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Infectious Disease

Fluoroquinolone Prophylaxis Is Highly Effective for the Prevention of Central Line–Associated Bloodstream Infections in Autologous Stem Cell Transplant Patients

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A B S T R A C T

Patients undergoing stem cell transplant (SCT) for the treatment of hematologic malignancy are at increased risk for central line–associated bloodstream infections (CLABSIs). The use of prophylactic antibiotics to prevent CLABSIs in the setting of autologous SCT is of unclear benefit. We aimed to evaluate the impact of levofloxacin prophylaxis on reducing CLABSIs in this high-risk population. Patients undergoing autologous SCT at a tertiary care hospital received levofloxacin prophylaxis from January 13, 2016 to January 12, 2017. Levofloxacin was administered from autologous SCT (day 0) until day 13, absolute neutrophil count $> 500/mm^3$, or neutropenic fever, whichever occurred first. Clinical outcomes were compared with a baseline group who underwent autologous SCT but did not receive antibacterial prophylaxis during the previous year. The primary endpoint was incidence of CLABSIs assessed using Cox proportional hazards regression. A total of 324 patients underwent autologous SCT during the entire study period, with 150 receiving levofloxacin prophylaxis during the intervention period. The rate of CLABSIs was reduced from 18.4% during the baseline period to 6.0% during the intervention period. On multivariable analysis levofloxacin prophylaxis significantly reduced CLABSI incidence (hazard ratio, .33; 95% confidence interval [CI], .16 to .69; $P = .003$). There was also a reduction in the risk of neutropenic fever (odds ratio [OR], .23; 95% CI, .14 to .39; $P < .001$) and a trend toward a reduction in intensive care unit transfer for sepsis (OR, .33; 95% CI, .09 to 1.24; $P = .10$) in patients receiving levofloxacin prophylaxis. Notably, there was no increase in *Clostridium difficile* infection in the levofloxacin group (OR, .66; 95% CI, .29 to 1.49; $P = .32$). Levofloxacin prophylaxis was effective in reducing CLABSIs and neutropenic fever in patients undergoing autologous SCT. Further studies are needed to identify specific patient groups who will benefit most from antibiotic prophylaxis.

INTRODUCTION

Over the past decade rates of central line–associated bloodstream infections (CLABSIs) have been reduced by over 50% among hospitalized patients through the implementation of standardized infection prevention strategies [1,2]. However, CLABSIs remain common in patients with hematologic malignancy and are associated with significant morbidity and mortality, including an increased risk of acute graft-versus-host disease, prolonged lengths of stay, and up to a 7-fold increased risk of death [3-8]. In patients undergoing autologous stem cell transplant (SCT), rates of CLABSIs have been estimated to be as high as 20% to 40% [6,9].

Patients undergoing SCT are at increased risk of infection because of their underlying malignancy, frequent hospitalizations, chemotherapy-induced immune suppression, and neutropenia. Most patients require prolonged use of central venous access devices for the receipt of chemotherapy and transfusion of blood products. In addition, myeloablative regimens before SCT result in neutropenia of days to weeks and typically result in mucosal barrier injury (MBI) in the gastrointestinal tract [10]. Translocation of gut bacteria can then result in primary BSIs, an infection termed "mucosal barrier injury laboratory-confirmed bloodstream infection" for surveillance purposes by Centers for Disease Control and Prevention's

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National Healthcare Safety Network [11]. Importantly, these MBI-CLABSI events may not be preventable with common infection prevention strategies such as aseptic catheter insertion, chlorhexidine gluconate (CHG) bathing, and optimal central line care [12]. However, MBI-CLABSIs are associated with similar morbidity and mortality as CLABSIs associated with typical, non-MBI pathogens and as such represent a critical target for prevention in hospitalized patients [5,11].

Two randomized trials of levofloxacin prophylaxis among cancer patients conducted more than a decade ago demonstrated conflicting results for the prevention of BSIs and were limited by inclusion of patients with both solid and hematologic malignancy and varied timing and duration of prophylaxis regimens [13-15]. Since these studies, the utility of antibiotic prophylaxis has become less clear, due in part to increasing rates of fluoroquinolone resistance and the risk of *Clostridium difficile* infection associated with these agents [16-18]. Additionally, the complexity of these patients and delivery of care (eg, chemotherapy regimens) have significantly increased. Given the paucity of evidence for the impact of routine antibiotic prophylaxis in patients undergoing autologous SCT, there has been a lack of standardized recommendations from hematology oncology society guidelines and significant variation in application by cancer treatment programs [19-21]. Thus, we aimed to investigate not only the benefit of levofloxacin prophylaxis for the prevention of CLABSIs but also potential risks in a current group of patients undergoing autologous SCT at a tertiary care center.

METHODS

Study Design and Setting

We performed a retrospective cohort study of autologous SCT patients admitted to the Hospital of the University of Pennsylvania from January 13, 2015 to January 12, 2017. The Hospital of the University of Pennsylvania is a 776-bed tertiary care medical center and a National Cancer Institute Comprehensive Cancer Care designated center.

Study Population

Levofloxacin prophylaxis in patients undergoing autologous SCT was initiated on January 13, 2016 as an infection prevention initiative. Before January 13, 2016 no routine antibiotic prophylaxis was provided to these patients. With the initiation of levofloxacin prophylaxis, patients undergoing autologous SCT were prescribed levofloxacin 500 mg oral daily (with dosing adjustments made based on creatinine clearance), from the date of SCT (day 0) until day 13, engraftment (absolute neutrophil count $>$ 500 cells/mm^3), or neutropenic fever (absolute neutrophil count $<$ 500 cells/mm^3 with oral temperature $>$100.4°F), whichever occurred earliest. With the onset of neutropenic fever, patients were switched to cefepime or meropenem as per institutional neutropenic fever guidelines. No alternative antibiotics were provided for prophylaxis in the setting of an allergy or contraindication to fluoroquinolones (eg, prolonged QT interval). During the entire study period there was also an ongoing infection prevention educational campaign to improve compliance with daily CHG bathing. No additional co-occurring interventions were targeted toward the reduction of CLABSIs during the study period. Additionally, no routine surveillance cultures were performed. The group of patients who received levofloxacin prophylaxis during the year after initiation of this intervention (January 13, 2016 to January 12, 2017) were compared with those who did not receive prophylaxis in the previous year (January 13, 2015 to January 12, 2016). Therefore, the exposure of interest for this cohort study was the receipt of levofloxacin prophylaxis. The study was reviewed and approved by the University of Pennsylvania institutional review board.

Data Collection

Clinical data were collected via electronic medical record review, including demographics and comorbidities. Specific oncology data were ascertained, including type of malignancy, history of relapsed or recurrent primary malignancy, the chemotherapy regimen received during autologous SCT, duration of neutropenia, development of mucositis, inpatient medications, and compliance with CHG bathing. CHG bathing compliance was measured as the number of days with documented completion in the nursing flowsheet during the day of SCT and the following 7 days (days 0 to 7).

Study Outcomes

The primary outcome of interest was incidence of CLABSI, including both MBI and non-MBI primary BSI events. CLABSI events had been previously ascertained by standardized review by the Department of Healthcare Epidemiology and Infection Prevention using National Healthcare Safety Network surveillance criteria [11], defined as a primary BSI with the presence of a central venous catheter. Within the definition of CLABSI, these events may be classified as either MBI or non-MBI depending on the pathogen (ie, intestinal organisms) and clinical characteristics of the patient (eg, neutropenia, diarrhea, or graft-versus-host disease of the gut). Secondary BSIs were attributed when there was a known primary site of infection (eg, pneumonia). Secondary outcomes included in-hospital mortality, requirement for medical intensive care unit (ICU) transfer, *C. difficile* infection, BSI other than primary CLABSI, neutropenic fever, and broad-spectrum antibiotic use, all within 30 days of SCT. Inpatient antibiotics were reviewed from patient charts and recorded as days of therapy. Additional outcomes included total length of stay after SCT and readmission to any University of Pennsylvania Health System hospital within 30 days from discharge.

All blood cultures were performed in the Hospital of the University of Pennsylvania Clinical Microbiology Laboratory using the BACTEC FX system (Becton Dickinson, Franklin Lakes, NJ), organism identification using the Vitek MS Matrix Assisted Laser Desorption/Ionization (bioMérieux, Durham, NC), and antibiotic susceptibilities using the Vitek 2 automated platform (bioMérieux) with Clinical and Laboratory Standards Institute breakpoints [22]. *C. difficile* testing was performed using a commercial EIA for detection of toxins A and B and glutamate dehydrogenase (C Diff Quik Check Complete; Alere, Waltham, MA). Samples negative for toxins A and B but positive for glutamate dehydrogenase were subsequently tested using PCR for toxin genes (BD MAX Cdiff Assay; Becton Dickinson).

Statistical Analysis

Primary outcome analysis was conducted using survival analysis to determine the association between levofloxacin prophylaxis and time to development of a CLABSI. Time zero for all patients was defined as the day of SCT (day 0). The failure event was defined as development of CLABSI. Patients who did not develop a CLABSI were censored at death, discharge, or day 30 of hospital stay. Evaluation of the time to development of CLABSI was assessed with the Kaplan-Meier product-limit survival curve estimates and the log-rank statistic for comparison of multiple hazard ratios (HRs) for unadjusted comparison of groups and Cox proportional hazards regression covariate adjustment. Multivariable Cox proportional hazards regression analysis was performed to determine the adjusted association between levofloxacin prophylaxis and time to development of CLABSI. This multivariable model was developed beginning with the primary risk factor of interest, admission during the time period after routine antibiotic prophylaxis with levofloxacin. A manual stepwise selection procedure was used, with variables with $P < .25$ on bivariable analysis considered as candidate variables and maintained in the final model if their inclusion was statistically significant on likelihood ratio testing. Underlying malignancy was a priori selected for inclusion in the model regardless of significance on bivariable analysis because of its clinical importance. The proportional hazards assumption was assessed visually using a log-log plot and by plotting Kaplan-Meier survival against predicted survival. Primary analysis was performed per protocol, and an intention-to-treat analysis was performed as a secondary analysis. Additionally, subanalysis was performed using a bivariable Cox proportional hazard regression model to evaluate the differential impact of levofloxacin prophylaxis on MBI-CLABSIs versus non-MBI-CLABSIs. In this subanalysis all patients were censored at time of CLABSI, with separate failure events of MBI-CLABSI and non-MBI-CLABSI. Two-tailed $P < .05$ were considered statistically significant.

Categorical secondary outcomes were analyzed using logistic regression. To determine the strength of the association between receipt of levofloxacin and the categorical secondary outcomes, an odds ratio (OR) and 95% confidence interval (CI) were calculated. The association between receipt of levofloxacin and the continuous secondary outcomes, length of stay and antibiotic duration, was assessed using linear regression. All analyses were performed using STATA v.14.2 (StataCorp, College Station, TX).

RESULTS

Study Population

A total of 324 patients received an autologous SCT during the 2-year study period, with 174 patients included in the baseline group and 150 patients in the levofloxacin prophylaxis group. Baseline characteristics were similar in both groups (Table 1). In the total population, the median age was 59 years (interquartile range, 52 to 65), 194 (60%) were men, and 83 (26%) were categorized as nonwhite race. Comorbidities were common in the study population, with 83 patients

Table 1
Characteristics of Patients Undergoing Autologous SCT, Comparing the Baseline Group to Those Who Received Levofloxacin Prophylaxis

Characteristics	Total Population (N = 324)	Baseline Group (n = 174)	Levofloxacin Group (n = 150)	*P*
Median age, yr (IQR)	59 (52-65)	59 (52-66)	59 (52-64)	0.72
Male sex	194 (60)	102 (59)	92 (61)	0.62
Nonwhite race	83 (26)	36 (26)	37 (25)	0.72
Malignancy				
Multiple myeloma	247 (76)	126 (72)	121 (81)	0.01
Non-Hodgkin lymphoma	41 (13)	30 (17)	11 (7)	
Hodgkin lymphoma	16 (5)	11 (6)	5 (3)	
Other	20 (6)	7 (4)	13 (9)	
Recurrent disease*	37 (11)	22 (13)	15 (10)	0.46
Chemotherapy				
Melphalan 200 mg/m^2	204 (63)	97 (56)	107 (71)	
Melphalan, reduced dose	47 (14)	33 (19)	14 (9)	
BCV	45 (14)	30 (17)	15 (10)	0.002
BEAM	16 (5)	11 (6)	5 (3)	
Other	12 (4)	3 (2)	9 (6)	
Median neutropenia (days of ANC < 500 cells/mm^3) (IQR)	6 (5-7)	6 (5-7)	6 (5-7)	0.45
CHG compliance (documented from date of SCT to day 7)				
<50%	211 (65)	140 (80)	71 (47)	
50%-75%	99 (31)	32 (18)	67 (45)	<.001
>75%	14 (4)	2 (1)	12 (8)	
Comorbidities				
Chronic liver disease†	8 (2)	2 (1)	6 (4)	0.10
Chronic lung disease‡	17 (5)	9 (5)	8 (5)	0.95
Chronic kidney disease	58 (18)	28 (16)	30 (20)	0.36
Acute kidney injury	83 (26)	47 (27)	36 (24)	0.54
Coronary artery disease	32 (10)	17 (10)	15 (10)	0.94
Congestive heart failure	13 (4)	7 (4)	6 (4)	0.99
Diabetes mellitus	31 (10)	12 (7)	19 (13)	0.08
Mucositis of any grade	207 (64)	112 (64)	95 (63)	0.85

Values are n (%) unless otherwise defined. IQR indicates interquartile range; BCV, busalfan, cyclophosphamide, and etoposide; BEAM, caramustine, etoposide, cytarabine, and melphalan.
*History of same hematologic malignancy with relapsed disease.
†Chronic liver disease includes cirrhosis and chronic viral hepatitis.
‡Chronic lung disease includes chronic obstructive pulmonary disease, emphysema, asthma, and pulmonary fibrosis.

(26%) with acute kidney injury and 207 patients (64%) with mucositis.

There was a greater proportion of patients with multiple myeloma in the levofloxacin prophylaxis group (n = 121; 81%) compared with the baseline group that did not receive antibiotic prophylaxis (n = 126; 72%) ($P = .01$). Rates of relapsed or recurrent hematologic malignancy were similar between the levofloxacin and the baseline group, 22 (13%) and 15 (10%), respectively ($P = .46$). Compliance with CHG bathing was lower in the baseline group, with 140 patients (80%) receiving CHG on <50% of days, compared with 71 (47%) in the levofloxacin group ($P < .001$).

Primary Outcome

The incidence of CLABSI was 18.4% in the baseline group (32 episodes) and 6.0% in the levofloxacin group (9 episodes). MBI-CLABSI represented 67% of all CLABSIs in the baseline group and 56% in the intervention group. On bivariable analysis receipt of levofloxacin prophylaxis was associated with a significant reduction in the hazard of CLABSI (HR, .30; 95% CI, .14 to .62; $P < .001$) (Table 2). CLABSI-free survival from autologous SCT is shown in Figure 1. On multivariable analysis adjusting for age and underlying malignancy, receipt of levofloxacin significantly decreased the hazard of CLABSI with an adjusted HR of .33 (95% CI, .16 to .69; $P = .003$) (Table 2). On subanalysis, receipt of levofloxacin prophylaxis was associated with a significant reduction in MBI-CLABSI (HR, .24; 95% CI, .09 to .64; $P = .004$) but not non-MBI-CLABSI (HR, .42; 95% CI, .13-1.37; $P = .15$).

On intention-to-treat analysis an additional 8 patients were included who did not receive levofloxacin during the intervention period. Reasons for withholding levofloxacin prophylaxis included reported levofloxacin allergy (n = 2), prolonged QT interval at baseline (n = 2), history of tendon injury (n = 1), history of foot drop (n = 1), and ongoing treatment with broad-spectrum gram-negative antibiotics (n = 2). On intention-to-treat analysis, there was a similar reduction in hazard of CLABSI with levofloxacin on multivariable analysis, with an HR of .34 (95% CI, .17 to .70; $P = .003$).

Secondary Outcomes

Receipt of levofloxacin was associated with a significant reduction in neutropenic fever (OR, .23; 95% CI, .14 to .39; $P < .001$) and a trend toward a significant reduction in ICU transfer for sepsis (OR, .33; 95% CI, .09 to 1.234; $P = .10$) (Table 3). There was no significant association of levofloxacin prophylaxis with in-hospital mortality, hospital readmission, or *C. difficile* infection.

Of the primary and secondary BSIs, there were a total of 61 organisms identified among 50 infections in both groups; 33 (67%) were gram-negative organisms and 16 (33%) were gram-positive organisms in the baseline group compared with 4 (33%) and 8 (67%), respectively, in the levofloxacin group. Among gram-negative organisms, the susceptibility rate to levofloxacin was 94% in the baseline group compared with 0% in the levofloxacin group. In the baseline group most blood culture isolates were levofloxacin-susceptible *Klebsiella* species (35%), *Pseudomonas aeruginosa* (12%), and *Escherichia coli* (12%). In the levofloxacin prophylaxis group most isolates were levofloxacin-resistant or nonsusceptible organisms including *E. coli* (33%) and enterococci (25%).

Table 2
Survival Analysis for Time to Development of CLABSI in Patients Undergoing Autologous SCT

Variable	Bivariable HR (95% CI)	*P*	Multivariable HR (95% CI)	*P*
Levofloxacin prophylaxis	.30 (.14-.63)	<.001	.33 (.16-.69)	.003
Age	1.02 (.99-1.05)	.22	1.03 (1.00-1.06)	.05
Male sex	1.33 (.70-2.54)	.38		
Nonwhite race	.93 (.47-1.86)	.84		
Multiple myeloma	.42 (.23-.79)	.005	.36 (.19-.69)	.002
Recurrent disease*	1.65 (.73-3.73)	.22		
Neutropenia (days of ANC < 500 cells/mm^3)	1.18 (1.07-1.29)	<.001		
CHG compliance < 50% (documented from date of SCT to day 7)	1.99 (.95-4.17)	.06		
Chronic liver disease†	2.11 (.51-8.74)	.29		
Chronic lung disease‡	.42 (.06-3.12)	.39		
Chronic kidney disease	1.25 (.60-2.63)	.54		
Acute kidney disease	1.90 (1.01-3.56)	.04		
Coronary disease	1.56 (.66-3.71)	.31		
Congestive heart failure	.56 (.08-4.10)	.56		
Diabetes mellitus	.74 (.23-2.40)	.61		
Mucositis	1.22 (.63-2.36)	.55		

*History of same hematologic malignancy with relapsed disease.
†Chronic liver disease includes cirrhosis and chronic viral hepatitis.
‡Chronic lung disease includes chronic obstructive pulmonary disease (COPD), emphysema, asthma, and pulmonary fibrosis.

Mean total days of levofloxacin therapy was greater in the levofloxacin group versus the baseline group (mean 9.2 versus 0.9 days, respectively; $P < .001$). However, the levofloxacin group compared with the baseline group demonstrated significant reductions in the use of cefepime (mean 3.1 versus 4.7 days, respectively; $P < .001$) and piperacillin-tazobactam (mean 0.1 versus 0.8 days, respectively; $P = .001$) (Table 4). There was also a trend toward a decrease in the use of aminoglycosides (mean 0.2 versus 0.4 days, $P = .07$) and intravenous vancomycin (mean 1.1 versus 1.7 days, $P = .06$) in the levofloxacin prophylaxis group.

DISCUSSION

In this study we demonstrated that receipt of levofloxacin prophylaxis was associated with a significant reduction in the incidence of CLABSI in patients undergoing autologous SCT. Additionally, the use of levofloxacin resulted in a reduction in neutropenic fever and a trend toward reduced ICU transfers for sepsis, without an increase in rates of *C. difficile* infection. These findings suggest that the use of routine levofloxacin prophylaxis in autologous SCT patients may be beneficial in certain settings where rates of CLABSIs are particularly high. The results of our study are strengthened by a large sample size, use of a current cohort, and detailed collection of both patient characteristics and concomitant interventions (eg, CHG bathing) that may have impacted the risk of CLABSI.

CLABSIs are associated with significant morbidity and mortality in patients with hematologic malignancy [5]. Our study demonstrated a 67% reduction in hazard of CLABSI with receipt of levofloxacin prophylaxis. To our knowledge, our study is only the second to date to investigate the utility of antibiotic prophylaxis in patients undergoing autologous SCT and the first to include patients receiving autologous SCT for all malignancy diagnoses [9]. A previous study also found a reduction in BSIs with the use of levofloxacin prophylaxis (41.2% to 14.7%) but was restricted to autologous SCT patients with multiple myeloma and focused on a composite outcome of primary and secondary BSIs [9]. We were primarily

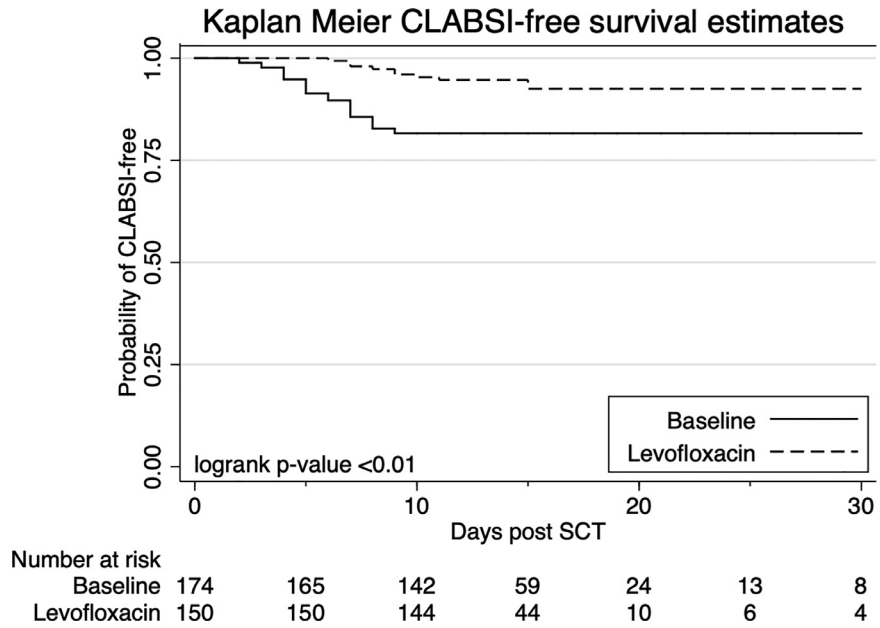

Figure 1. Kaplan-Meier CLABSI-free survival estimates comparing those who received levofloxacin prophylaxis with those who did not.

Table 3
Comparison of Secondary Outcomes between the Baseline Group and the Levofloxacin Prophylaxis Group in Patients Undergoing Autologous SCT

Outcome	Baseline Group (n = 174)	Levofloxacin Group (n = 150)	OR (95% CI)	*P*
Secondary BSI	7 (4)	2 (1)	.32 (.07-1.58)	.16
Neutropenic fever	143 (82)	78 (52)	.23 (.14-.39)	<.001
ICU transfer*	12 (7)	8 (5)	.76 (.30-1.91)	.56
ICU transfer for sepsis	10 (6)	3 (2)	.33 (.09-1.24)	.10
*C. difficile**	17 (10)	10 (7)	.66 (.29-1.49)	.32
Mortality*	2 (1)	2 (1)	1.16 (.16-8.35)	.88
Median length of stay (IQR)	14 (12-16)	14 (13-15)	.20 (−1.07 to 1.48)	.75
Readmission*	18 (10)	18 (12)	1.18 (.59-2.36)	.64

Values are n (%) unless otherwise defined.
*Within 30 days of stem cell transplant.

interested in the ability of antibiotic prophylaxis to prevent CLABSIs because of high rates in this population and prior studies demonstrating increased mortality with these infections [5,23,24]. We demonstrated that the greatest reduction in BSI with levofloxacin prophylaxis was the prevention of MBI-CLABSI. This distinction is important because it suggests that antibiotic prophylaxis, in concert with traditional methods to reduce CLABSI such as central line care and CHG bathing, may be a particularly beneficial strategy in institutions that provide care for oncology populations.

Our study also demonstrated a substantial reduction of 77% in the odds of neutropenic fever with the use of routine levofloxacin prophylaxis. Neutropenic fever results in prolonged lengths of stay and cost, with an average length of stay of 20 days and a cost of $38,000 per episode [25-27]. Thus, strategies for the prevention of neutropenic fever are important in this population independent of reductions in BSIs. Additionally, prior studies have demonstrated that episodes of neutropenic fever result in over 3 weeks of antibiotic use per patient [28]. Exposure to broad-spectrum antibiotics, including vancomycin and aminoglycosides, increase the risk of antibiotic resistance, *C. difficile*, and other antibiotic-associated adverse events (eg, renal failure) that could be potentially limited by use of prophylactic antibiotic therapy. Although levofloxacin use increased in our intervention, there was a corresponding reduction in the exposure to broad-spectrum antibiotic therapy and a trend toward decreased transfers to the ICU for neutropenic sepsis. Antibiotic stewardship programs will need to balance the potential benefits of levofloxacin prophylaxis with other factors such as local antibiotic resistance patterns and ongoing interventions that may restrict fluoroquinolone use.

In patients with hematologic malignancy, gut microbiome diversity has been associated with important clinical outcomes, including mortality [29]. Prior studies have shown a differential impact of antibiotic classes on microbiome measures and that the impact of fluoroquinolones is of shorter duration and less severity than beta-lactam antibiotics [30-34]. Thus, it possible that exposure to fluoroquinolone prophylaxis may result in less disruption of the gut microbiome if patients are spared subsequent broad-spectrum beta-lactam antibiotic exposure for neutropenic fever. Further studies are needed to investigate the impact of prophylactic antibiotics versus those administered for the treatment of neutropenic fever on the gut microbiome in this population.

The use of fluoroquinolones has previously been associated with an over 2-fold increased risk of *C. difficile* infection among hospitalized adult patients [35-37]. However, we found no increase in the rate of *C. difficile* among autologous SCT patients receiving levofloxacin prophylaxis. These results are similar to a previous study evaluating fluoroquinolone prophylaxis in multiple myeloma patients undergoing autologous SCT, where rates of *C. difficile* were 7% and 3% in the intervention versus baseline groups, respectively ($P = .75$) [9]. It is likely that our intervention did not result in an increase in *C. difficile* rates because of the reduction in broad-spectrum antibiotics used for neutropenic fever, which have also been implicated in *C. difficile* infection [38].

Not surprisingly, in our study we saw an overall shift in the proportion of levofloxacin-resistant gram-negative organisms isolated from blood cultures with receipt of levofloxacin prophylaxis. However, the absolute increase was small (2 isolates in the baseline group versus 4 in the levofloxacin group). This is similar to the prior study in this population where the investigators found an increase in the rate of BSIs due to levofloxacin-resistant Enterobacteriaceae from 1% to 5% with the introduction of levofloxacin prophylaxis [9]. These findings suggest a relatively low rate of levofloxacin-resistant BSIs in our population. However, rates of levofloxacin-resistant gram-negative organisms should be systematically monitored in institutions where levofloxacin prophylaxis is used. Future studies should also focus on rates of gastrointestinal colonization with fluoroquinolone-resistant Enterobacteriaceae with the introduction of fluoroquinolone prophylaxis.

There are potential limitations to our study. First, a retrospective study design was used, which can lead to greater misclassification of variables. However, we performed detailed medical record review of patient factors including comorbidities, medications, and laboratory results rather than using diagnostic or billing codes. Second, although the impact of antibiotic prophylaxis on rates of detection of *C. difficile* was assessed, we were unable to ascertain if positive *C. difficile* tests represented colonization or active infection, because approximately 65% of

Table 4
Antibiotic Use in Days of Therapy in Patients Undergoing Autologous SCT

Antibiotic	Baseline Group Mean (SD)	Levofloxacin Group Mean (SD)	*P*
Levofloxacin	.9 (2.2)	9.2 (2.9)	<.001
Cefepime	4.7 (3.9)	3.1 (3.6)	<.001
Meropenem	1.1 (2.9)	1.5 (2.9)	.22
Piperacillin-tazobactam	.8 (2.5)	.1 (.7)	.001
Aminoglycosides	.4 (1.3)	.2 (.8)	.07
Vancomycin, intravenous	1.7 (2.9)	1.1 (2.7)	.06

cases were associated only with a positive molecular assay for toxin gene and not with detectable *C. difficile* toxin in the stool specimen. However, colonization with toxigenic *C. difficile* remains a clinically important outcome because colonization with *C. difficile* increases the risk of infection and contributes to transmission in the hospital setting [18,39]. Third, although rates of fluoroquinolone resistance were tracked in bloodstream isolates, we did not perform patient screening for gastrointestinal colonization with fluoroquinolone-resistant gram-negative organisms. Fourth, although we were powered to detect a difference in our primary outcome, we may not have had sufficient power to detect a difference in our less common secondary outcomes, including ICU transfer for sepsis. Finally, this study was conducted in a tertiary care center and may not be generalizable to other centers performing autologous SCT that may have different patient characteristics, prevention practices, or risk of *C. difficile* infection.

In conclusion, we found that levofloxacin prophylaxis significantly reduced rates of CLABSI and neutropenic fever in patients undergoing autologous SCT. Further studies are needed to identify individual patient factors and patient groups at highest risk of MBI-CLABSI who would benefit most from antibiotic prophylaxis.

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REFERENCES

1. Magill SS, Edwards JR, Bamberg W, et al. Multistate point-prevalence survey of health care-associated infections. *N Engl J Med*. 2014;370:1198–1208.
2. O'Grady NP, Alexander M, Burns LA, et al. Guidelines for the prevention of intravascular catheter-related infections. *Clin Infect Dis*. 2011;52:e162–e193.
3. Blennow O, Mattsson J, Remberger M. Pre-engraftment blood stream infection is a risk factor for acute GVHD grades II-IV. *Bone Marrow Transplant*. 2013;48:1583–1584.
4. Kikuchi M, Akahoshi Y, Nakano H, et al. Risk factors for pre- and post-engraftment bloodstream infections after allogeneic hematopoietic stem cell transplantation. *Transpl Infect Dis*. 2015;17:56–65.
5. Lukenbill J, Rybicki L, Sekeres MA, et al. Defining incidence, risk factors, and impact on survival of central line-associated blood stream infections following hematopoietic cell transplantation in acute myeloid leukemia and myelodysplastic syndrome. *Biol Blood Marrow Transplant*. 2013;19:720–724.
6. Wang CH, Chang FY, Chao TY, et al. Characteristics comparisons of bacteremia in allogeneic and autologous hematopoietic stem cell-transplant recipients with levofloxacin prophylaxis and influence on resistant bacteria emergence. *J Microbiol Immunol Infect*. 2016;51(1):123–131.
7. Poutsiaka DD, Price LL, Ucuzian A, Chan GW, Miller KB, Snydman DR. Blood stream infection after hematopoietic stem cell transplantation is associated with increased mortality. *Bone Marrow Transplant*. 2007;40:63–70.
8. Poutsiaka DD, Munson D, Price LL, Chan GW, Snydman DR. Blood stream infection (BSI) and acute GVHD after hematopoietic SCT (HSCT) are associated. *Bone Marrow Transplant*. 2011;46:300–307.
9. Satlin MJ, Vardhana S, Soave R, et al. Impact of prophylactic levofloxacin on rates of bloodstream infection and fever in neutropenic patients with multiple myeloma undergoing autologous hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant*. 2015;21:1808–1814.
10. Tomblyn M, Chiller T, Einsele H, et al. Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective. *Biol Blood Marrow Transplant*. 2009;15:1143–1238.
11. CDC. National Healthcare Safety Network (NHSN) patient safety component manual. 2017. https://www.cdc.gov/nhsn/pdfs/validation/2017/pcsmanual_2017.pdf. Accessed 3 May 2018.
12. CDC. Bloodstream infection event (central line-associated bloodstream infection and non-central line-associated bloodstream infection). *Device-associated Module BSI*. 2017. https://nhsn.cdc.gov/nhsntraining/courses/2017/C03/. Accessed 3 May 2018.
13. Bucaneve G, Micozzi A, Menichetti F, et al. Levofloxacin to prevent bacterial infection in patients with cancer and neutropenia. *N Engl J Med*. 2005;353:977–987.
14. Cullen M, Steven N, Billingham L, et al. Antibacterial prophylaxis after chemotherapy for solid tumors and lymphomas. *N Engl J Med*. 2005;353:988–998.
15. Rashidi A, Wangjam T, Bhatt AS, Weisdorf DJ, Holtan SG. Antibiotic practice patterns in hematopoietic cell transplantation: a survey of blood and marrow transplant clinical trials network centers. *Am J Hematol*. 2018;93:E348–e350.
16. Hauck CG, Chong PP, Miller MB, et al. Increasing rates of fluoroquinolone resistance in Escherichia coli isolated from the blood and urine of patients with hematologic malignancies and stem cell transplant recipients. *Pathog Immun*. 2016;1:234–242.
17. Mikulska M, Del Bono V, Raiola AM, et al. Blood stream infections in allogeneic hematopoietic stem cell transplant recipients: reemergence of gram-negative rods and increasing antibiotic resistance. *Biol Blood Marrow Transplant*. 2009;15:47–53.
18. Bruminhent J, Wang ZX, Hu C, et al. *Clostridium difficile* colonization and disease in patients undergoing hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant*. 2014;20:1329–1334.
19. Baden LR, Swaminathan S, Angarone M, et al. Prevention and treatment of cancer-related infections, version 2.2016, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw*. 2016;14:882–913.
20. Flowers CR, Seidenfeld J, Bow EJ, et al. Antimicrobial prophylaxis and outpatient management of fever and neutropenia in adults treated for malignancy: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol*. 2013;31:794–810.
21. Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2011;52:e56–e93.
22. CLSI. Wayne, PA: Clinical and Laboratory Standards Institute; 2018.
23. Dandoy CE, Haslam D, Lane A, et al. Healthcare burden, risk factors, and outcomes of mucosal barrier injury laboratory-confirmed bloodstream infections after stem cell transplantation. *Biol Blood Marrow Transplant*. 2016;22:1671–1677.
24. Ziegler MJ, Pellegrini DC, Safdar N. Attributable mortality of central line associated bloodstream infection: systematic review and meta-analysis. *Infection*. 2015;43:29–36.
25. Hathorn JW, Rubin M, Pizzo PA. Empirical antibiotic therapy in the febrile neutropenic cancer patient: clinical efficacy and impact of monotherapy. *Antimicrob Agents Chemother*. 1987;31:971–977.
26. Kuderer NM, Dale DC, Crawford J, Cosler LE, Lyman GH. Mortality, morbidity, and cost associated with febrile neutropenia in adult cancer patients. *Cancer*. 2006;106:2258–2266.
27. Zuckermann J, Moreira LB, Stoll P, Moreira LM, Kuchenbecker RS, Polanczyk CA. Compliance with a critical pathway for the management of febrile neutropenia and impact on clinical outcomes. *Ann Hematol*. 2008;87:139–145.
28. Kroll AL, Corrigan PA, Patel S, Hawks KG. Evaluation of empiric antibiotic de-escalation in febrile neutropenia. *J Oncol Pharm Pract*. 2016;22:696–701.
29. Taur Y, Jenq RR, Perales MA, et al. The effects of intestinal tract bacterial diversity on mortality following allogeneic hematopoietic stem cell transplantation. *Blood*. 2014;124:1174–1182.
30. Abeles SR, Jones MB, Santiago-Rodriguez TM, et al. Microbial diversity in individuals and their household contacts following typical antibiotic courses. *Microbiome*. 2016;4:39.
31. Dethlefsen L, Relman DA. Incomplete recovery and individualized responses of the human distal gut microbiota to repeated antibiotic perturbation. *Proc Natl Acad Sci USA*. 2011;108(Suppl 1):4554–4561.
32. Falony G, Joossens M, Vieira-Silva S, et al. Population-level analysis of gut microbiome variation. *Science*. 2016;352:560–564.
33. Shono Y, Docampo MD, Peled JU, et al. Increased GVHD-related mortality with broad-spectrum antibiotic use after allogeneic hematopoietic stem cell transplantation in human patients and mice. *Sci Transl Med*. 2016;8:339–371.
34. Donskey CJ, Helfand MS, Pultz NJ, Rice LB. Effect of parenteral fluoroquinolone administration on persistence of vancomycin-resistant Enterococcus faecium in the mouse gastrointestinal tract. *Antimicrob Agents Chemother*. 2004;48:326–328.

35. Loo VG, Poirier L, Miller MA, et al. A predominantly clonal multi-institutional outbreak of Clostridium difficile-associated diarrhea with high morbidity and mortality. *N Engl J Med*. 2005;353:2442–2449.
36. Muto CA, Pokrywka M, Shutt K, et al. A large outbreak of *Clostridium difficile*-associated disease with an unexpected proportion of deaths and colectomies at a teaching hospital following increased fluoroquinolone use. *Infect Control Hosp Epidemiol*. 2005;26:273–280.
37. Pepin J, Saheb N, Coulombe MA, et al. Emergence of fluoroquinolones as the predominant risk factor for *Clostridium difficile*-associated diarrhea: a cohort study during an epidemic in Quebec. *Clin Infect Dis*. 2005;41:1254–1260.
38. McDonald LC, Gerding DN, Johnson S, et al. Clinical practice guidelines for *Clostridium difficile* infection in adults and children: 2017 update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). *Clin Infect Dis*. 2018;66:987–994.
39. Guerrero DM, Becker JC, Eckstein EC, et al. Asymptomatic carriage of toxigenic *Clostridium difficile* by hospitalized patients. *J Hosp Infect*. 2013;85:155–158.