

ORIGINAL ARTICLE

Early antimicrobial prophylaxis in autologous stem cell transplant recipients: Conventional versus an absolute neutrophil count-driven approach

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Abstract

Background: Autologous hematopoietic stem cell transplantation (HSCT) recipients are at increased risk of developing life-threatening infections. There is discordance in published recommendations for timing of pre- and post-transplant antimicrobial prophylaxis in this patient population, and these recommendations are unsubstantiated by any published comparative analyses.

Methods: An observational, pre- and post-intervention study of consecutive autologous HSCT recipients was conducted over a 2-year period. In the pre-intervention cohort, antimicrobial prophylaxis was initiated on the day prior to transplant. In the post-intervention cohort, antimicrobials were initiated once absolute neutrophil count (ANC) reached ≤ 500 cells/mm³. The primary outcome assessed was frequency of febrile occurrences. Secondary outcomes included total days of prophylaxis, positive blood cultures, all-cause mortality, *Clostridioides difficile* infection rates, and length of stay.

Results: A total of 208 patients were included in the final analysis, with 105 and 103 patients in the pre- and post-intervention cohorts, respectively. The majority of patients included were male. Lower rates of fever occurrences were observed in the post-intervention cohort (83% pre- vs. 69% post-intervention; $p = 0.019$). A significant reduction in the mean antibacterial days per patient was identified (9.7 vs. 4.6 days; $p < 0.001$). Other than lower rates of febrile neutropenia in the post-intervention cohort, no differences were identified in secondary outcomes. In multivariable analyses, ANC-driven prophylaxis was independently associated with decreased febrile events.

Conclusions: Delaying prophylaxis until severe neutropenia was not associated with increased febrile events or other secondary clinical outcomes evaluated. This approach is associated with a significant reduction in antimicrobial exposure.

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KEYWORDS

absolute neutrophil count, antimicrobial stewardship, hematopoietic stem cell transplant, prophylaxis

1 | INTRODUCTION

Infections are a significant post-transplant complication in hematopoietic stem cell transplant (HSCT) recipients.¹ Patients undergoing HSCT develop profound neutropenia following conditioning therapy and are at an increased risk for febrile neutropenia.² Infectious bacterial complications occur in over 70% of transplant patients and are associated with significant morbidity and mortality.²⁻⁶ Antibacterial prophylaxis has proven to be beneficial in reducing rates of febrile neutropenia and infection throughout the duration of neutropenia and may reduce mortality.⁷⁻¹¹ Additionally, randomized trials and large group analyses have supported antifungal prophylaxis with fluconazole demonstrating reduced invasive and superficial fungal infections, as well as candidiasis-related deaths.¹²⁻¹⁴

While the role of antimicrobial prophylaxis has been well-established, clinical data supporting the optimal timing for initiating these agents in HSCT patients are limited.¹⁵ The American Society of Blood and Marrow Transplantation guidelines recommend beginning antibacterial prophylaxis at the time of stem cell infusion.¹⁶ The American Society of Clinical Oncology (ASCO) guidelines recommend starting prophylactic antibacterial therapy during the period of neutropenia.¹⁷ Both guidelines are endorsed by the Infectious Diseases Society of America (IDSA).^{16,17} This discrepancy on timing of antimicrobial prophylaxis is of unique interest as neither guidance document cites literature to support this nuanced difference. Moreover, this discordance in recommendation is seen in clinical practice. A recent survey by the European Group for Blood and Marrow Transplantation identified that 57% of respondents begin fluoroquinolone (FQ) prophylaxis at the onset of conditioning as compared to 32% at the onset of neutropenia.¹⁸

Currently, literature is limited regarding optimal timing for initiation of antimicrobial prophylaxis in HSCT recipients. Patients are at greatest risk of infection when severely neutropenic which typically occurs several days following chemotherapy.¹⁹ Therefore, consistent with ASCO/IDSA recommendations, prophylaxis may be optimized if centered around the time of neutrophil nadir, rather than the time of stem cell infusion.

Alignment of antimicrobial prophylaxis initiation at the time of neutropenia may minimize unnecessary antimicrobial exposure. This difference in antimicrobial utilization can have profound benefits for HSCT patients and potentially influence antimicrobial resistance. Antimicrobial exposure is associated with an increased risk of multi-drug resistant organisms, *Clostridioides difficile* (*C. difficile*) infections, drug-drug interactions, toxicities, and dysbiosis.²⁰ Consequently, antimicrobial stewardship has implications for acute and long-term outcomes in HSCT recipients.

To the best of our knowledge, there have been no comparative studies evaluating the timing of antimicrobial prophylaxis initiation and

outcomes in autologous HSCT patients. The aim of this study was to determine whether initiating antimicrobials at the time of neutropenia instead of prior to stem cell infusion in autologous HSCT patients is safe and efficacious.

2 | METHODS

2.1 | Study design and setting

A retrospective chart review was conducted of all consecutive adult HSCT recipients transplanted between November 2016 and November 2018 at a 900+ bed tertiary hospital. The Institutional Review Board approved this evaluation. The change in antimicrobial prophylaxis timing was initiated in November 2017. The pre-intervention cohort was defined as patients receiving antimicrobial prophylaxis beginning day -1 before stem cell infusion (day 0) between November 1, 2016 through October 31, 2017, and the post-intervention cohort was defined as patients who received absolute neutrophil count (ANC)-driven antimicrobial prophylaxis, defined as initiation upon ANC of ≤ 500 cells/mm³, beginning December 1, 2017 through November 30, 2018.

2.2 | Patients

This investigation included patients admitted to an inpatient unit for autologous HSCT. Patients were excluded if they were less than 18 years of age at the time of transplant, received an allogeneic stem cell transplant, or had an ANC of ≤ 500 cells/mm³ prior stem cell infusion. Patients were also excluded if they had an active infection, fever, or received antibiotics prior to day -1 during hospital transplant admission. Lastly, patients were excluded if they deviated from the cohort's antimicrobial initiation approach.

2.3 | Antimicrobial prophylaxis

Patients received levofloxacin 500 mg and fluconazole 400 mg daily adjusted for renal function. Cefdinir or micafungin was the alternative option if the patient was intolerant to levofloxacin and/or fluconazole, respectively. All patients continued anti-herpes therapy beginning on day -1. Antibacterial prophylaxis was discontinued upon neutrophil engraftment, defined as ANC ≥ 500 cells/mm³ following nadir, or with the development of a febrile episode in which the febrile neutropenia treatment protocol described below was initiated. Antifungal prophylaxis was discontinued upon neutrophil recovery. Patients received granulocyte colony stimulating factor (G-CSF), tbo-filgrastim, daily beginning on day +7 and continued until their was ANC ≥ 500 cells/mm³.

2.4 | Febrile neutropenia treatment protocol

At time of first fever, defined as 38.0°C (oral) or above, a standardized protocol was initiated which included escalation to an anti-pseudomonal beta-lactam (cefepime, piperacillin-tazobactam, or meropenem), collection of two sets of blood cultures, a urine culture, serum lactic acid and procalcitonin labs, a chest X-ray, intravenous fluids in the setting of hypotension, and discontinuation of oral antibacterial prophylaxis. Anti-pseudomonal beta-lactams were continued through neutrophil engraftment, completion of treatment for an identified infection, or antibiotics were de-escalated after neutrophil engraftment.

2.5 | Outcomes

The primary outcome evaluated was febrile events, defined by a fever occurrence of $\geq 38.0^{\circ}\text{C}$, beginning day -1 through discharge from HSCT admission. This interval was selected to account for engraftment syndrome-associated fevers. Secondary outcomes were evaluated from day -1 through discharge and included rates of febrile neutropenia, *Clostridioides difficile* infection rates, in-hospital all-cause mortality, intensive care unit (ICU) admissions, bloodstream and invasive fungal infections, utilization of prophylaxis, and treatment with anti-pseudomonal beta-lactams. Length of stay was also evaluated as a secondary outcome and was defined as hospital admission from stem cell infusion, (day 0) through discharge.

A bloodstream infection event was defined as one or more positive blood cultures obtained during a febrile episode and determined to be a true pathogen versus contaminant by the transplant physician. Analyses further identified patients developing breakthrough infections resistant to the prophylactic agent, as these patients could theoretically develop bacteremia irrespective of timing of the antimicrobial prophylaxis. Antimicrobial susceptibilities were determined following Clinical and Laboratory Standards Institute standards and guidance.²¹

2.6 | Statistical analyses

The sample size calculation was based on the primary outcome of occurrence of febrile episodes. Previously published data suggest an outcome rate of 77% with prophylaxis with a fluoroquinolone.²² Using an effect size of 20%, α value of 0.05, it was determined *a priori* that a sample size of 98 patients was needed in each intervention group to achieve 80% power.

A chi-square or Fisher's exact test was used to compare the primary outcome of febrile episodes and for other categorical data, including demographic characteristics and outcomes. Student's *t*-tests were used for normally distributed continuous data, and Wilcoxon-rank sum tests were used for non-normally distributed continuous data. A multivariable logistic regression analysis for the primary outcome of occurrence of febrile episodes was conducted. Age, hematopoietic cell transplantation-specific comorbidity index (HCT-CI), intervention group, days of neutropenia, and variables in the univariate analyses

with a *p*-value < 0.1 were entered into the model (Table S1).²³ To assess association of intervention groups, hazard ratios (HRs) were calculated with 95% confidence intervals (CIs) using Cox-proportional hazards model and adjusted for HCT-CI, conditioning regimen, and days of neutropenia. SPSS 24.0 (IBM Corp, Armonk, NY, USA) was used for all statistical analyses. Statistical significance was calculated using a *p*-value of < 0.05 .

3 | RESULTS

Of the 351 transplanted patients, a total of 208 patients were included in the final analysis (Figure 1). One hundred ten patients were excluded as they had undergone allogeneic HSCT, and 33 additional patients were excluded due to deviation from intervention period protocol or incomplete data.

Of the 208 autologous transplant recipients, 105 were in the pre-intervention cohort and 103 in the post-intervention cohort. The majority of patients were male (61%) with a mean age of 54 years. The primary indication for transplant was plasma cell disorders, followed by non-Hodgkin lymphoma. No statistically significant differences were identified in baseline characteristics between cohorts (Table 1).

A significant difference was observed in rates of febrile episodes between the pre- and post-intervention cohorts (83% vs. 69%, respectively; *p* = 0.019). Three patients in both the pre- and post-intervention cohorts developed fever prior to neutropenia (2.8% vs. 2.9%). Additionally, rates of febrile neutropenia were also higher in the pre-intervention group (*p* = 0.032; Table 2). Characteristics of those with febrile episodes and no febrile episodes are described in Table S1. In multivariable analysis, treatment during the pre-intervention period was independently associated with febrile events (aOR 2.71, 95% CI, 1.36–5.59; Table 3).

Time to first febrile event was shorter in the post-intervention than pre-intervention cohort. However, the intervention group was not a significant predictor in the Cox-proportional hazard model (Figure 2). Duration of G-CSF use from stem cell infusion did not show a statistically significant difference between cohort groups.

Regarding secondary outcomes, rates of bloodstream infections did not differ between groups (pre-intervention 8.6% vs. 14.5% post-intervention; *p* = 0.493). No patients in either group developed invasive fungal infection. Only one patient developed *E. coli* bacteremia prior to initiation of prophylaxis, which occurred in the post-intervention cohort. Moreover, the rates of ICU admissions, hospital length of stay, or in-hospital-all-cause mortality also did not differ (Table 2). Three deaths occurred during the hospital admission; in the pre-intervention cohort, one patient died of cardiac arrhythmia and the other due to pan-resistant *Pseudomonas* bacteremia. One patient in the post-intervention cohort died of influenza A pneumonia.

3.1 | Antimicrobial utilization

The utilization of antimicrobials, both prophylactic and treatment, was evaluated between the pre- and post-intervention cohorts (Table S2). Across all transplant patients evaluated, significant differences were

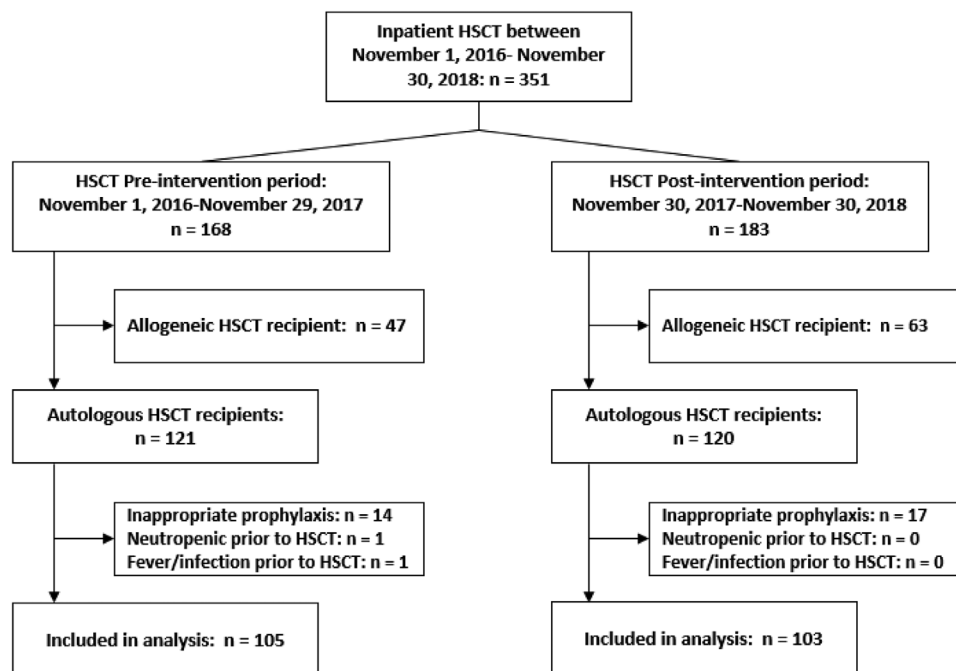


FIGURE 1 Flow chart of study population

TABLE 1 HSCT patient characteristics

Variable	Pre-intervention n = 105	Post-intervention n = 103	p-Value ^{a,b}
Age; median (IQR)	58 (17)	56 (25)	0.430
Sex, male; n (%)	60 (57)	67 (65)	0.242
White race; n (%)	95 (90)	95 (92)	0.384
HCT-CI; median (IQR)	2 (3)	3 (4)	0.397
Pre-transplant diagnosis; n (%)			
Hodgkin lymphoma	15 (14)	12 (12)	0.572
Non-Hodgkin lymphoma	25 (24)	28 (27)	0.577
Germ cell tumor	3 (3)	7 (7)	0.212
Plasma cell disorders	62 (59)	56 (54)	0.496
Conditioning regimen; n (%)			
Myeloablative	100 (95)	101 (98)	0.259
Reduced-intensity/Non-myeloablative	5 (5)	2 (2)	0.445
History of multi-drug resistant organism; n (%)	2 (2)	0	0.498
Days of ANC ≤ 500; median (IQR)	7 (2)	7 (2)	0.194
Number of GCSF doses per patient; median (IQR)	5 (1)	4 (1)	0.140

Abbreviations: ANC, absolute neutrophil count; GCSF, granulocyte-colony stimulating factor; HCT-CI, hematopoietic cell transplantation-specific comorbidity index.²³

^an (%) calculated using Fisher's exact test.

^bMedians, interquartile range (IQR) (displayed as difference between Q3 and Q1); calculated using Wilcoxon rank sum.

seen in utilization of prophylactic antibacterials and antifungals (Figure 3). Total antibacterial prophylactic days of therapy were 1021 and 439 in the pre- and post-intervention cohorts, respectively. This accounted for a difference of 9.7 versus 4.6 days of antibiotic prophylaxis per patient ($p < 0.001$). Antifungal prophylactic days of therapy

also differed with a total of 1303 versus 679 antifungal days, which was associated with 12.4 versus 6.6 days per patient when comparing cohorts ($p < 0.001$). Total anti-pseudomonal beta-lactam days of therapy did not differ significantly with 521 and 461 days of therapy in the respective pre- and post-intervention groups, which was

TABLE 2 HSCT clinical outcomes

Outcome	Pre-intervention n = 105	Post-intervention n = 103	p-Value ^{a,b}
Febrile event; n (%)	87 (83)	71 (69)	0.019
Fever and ANC ≤ 500; n (%)	85 (81)	70 (68)	0.032
Interval between transplant and fever; median (IQR)	7 (4)	6 (4)	0.034
<i>C. difficile</i> infection; n (%)	5 (4.8)	10 (9.7)	0.168
In-hospital-all-cause mortality; n (%)	2 (2)	1 (1)	0.572 ^a
Length of stay; median (IQR)	16 (3)	16 (4)	0.760
ICU admission; n (%)	4 (4)	7 (7)	0.371 ^a
Bloodstream infection, n (%) ^{c,d}	9 (8.6)	15 (14.5)	0.493
Number of positive cultures per person; median (IQR)	2 (1)	1 (1)	0.300
Bloodstream infection with FQ-resistant organism, n (%) ^d	4 (3.8)	6 (5.8)	0.277
Bloodstream infection with ceftriaxone-resistant organism, n (%) ^d	0	2 (1.9)	0.349

Abbreviations: ANC, absolute neutrophil count; *C. difficile*, *Clostridioides difficile*; FQ, fluoroquinolone; ICU, intensive care unit.

^an (%) calculated using Fisher's exact test.

^bMedians, interquartile range (IQR) (displayed as difference between Q3 and Q1); calculated using Wilcoxon rank sum.

^cNo fungal organisms were identified. Pathogens identified by blood culture can be found in Table S3.

^dSusceptibility testing was conducted according to institutional clinical microbiological protocols.

TABLE 3 Multivariable analysis for febrile events

	Adjusted odds ratio (95% Confidence Interval) ^a	p-Value ^a
Pre-intervention ^b	2.71 (1.36–5.59)	0.005
HCT-CI	1.00 (0.84–1.20)	0.999
Non-Hodgkin lymphoma ^c	4.81 (1.03–22.47)	0.046
Plasma cell disorders ^c	0.73 (0.22–2.47)	0.611
Days of neutropenia	1.00 (0.97–1.04) ^d	0.819
Age	0.97 (0.94–1.01)	0.101

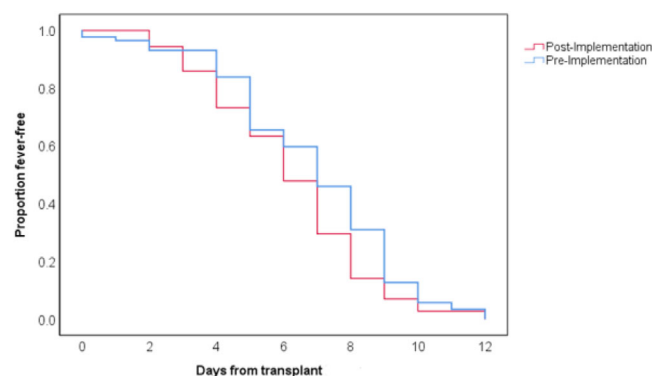
Abbreviation: HCT CI, hematopoietic cell transplantation-specific comorbidity index.²³

^aCalculated using logistic regression.

^bReference: Post-intervention.

^cReference: Hodgkin lymphoma.

^dOdds ratio for 1-day increase.

**FIGURE 2** Febrile events over time in HSCT recipients who febriled

associated with a non-statistically significant difference in therapy days per patient (5.0 vs. 4.5 days; $p = 0.365$).

4 | DISCUSSION

This study was the first of its kind to evaluate timing of prophylactic antimicrobial initiation in autologous HSCT recipients. Our data support an ANC-driven approach to antimicrobial initiation and discontinuation, which appears to be safe and at least equally effective in preventing febrile events in this at-risk population.

A large reduction in antimicrobial utilization was demonstrated using the ANC-driven approach. Roughly 5 days of both prophylactic antibacterial and antifungal therapy per patient were saved, accounting for a significant overall reduction in total days of antimicrobial exposure. This practice is associated with a relatively higher reduction in antimicrobial utilization compared to other stewardship approaches.^{24–27}

Interestingly, we saw fewer events of neutropenic fever when antimicrobial prophylaxis was delayed until neutropenia; these rates are consistent with what has previously been reported in the literature.²⁸ This finding was further validated in the multivariable analysis. Although the direct cause for reduced febrile events cannot be fully explained, this finding supports the safety of reducing antimicrobials. To our knowledge, there is sparse literature to suggest drug-induced fever caused by levofloxacin and/or fluconazole. Furthermore, these rates of FN are consistent with previously reported rates in the literature.²

An appreciable difference in anti-pseudomonal beta-lactam use between the pre- and post-implementation was not seen. Given that the use of these broad-spectrum agents serves as a surrogate for fever

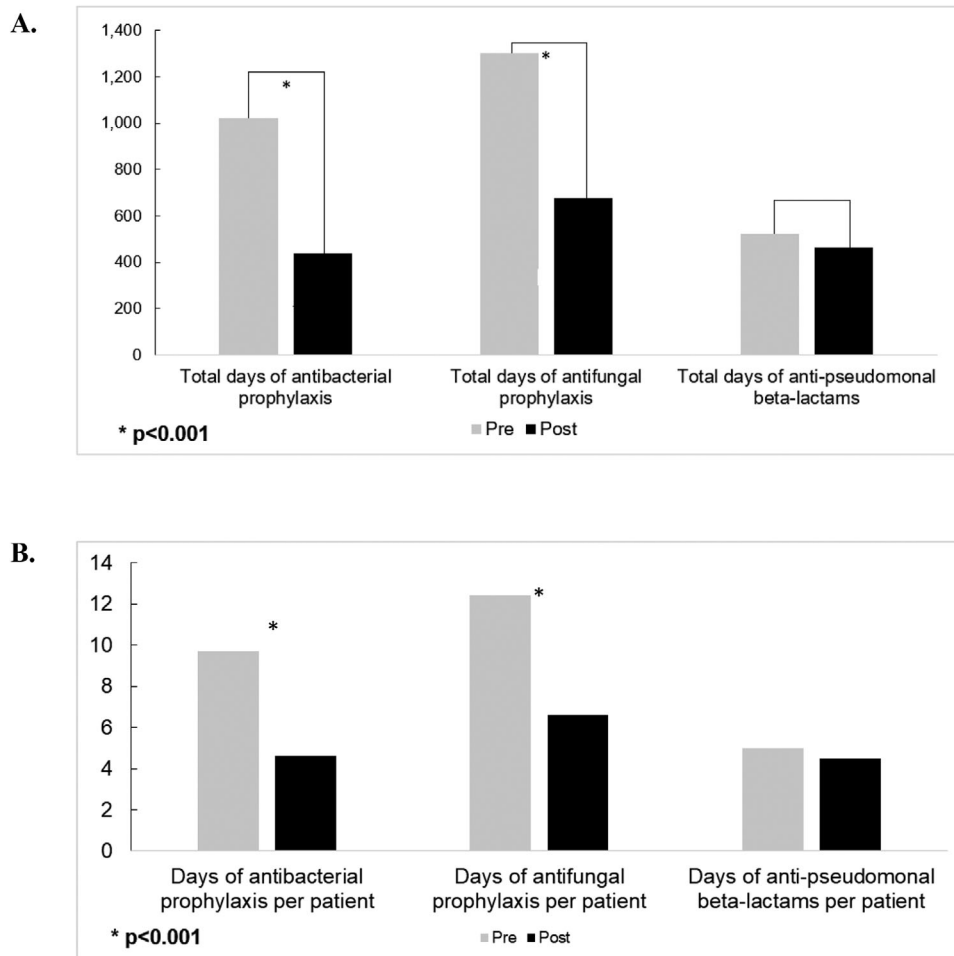


FIGURE 3 Antimicrobial utilization

and infection, this finding reinforces the safety and efficacy of this novel approach to prophylaxis.

Although the use of prophylactic antibacterial therapies has been shown to decrease gram-negative bacteremia, infection-related outcomes, and mortality, overutilization and unwarranted use of antimicrobials can be associated with adverse events in HSCT recipients.^{7–11} The well-established toxicities of FQs should be appreciated, along with the decreased susceptibilities of gram-negative pathogens to this drug class.²⁸ Our study showed a 53% reduction in combined antibacterial and antifungal therapies without adversely impacting clinical outcomes.

With the incorporation of nearly universal FQ prophylaxis in HSCT patients, resistance continues to be a major concern.²⁹ Overexposure to FQs does not only lead to FQ resistance, but it has been shown that FQ prophylaxis was an independent predictor for bacteremia with breakthrough meropenem-non-susceptible *Pseudomonas aeruginosa* isolates in this patient population.³⁰

This study did not show a difference in rates of *Clostridioides difficile*. Of note, testing methodology at our facility did not change during the period of this analysis. Given antibiotic exposure is not the only risk

factor for *Clostridioides difficile* in HSCT patients, the abundance of data surrounding the reduction of FQ use and the impact on *Clostridioides difficile* rates in other larger scale studies must be acknowledged.³¹ These rates of *Clostridioides difficile* are consistent with previously reported literature, but we hypothesize that larger sample sizes may have showed an appreciable difference in *Clostridioides difficile* infections.^{32,33}

This study is not without limitations as it is a single center, retrospective, non-randomized, and unblinded investigation. As with pre- and post-intervention analyses, undetected confounding factors impacting outcomes could have been introduced. Because interpretation of cultures from non-sterile sites (i.e., sputum, urine, skin) can be variable, our definition of infection only included positive blood cultures. It is possible that other microbiologically significant infections were not identified with this focus, although our primary outcome of fever may have captured these patients. Our analysis serves as a foundation to a better understanding of where antimicrobial stewardship in HSCT impacts patient outcomes and may stimulate further investigations, including in the allogeneic HSCT population where the intricate synergism of the gut microbiota and risk for graft-versus-host disease is of particular interest.^{34–36}

5 | CONCLUSION

Utilizing an ANC-driven approach to guide antimicrobial prophylaxis initiation appears to be feasible and safe in this highly immunocompromised population. This approach is associated with a reduction in antimicrobial exposure. These results support ASCO guideline recommendations for initiation of antimicrobials upon neutropenia and suggest opportunity in reducing unnecessary antimicrobial exposure, which may have numerous deleterious downstream effects in HSCT patients.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Concept design: Justin G. Horowitz, Gerard W. Gawrys, Grace C. Lee, Brittney A. Ramirez, Carole M. Elledge, and Paul J. Shaughnessy. Data collection: Justin G. Horowitz, Gerard W. Gawrys, and Brittney A. Ramirez. Data analysis: Justin G. Horowitz, Gerard W. Gawrys, Grace C. Lee, Brittney A. Ramirez, and Paul J. Shaughnessy. Data interpretation: Justin G. Horowitz and Gerard W. Gawrys. Manuscript drafting: Justin G. Horowitz, Gerard W. Gawrys, Grace C. Lee, Brittney A. Ramirez, and Carole M. Elledge. Revisions and manuscript approval: Justin G. Horowitz, Gerard W. Gawrys, Grace C. Lee, Carole M. Elledge, Paul J. Shaughnessy, and Brittney A. Ramirez. Statistical analysis: Grace C. Lee.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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