growth though not currently substantiated by any known data.[11–13] Although there was no documented VRE in this study, only clinical cultures from the HSCT admission were analyzed. Future studies should consider assessing the long-term risk of VRE colonization and infections both in the early and late posttransplant stages after receiving OVP.

Another concern regarding the extended duration of vancomycin is the emergence of vancomycin-resistant *C. difficile* strains. Darkoh and colleagues conducted a study where they analyzed CDI stool samples from patients in Houston, Texas, and Nairobi, Kenya, for vancomycin nonsusceptibility.[14] In Houston, 26% of samples showed nonsusceptibility to vancomycin, and in Nairobi, 67% of isolates were non-susceptible. Greentree and colleagues conducted a similar investigation looking for strains with reduced vancomycin susceptibility in an Ohio hospital.[15] Of the 176 samples analyzed, they did not find any with reduced susceptibility to vancomycin. Because oral vancomycin is a potential first-line treatment option for CDI, it is a serious public health concern that vancomycin nonsusceptibility and resistance seem to be emerging in various areas. Increased surveillance of vancomycin-resistant *C. difficile* strains will help providers weigh the risks and benefits of using vancomycin as CDI prophylaxis. Future studies should assess the potential risk that the use of OVP confers in the emergence of vancomycin-resistant *C. difficile* in HSCT and other populations.

Guidelines from the American College of Gastroenterology discuss the evidence for primary OVP but only state that "OVP may be considered in high-risk patients who have been recently treated for CDI and require subsequent treatment with systemic antibiotics," while also noting the importance of analyzing OVP impact on the gut microbiome and risk of drug resistance.[16] Future large clinical trials are needed for more rigorous assessment prior to incorporation into clinical practice guidelines.

Our study had several limitations. First, it was a single-center, retrospective study of nonconsecutive patients from 2015 to 2022—our study sampled consecutive patients immediately before and after the implementation of OVP and then a random sample throughout the remainder for data abstraction feasibility. Inherently, this limits generalizability for populations that may differ at different institutions. For example, most of our patients had autologous HSCT which may have a lower risk of CDI than allogeneic HSCT. The study was unable to control for secular trends, such as changes in oncologic treatment strategies, but there were no identified changes in practice for CDI management over the study duration other than potential increases in infection prevention measures during the coronavirus disease 2019 pandemic. Second, due to incomplete or inaccessible outpatient prescription records, we were unable to fully capture each patient's antibiotic exposure prior to their HSCT or incidence of postdischarge CDI. During the admissions, there were no between-group differences among the antibiotics that patients received other than levofloxacin. More patients in the OVP group received levofloxacin than in the no OVP group. Interestingly, fluoroquinolones have a high CDI risk; however, there were still fewer CDI cases in the OVP group. Third, there was no data on baseline *C. difficile* colonization as this is not routinely assessed for clinical purposes; therefore, this data was unavailable. Last, there is potential that the implementation of universal prophylaxis could affect testing practices, a potential confounder if the testing volume was affected, but there were no changes to testing recommendations or the clinical practice of testing patients for CDI if there is a compatible clinical presentation (ie, new onset diarrhea). The ecological assessment of hospital testing volume was not available, and even if so, these data in and of itself are a limited measure due to ecological fallacy. Other limitations include incomplete documentation by providers as well as loss of follow-up and inability to assess records from other healthcare systems for the exploratory end points.

https://doi.org/10.1017/ash.2024.90 Published online by Cambridge University Press

Table 2. Disease and transplant characteristics

Characteristic	No OVP (n = 75)	OVP (n = 81)	P-value
HSCT type, n, (%)			.0722
Allogeneic	17 (22.67)	29 (35.80)	
Autologous	58 (77.33)	52 (64.20)	
Previous transplant prior to study period, n (%)			.6437
Yes	5 (6.67)	7 (8.64)	
No	70 (93.33)	74 (91.36)	
Indication for transplant, n (%)			.1031
Acute myeloid leukemia	6 (8.00)	17 (20.00)	
Acute lymphoblastic leukemia	4 (5.33)	2 (2.47)	
Myelodysplastic syndromes	0 (0.00)	4 (4.94)	
Chronic myeloid leukemia	0 (0.00)	2 (2.47)	
Myelofibrosis	3 (4.00)	4 (4.94)	
Chronic lymphocytic leukemia	1 (1.33)	0 (0.00)	
Hodgkin lymphoma	7 (9.33)	7 (8.64)	
Multiple myeloma	34 (45.33)	30 (37.04)	
Other[a]	19 (25.33)	15 (18.52)	
Donor source, n (%)			
Self	58 (77.33)	52 (64.20)	.0722
Related	12 (16.00)	14 (17.28)	.8298
Unrelated	4 (5.33)	15 (18.54)	.0119
Conditioning regimen, n (%)			.1786
Melphalan	36 (48.00)	30 (37.04)	
Thiotepa, fludarabine, busulfan	9 (12.00)	22 (27.16)	
Carmustine, etoposide, cytarabine, melphalan	12 (16.00)	14 (17.28)	
Carboplatin, etoposide	2 (2.67)	5 (6.17)	
Carmustine, thiotepa	5 (6.67)	2 (2.47)	
Fludarabine, melphalan	2 (2.67)	3 (3.70)	
Other[b]	9 (12.00)	5 (6.17)	
Conditioning intensity, n (%)			.8906
High dose	65 (86.67)	70 (86.42)	
Reduced intensity	10 (13.33)	11 (13.58)	
GVHD prophylaxis, n (%)			.0041
Tacrolimus/mycophenolate/cyclophosphamide	17 (22.67)	25 (30.86)	
None (autologous)	58 (77.33)	52 (64.20)	
Tacrolimus/mycophenolate	0 (0.00)	4 (4.91)	

Note. OVP, oral vancomycin prophylaxis; HSCT, hematopoietic stem cell transplants; GVHD, graft-versus-host disease.
[a]Other: Diffuse large B-cell lymphoma; Light chain amyloidosis, nonseminomatous germ cell tumor, central nervous system (CNS) lymphoma; T-cell lymphoma; plasmablastic lymphoma; seminoma; natural killer (NK) T-cell lymphoma; mantle cell lymphoma, mixed-lineage leukemia, and acute lymphoblastic leukemia.
[b]Other: Total body irradiation (TBI); TBI with cranial boost; TBI, fludarabine; fludarabine, busulfan; fludarabine, cyclophosphamide, TBI; fludarabine, melphalan, TBI; carmustine, thiotepa; carmustine, thiotepa, etoposide; busulfan, melphalan; melphalan, thiotepa, fludarabine.

Despite the limitations of this study, there were still significant strengths including focusing on a population that is vulnerable to CDI. Patients undergoing HSCT have multiple relatively non-modifiable CDI risk factors and are among the ones who may benefit the most from CDI prophylaxis. This study adds to the limited evidence currently available on the practice of using OVP for CDI prophylaxis in HSCT patients. In addition, our institution initiated the universal CDI prophylaxis protocol in December 2019, which gave us the ability to analyze patients before and after the implementation. This decreased the risk of selection bias among our patient sample (ie, a quasi-experimental study of a universal clinical practice change).

There were significantly less patients diagnosed as having CDI during admission for HSCT in the prophylaxis group compared with the no prophylaxis group which demonstrates that OVP may be effective at preventing CDI in patients receiving HSCT. These findings are promising considering infections such as CDI are among the most common complications affecting HSCT patients.

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Table 3. Antibiotic exposure during hospital admission

Antibiotic	No OVP ($n = 75$)	OVP ($n = 81$)	*P*-value
Cefazolin, *n* (%)	4 (5.33)	10 (12.35)	.1258
Cefepime, *n* (%)	60 (80.00)	59 (72.84)	.2935
Levofloxacin, *n* (%)	52 (69.33)	72 (88.89)	.0025
Meropenem, *n* (%)	24 (32.00)	18 (22.22)	.1689
Piperacillin-tazobactam, *n* (%)	3 (4.00)	0 (0.00)	.1088
IV vancomycin, *n* (%)	15 (20.00)	11 (13.58)	.2824
Clindamycin, *n* (%)	1 (1.33)	0 (0.00)	.4808
Metronidazole, *n* (%)	6 (8.00)	3 (3.70)	.3140
Daptomycin, *n* (%)	1 (1.33)	1 (1.23)	1.0000
Linezolid, *n* (%)	3 (4.00)	0 (0.00)	.1088
Sulfamethoxazole-trimethoprim, *n* (%)	2 (2.67)	0 (0.00)	.2295
Days of antibiotics during admission, median (IQR)	11 (10–14)	12 (10–15)	.0305

Note. IQR, interquartile range; OVP, oral vancomycin prophylaxis.

Table 4. Study outcomes data

Outcome	No OVP ($n = 75$)	OVP ($n = 81$)	*P*-value
In-hospital CDI, *n* (%)	8 (10.67)	1 (1.23)	.0147
VRE bloodstream infection, *n* (%)	0 (0)	0 (0)	–
VRE in any clinical culture, *n* (%)	0 (0)	0 (0)	–
Gram-negative bloodstream infection, *n* (%)	7 (9.33)	9 (11.11)	.7146
Hospital survival, *n* (%)	74 (98.67)	80 (98.77)	1.0000
Hospital length of stay, median (IQR)	20 (16–24)	21 (17–25)	.5420
1-year survival, *n* (%)	64 (85.33)	62 (76.54)	.1640
1-year relapse, *n* (%)	11 (14.67)	14 (17.28)	.6562
1-year GVHD diagnosis, *n* (%)	5 (29.41)	15 (51.72)	.1306
1-year non-relapse mortality, *n* (%)	0 (0)	0 (0)	–
1-year GVHD-free, relapse-free survival, *n* (%)	7 (41.17)	4 (13.79)	.0765

Note. CDI, *Clostridioides difficile* infection; VRE, vancomycin-resistant *Enterococcus*; IQR, interquartile range; GVHD, graft-versus-host disease; OVP, oral vancomycin prophylaxis.

However, there are considerations with this practice that must be addressed with future research. Prospective clinical trials and cost-effectiveness studies are needed to more definitively assess the safety and efficacy of this practice. Although a prospective randomized study has been done in the general inpatient population demonstrating the effectiveness of OVP in the prevention of healthcare facility-onset CDI, studies specific to the HSCT population is necessary given their unique considerations and potential negative microbiome impacts.[17] Long-term clinical and public health concerns including increased VRE colonization, microbiome disruption, and emergence of vancomycin-resistant *C. difficile* strains need to be studied, and the risks need to be understood for an informed risk-benefit analysis of this practice before broad uptake across practice settings.

Acknowledgments. None.

Financial support. N.N. reports being supported by the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institute of Health (NIH) under Award Number K23AI159396.

Competing interests. N.N. reports grants/contracts from Merck and Shionogi and consulting/speaking fees from Astellas, Beckman-Coulter, Paratek, and T2 Biosystems.

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https://doi.org/10.1017/ash.2024.90 Published online by Cambridge University Press