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MAJOR ARTICLE

Preneutropenic Fever in Patients With Hematological Malignancies: A Novel Target for Antimicrobial Stewardship

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Background. Many patients with hematological malignancy develop fever after chemotherapy/conditioning but before chemotherapy-induced neutropenia (preneutropenic fever [PNF]). The proportion of PNF with an infectious etiology is not well established.

Methods. We conducted a single-center, prospective observational substudy of PNF (neutrophils >0.5 cells/μL, ≥38.0°C) in adults receiving acute myeloid leukemia (AML) chemotherapy, or allogeneic hematopoietic cell transplant (allo-HCT) conditioning enrolled in a neutropenic fever randomized controlled trial between 1 January and 31 October 2018. Eligible patients had anticipated neutropenia ≥10 days and exclusions included concurrent infection and/or neutropenia prior to chemotherapy or conditioning. PNF rates and infections encountered were described. Associations between noninfectious etiologies and fever were explored. Antimicrobial therapy prescription across preneutropenic and neutropenic periods was examined.

Results. Of 62 consecutive patients included (43 allo-HCT, 19 AML), 27 had PNF (44%) and 5 (19%) had an infective cause. Among allo-HCT, PNF occurred in 14 of 17 (82%) who received thymoglobulin; only 1 of 14 (7%) had infection. During AML chemotherapy, 18 of 19 received cytarabine, of which 8 of 18 (44%) had PNF and 3 of 8 (38%) had infection. Most patients with PNF had antimicrobial therapy continued into the neutropenic period (19/27 [70%]). Those with PNF were more likely to be escalated to broader antimicrobial therapy at onset/during neutropenic fever (5/24 [21%] vs 2/30 [7%]).

Conclusions. Rates of PNF were high, and documented infection low, leading to prolonged and escalating antimicrobial therapy. In the absence of infection, early cessation of empiric therapy after PNF is recommended as an important stewardship intervention.

Keywords. antimicrobial stewardship; bone marrow transplantation; chemotherapy; fever; infection.

Neutropenic fever is considered one of the oncological emergencies, with mortality rates in high-risk neutropenic fever (absolute neutrophil count [ANC] <0.1 cells/μL for >7 days) between 10% and 12% [1, 2]. However, little is known about the etiologies and outcomes of fever that develops *before* the onset of chemotherapy-induced neutropenia in these high-risk patients, henceforth referred to as "preneutropenic fever" (PNF). Fever due to infection must be excluded, as sepsis is associated with high rates of morbidity and mortality in cancer and transplant, even in the absence of neutropenia [3]. However, sepsis is not the only cause of fever in the preneutropenic setting, and prolonged antimicrobial treatment of noninfectious fever may be a target for antimicrobial stewardship (AMS) intervention.

Reports on the etiology of PNF in patients with hematological malignancies are few. Studies have reported that 5%–27% of nonneutropenic fevers were associated with bacteremia [4, 5] and 59%–64% of fevers were thought to have a noninfectious etiology [6, 7]. However, these reports generally included patients *after* neutrophil recovery in their definition of "nonneutropenic" and do not look specifically at fever in the *pre*-neutropenic setting. The hematological malignancy itself may be responsible for PNF [8], and patients with hematological malignancies frequently receive treatments with high fever-

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producing potential such as cytarabine chemotherapy for acute myeloid leukemia (AML), and antithymocyte globulin in allogeneic hematopoietic cell transplant (allo-HCT) [9, 10]. Similarly, recipients of haploidentical hematopoietic cell transplant (haplo-HCT) experience very high rates of fever shortly after cell infusion likely related to human leukocyte antigen mismatch, which is usually in the preneutropenic period [11, 12]. Therefore, it is quite likely that many patients with PNF have noninfectious fever.

In the setting of PNF, clinicians must balance the importance of adequate and urgent management of potential sepsis in high-risk patients with that of the consequences of excessive antimicrobial exposure. Increasing rates of antimicrobial resistance, particularly among patients with substantial and repeated exposure to antimicrobials and healthcare facilities, is associated with increased mortality and morbidity [13]. Furthermore, there are increasing concerns about the impact of empiric antimicrobials on the gut microbiome and its downstream consequences [14, 15]. Rigorous, up-to-date evidence outlining the likelihood of infectious etiology in PNF and causative organisms is essential to ensuring appropriate management in these high-risk patients.

We conducted a single-center prospective cohort study to determine the incidence of PNF among patients with acute leukemia or receiving allo-HCT, to explore the clinical entity of PNF and its impact on antimicrobial management in the preneutropenic and subsequent neutropenic periods.

METHODS

Setting

This is a substudy of the Prospective Investigation of PET/CT and PCR In high risk febrile Neutropenia (PIPPIN) study [16] of patients enrolled at the Royal Melbourne Hospital (RMH). The RMH is a tertiary referral hospital in Melbourne, Australia, with a dedicated acute leukemia and allo-HCT service, performing approximately 100 allo-HCTs and treating approximately 100 new acute leukemia patients annually.

Participants

The PIPPIN study was a prospective, multicenter, randomized trial of fluorodeoxyglucose-positron emission tomography combined with computed tomography versus conventional computed tomography for the investigation of persistent or recurrent neutropenic fever in high-risk patients with expected duration of neutropenia of at least 10 days [16]. Participants of the PIPPIN study were consented and enrolled prior to chemotherapy or conditioning commencement and observed for development of fever during the course of their treatment. Exclusion criteria for the PIPPIN study included severe renal impairment (estimated glomerular filtration rate <30 mL/minute), allergy to iodinated contrast media, pregnancy/lactation, and those with current infection on treatment. For the purposes of this substudy, patients admitted to the RMH for conventional induction, reinduction, and consolidation chemotherapy for AML or allo-HCT conditioning and enrolled in the PIPPIN study between 1 January 2018 and 31 October 2018 were included, irrespective of whether they eventually developed persistent or recurrent fever and were randomized (Figure 1). Other PIPPIN-enrolled participants who were admitted to other centers or receiving autologous transplant or acute lymphoblastic leukemia chemotherapy were excluded, as were patients who were neutropenic on admission, as they did not have a documented preneutropenic period. Data were prospectively collected on all participants for treatment administered, fever development, infections encountered, and antibiotic use from index admission until hospital discharge. For AML chemotherapy recipients, the first instance of chemotherapy within the study period per patient was included.

Patient Care and Prophylaxis

Haploidentical transplants were performed using posttransplant cyclophosphamide and these patients did not receive thymoglobulin. Patients were cared for as inpatients throughout the preneutropenic and neutropenic period in the dedicated hematology ward, which constitutes positively pressured, high-efficiency particulate absorbing–filtered single rooms only. Patients were prescribed mold-active antifungal prophylaxis (posaconazole) on chemotherapy commencement or on admission for allo-HCT and continued throughout the neutropenic period. Valacyclovir/acyclovir was prescribed on admission and throughout the neutropenic period for prophylaxis against herpesviruses in patients with positive serology for herpes simplex virus, varicella zoster virus, or both. Those who were prescribed FLAG chemotherapy (fludarabine, cytarabine, filgrastim) for AML received trimethoprim-sulfamethoxazole prophylaxis, beginning at the time of chemotherapy commencement and continuing throughout the neutropenic period. No fluoroquinolone prophylaxis was prescribed.

Data Collection

Data were extracted for demographics, Charlson Comorbidity Index [17], hospitalization in the preceding 30 days, primary diagnosis, antimicrobial prophylaxis during the index chemotherapy cycle or preengraftment, history of prior HCT, admission indication (chemotherapy for AML, or allo-HCT), chemotherapy protocol, HCT conditioning protocol, and date and time of cytarabine or thymoglobulin administration. Data related to the patients' clinical course during admission were collected, including presence/absence of fever before chemotherapy/conditioning receipt, presence/absence and date of onset of PNF, presence/absence of neutropenic fever, presence/absence of infection (based on chart review for clinically defined infections [CDIs] and culture results for microbiologically

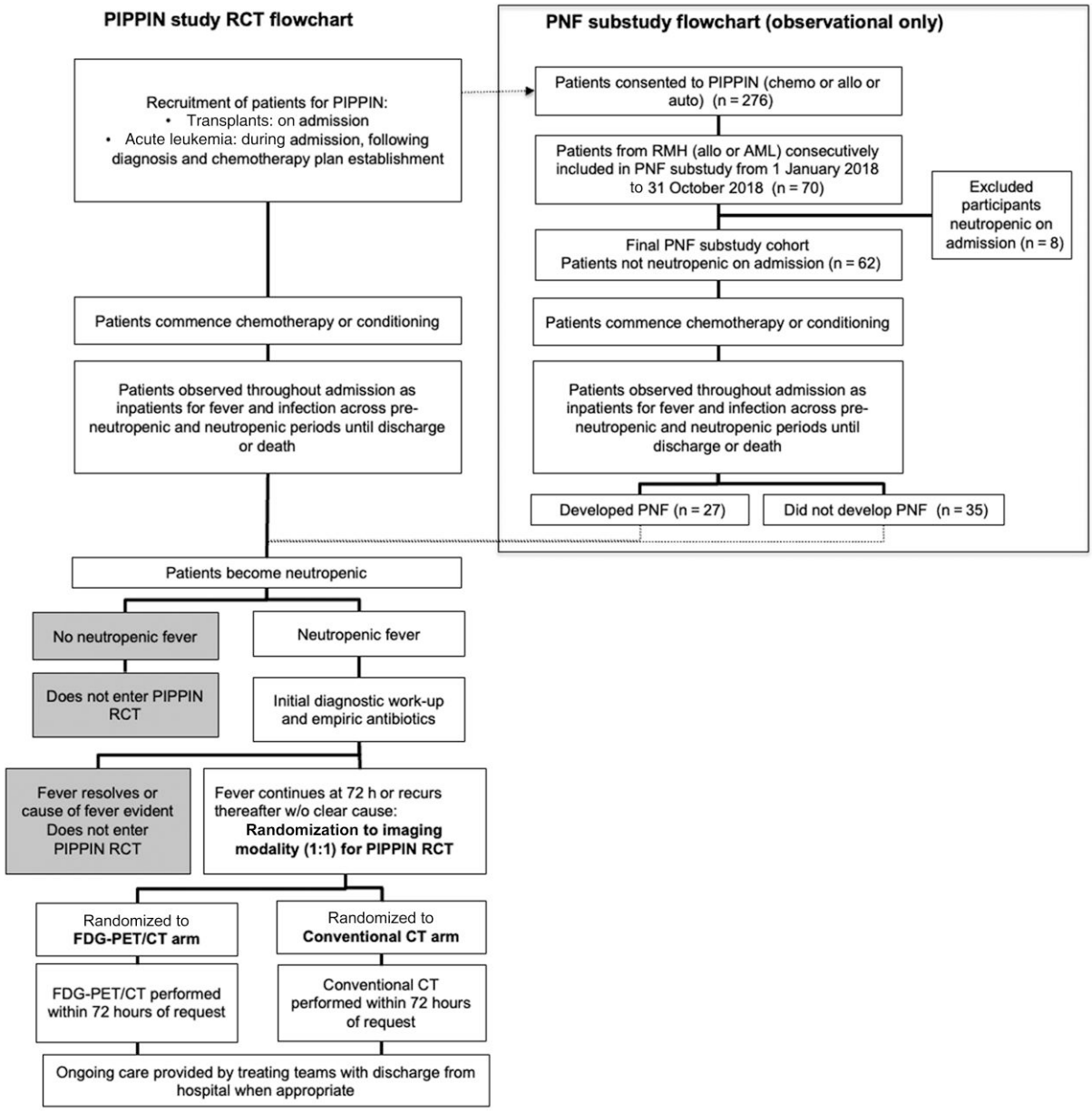

Figure 1. Flowchart of preneutropenic fever substudy inclusion as part of PIPPIN cohort. Abbreviations: allo, allogeneic hematopoietic cell transplant conditioning, AML, acute myeloid leukemia chemotherapy; auto, autologous hematopoietic cell transplant conditioning; CT, computed tomography; FDG-PET/CT, fluorodeoxyglucose-positron emission tomography combined with computed tomography; PIPPIN, Prospective Investigation of PET/CT and PCR In high risk febrile Neutropenia study; PNF, preneutropenic fever; RCT, randomized controlled trial; RMH, Royal Melbourne Hospital.

defined infections [MDIs]), type of infection, and type and duration of antibiotics started for empiric management of PNF and neutropenic fever.

Definitions

Fever was defined as a tympanic temperature of ≥38.0°C. Temperature assessments were performed routinely every 4 hours during admission. If a patient had a documented fever and met 2 or more systemic inflammatory response syndrome parameters, temperature assessment frequency was increased to half-hourly for 2 hours, and then hourly for the following 4 hours. Fevers experienced from the first day of chemotherapy/conditioning (inclusive) until the day before the patient's ANC reached <0.5 cells/μL were classified as PNF. Fevers experienced from the first day of neutropenia (ANC <0.5 cells/μL) and before ANC returned to ≥0.5 cells/μL were classified as neutropenic fever. Fevers were further classified according to the presence or absence of infectious etiology based on chart and

microbiology review by an infectious diseases physician [18], taking into account all medical and nursing notes and pathology and radiological data in the patient's medical record. Fevers with an infectious etiology were subclassified into MDI if a causative microorganism was identified in the patient's laboratory samples and confirmed as clinically significant in the progress notes by the treating team. Two sets of positive blood cultures for coagulase-negative staphylococci were required to be considered a true bloodstream infection. Infections were classified as CDI if the patient had compatible signs/symptoms with or without associated imaging findings, but no compatible causative pathogen identified, with cross-referencing from the patient's progress notes. Fevers were classified as "noninfectious" if no CDI or MDI was found. Due to low numbers of infection overall, CDI and MDI were combined into the variable "infection" for the purposes of analysis.

Patient Consent Statement

Ethics approval was granted by the Melbourne Health Human Research Ethics Committee, approval number HREC/17/MH/106. All patients provided written informed consent to participate in this study.

Data Analysis

Summary statistics were presented as mean and standard deviation or median and range for normally and nonnormally distributed continuous data, respectively, and percentages for categorical data. Outcomes were compared using the χ^2 and Fisher exact test for categorical variables as appropriate, and *t* test and Mann-Whitney *U* test were used for continuous variables of normal and skewed distribution, respectively. The receipt of cytarabine, thymoglobulin, or haplo-HCT were prespecified risk factors for preneutropenic fever, and these were analyzed both separately and in a composite variable of "risk factor for PNF." Univariate and multivariate logistic regression analysis was performed to test the association between potential risk factors and PNF and preneutropenic infection. A *P* value of <.05 was considered statistically significant. All analyses were performed with Stata version 15.1 software (StataCorp, College Station, Texas).

RESULTS

Of 70 patients meeting inclusion criteria, 8 had neutropenia prior to the commencement of chemotherapy/conditioning and were excluded from full analysis, leaving 62 remaining patients (Figure 1).

PNF: Demographic and Treatment Correlates

Demographic and clinical characteristics of the 62 patients with and without PNF are shown in Table 1. Of these 62 patients, 27 patients (44%) experienced PNF (Table 1). The median age of all patients was 57.5 years (range, 27–73 years), and neither age nor sex differed significantly between patients with and without PNF. Eight patients (8/19 [42%]) who received AML chemotherapy and 19 (19/43 [44%]) of those with allo-HCT experienced PNF (Table 1, Figure 2*A*). Matched unrelated donor recipients were significantly more likely to experience PNF than those receiving a sibling allograft (13/20 [65%] vs 2/18 [11%], respectively; $P < .01$). There was no statistically significant difference in the rates of PNF between the chemotherapy and allo-HCT groups (42% vs 44%, $P = .88$).

PNF and Infection

Overall, 5 patients experienced confirmed infection in the setting of PNF, with 1 each of methicillin-sensitive *Staphylococcus aureus* bacteremia, nontyphoidal *Salmonella* bacteremia, rhinovirus upper respiratory tract infection (URTI), and 2 clinically diagnosed infections: lobar pneumonia and cellulitis. The overall rate of infection was significantly higher among patients with PNF compared to without (5/27 vs 0/35, $P = .01$); however, the majority of patients with PNF did not have infection (82%). Table 2 demonstrates rates of infection-associated PNF stratified by admission indication. There was a nonsignificant trend toward increased infection-associated PNF in those admitted for AML chemotherapy, compared to allo-HCT. Univariate logistic regression analysis found no association between patient demographics and an infective cause of PNF (Supplementary Table 1). The low rate of infection overall limited the utility of multivariate logistic regression analysis (Supplementary Table 1).

PNF and Infection in Patients With Predetermined Risk Factors

Fourteen of 17 patients who received thymoglobulin experienced PNF (82%) compared to 19% of allo-HCT patients who did not ($P < .01$; Table 3, Figure 2*B*). One patient with PNF who received thymoglobulin had infection (7%). There was no association between PNF and infection in patients receiving thymoglobulin ($P = .42$) (Table 2). Of those receiving haplo-HCT, 4 of 5 (80%) experienced PNF (Table 1, Figure 2*B*), and there were no recorded infections in this group. Of 18 patients who received cytarabine, 8 (44%) experienced PNF, 3 (38%) of whom had infection (Table 2, Figure 2*B*).

In patients who received thymoglobulin or cytarabine or who had haplo-HCT (ie, an *a priori* noninfective fever "risk factor"), 26 of 40 (65%) developed PNF compared with 1 of 22 (5%) of patients who did not ($P < .01$, Table 3). In those with PNF with a risk factor, only 4 of 26 (15%) had a confirmed infection (Table 2). Conversely, only 1 of 22 patients without a risk factor had PNF; however, this episode was associated with an infection. All infections were identified clinically or microbiologically within 48 hours of fever onset.

Table 1. Demographics and Clinical Features of Study Patients With and Without Preneutropenic Fever

Characteristic	PNF (n = 27)	No PNF (n = 35)	Total (n = 62)	*P* Value
Age, y, median (range)	58 (27–73)	57 (27–72)	57.5 (27–73)	.50[a]
Male sex	19 (70)	17 (49)	36 (58)	.09
Age-adjusted Charlson score, median (range)	3 (0–8)	4 (2–6)	3 (0–7)	.96
PJP prophylaxis				
Cotrimoxazole	1 (4)	2 (6)	3 (5)	
Viral prophylaxis				
Valacyclovir	27 (100)	34 (97)	61 (98)	
Valganciclovir	0 (0)	1 (3)	1 (2)	
Fungal prophylaxis				
Posaconazole	27 (100)	32 (91)	59 (95)	
Amphotericin B	0 (0)	2 (6)	2 (3)	
Fluconazole	0 (0)	1 (3)	1 (2)	
Admission indication				
Chemotherapy for AML	8 (30)	11 (31)	19 (31)	.88
Allo-HCT	19 (70)	24 (69)	43 (69)	
Allo-HCT type (n = 43)	n = 19	n = 24		
Sibling allograft	2 (11)	16 (67)	18 (42)	<.01
Matched unrelated	13 (68)	7 (29)	20 (46)	
Haploidentical	4 (21)	1 (4)	5 (12)	
Diagnosis if admitted for allo-HCT (n = 43)	n = 19	n = 24		
Acute myeloid leukemia	6 (32)	9 (37)	15 (35)	.50
Acute lymphoblastic leukemia	3 (16)	4 (17)	7 (16)	
Chronic myeloid leukemia	1 (5)	0 (0)	1 (2)	
Chronic lymphoid leukemia	1 (5)	1 (4)	2 (5)	
Myelodysplastic syndrome	1 (5)	4 (17)	5 (12)	
Myeloproliferative disorder	3 (16)	0 (0)	3 (7)	
Non-Hodgkin lymphoma	1 (5)	2 (8)	3 (7)	
Hodgkin disease	1 (5)	0 (0)	1 (2)	
Other	2 (11)	4 (17)	6 (14)	
AML chemotherapy type (n = 19)	n = 8	n = 11		
Induction	5 (63)	6 (55)	11 (58)	.44
Reinduction	0 (0)	2 (18)	2 (10)	
Consolidation	3 (37)	3 (27)	6 (32)	
AML chemotherapy protocol (n = 19)	n = 8	n = 11		
HiDAC + 2	0 (0)	1 (9)	1 (5)	.44
HiDAC + 3	3 (38)	2 (18)	5 (26)	
7 + 3	3 (38)	2 (18)	5 (26)	
FLAG	0 (0)	1 (9)	1 (5)	
FLAG-Ida	0 (0)	1 (9)	1 (5)	
5 + 2	1 (13)	4 (36)	5 (26)	
Other	1 (13)	0 (0)	1 (5)	

Data are expressed as No. (%) unless otherwise specified; N = 62 unless otherwise specified.

Abbreviations: Allo-HCT, allogeneic hematopoietic cell transplant; AML, acute myeloid leukemia; FLAG, fludarabine, cytarabine, filgrastim chemotherapy; HiDAC, high dose ara-C chemotherapy; Ida, idarubicin; PJP, *Pneumocystis jirovercii* pneumonia; PNF, preneutropenic fever.

[a] *P* value for age determined using Kruskal-Wallis test.

Timing and Characteristics of Fever in Risk Factor–Related Fever

The height and timing of cytarabine- and thymoglobulin-related fevers is demonstrated in Supplementary Figure 1, and characteristics of fever are summarized in Table 4. The median time from thymoglobulin infusion to first fever was shorter compared to cytarabine infusion (7 vs 49 hours, respectively) as was the median time from infusion to fever resolution (46 vs 96 hours, respectively). In those with haplo-HCT–related fevers, 2 of 4 patients had fever postconditioning but prior to cell infusion, at 36 hours and 57 hours from conditioning commencement to first fever, and overall time to resolution of fever postconditioning commencement of 64 hours and 76 hours. The other 2 patients with fever had fever post–cell infusion, with first fever 12 hours and 20 hours after cell infusion, and overall time to resolution post–cell infusion of 31 hours and 46 hours, in the context of the prescription of hydrocortisone 100 mg intravenously stat to manage this fever.

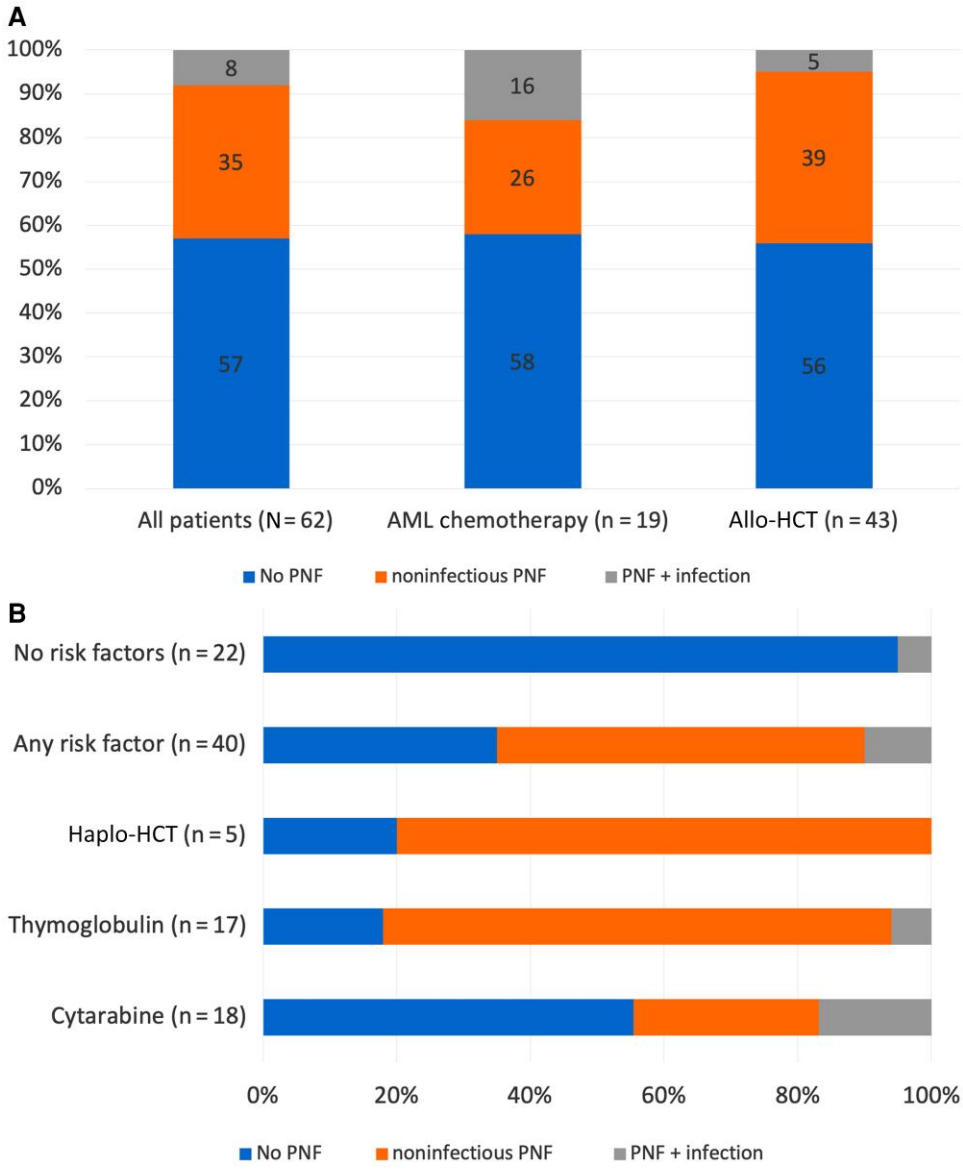

Figure 2. Proportion of infective and noninfectious preneutropenic fever (PNF), stratified by all patients, AML chemotherapy subgroup and allo-HCT subgroup (*A*), and proportion of patients with infective and noninfectious preneutropenic fever or no PNF by combined and individual risk factors (*B*). Abbreviations: Allo-HCT, allogeneic hematopoietic cell transplant; AML, acute myeloid leukemia; Haplo-HCT, haploidentical hematopoietic cell transplant; PNF, preneutropenic fever.

Impact of PNF on Antimicrobial Prescribing

Figure 3 demonstrates the impact of PNF on antimicrobial prescribing. Of 27 patients with PNF, 19 patients (70%) continued antimicrobials into the neutropenic period and in this group the median duration of overall antimicrobial therapy across preneutropenic and neutropenic periods (including for neutropenic fever) was 16 days (interquartile range [IQR], 11.0–22.0 days) compared to 13 days (IQR, 10.8–18.3 days) if antimicrobials were ceased prior to neutropenia onset. In comparison, those who did not develop PNF and subsequently developed neutropenic fever had a median duration of 10 days (IQR, 7.3–13.8 days) of empiric antimicrobial therapy.

Twenty-four of 27 patients with PNF went on to develop neutropenic fever, and in this setting, 5 of 24 (21%) were escalated to broader antimicrobial therapy such as a carbapenem and/or glycopeptide during treatment for fever and neutropenia. In comparison, in those who did not have PNF and subsequently developed neutropenic fever, only 2 of 30 (7%) were escalated to broader therapy during antimicrobial treatment. When focusing on the PNF group (Supplementary Table 2), the duration of and tendency to broaden therapy was higher in those with PNF

Table 2. Association Between Preneutropenic Fever and Infection Stratified by Admission Type and Predefined Risk Factors

Characteristic	Infection-Associated PNF (n = 5)	Non-Infection-Associated PNF (n = 22)	Total (n = 27)	*P* Value
Admission type				
Chemotherapy	3 (38)	5 (62)	8	.10
Allo-HCT	2 (11)	17 (89)	19	.19
Any risk factor	4 (15)	22 (85)	26	.28
Cytarabine	3 (38)	5 (62)	8	.07
Thymoglobulin	1 (7)	13 (93)	14	.42
Haplo-HCT	0 (0)	4 (100)	4	1[a]
No risk factor	1 (100)[b]	0 (0)	1	.05

Data are expressed as No. (%).

Abbreviations: Allo-HCT, allogeneic cell transplant; Haplo-HCT, haploidentical hematopoietic cell transplant; PNF, preneutropenic fever.

[a]Presence of cells in the contingency table with the value zero rendering statistical analysis of insufficient power.

[b]Infection-associated PNF in patient without *a priori* risk factors was a *Staphylococcus aureus* central line–associated infection.

Table 3. Rate and Risk of Preneutropenic Fever in Predefined Risk Groups

Characteristic	PNF (n = 27)	No PNF (n = 35)	Total (n = 62)	Unadjusted OR for PNF (95% CI)	*P* Value[a]
Any risk factor	26 (65)	14 (35)	40	39 (4.7–321.3)	<.01
Cytarabine	8 (44)	10 (56)	18	1[b]	1[c]
Thymoglobulin	14 (82)	3 (18)	17	19.6 (4.0–95.5)	<.01
Haplo-HCT[d]	4 (80)	1 (20)	5	6.1 (.6–60.3)	.15
No risk factors	1 (5)	21 (95)	22	0.03 (.003–.21)	<.01

Data are expressed as No. (%) who developed did or did not develop PNF.

Abbreviations: CI, confidence interval; Haplo-HCT, haploidentical hematopoietic cell transplant; OR, odds ratio; PNF, preneutropenic fever.

[a]*P* value based on χ^2 or Fisher exact test.

[b]Only 1 patient did not receive cytarabine, rendering regression impossible.

[c]Presence of cells in the contingency table with the value zero rendering statistical analysis of insufficient power.

[d]No haploidentical transplants received thymoglobulin.

Table 4. Fever Characteristics of Cytarabine and Thymoglobulin-Associated Fevers

Characteristic	Cytarabine	Thymoglobulin
Median time to first fever, h (IQR)	49.0 (27.3–78.3)	7.0 (6.0–29.0)
Median duration of fever, h (IQR)	25.5 (4.8–51.5)	34.0 (3.5–59.5)
Median time from infusion to fever resolution, h (IQR)	96.0 (54.3–113.8)	46.0 (12.0–100.0)

Abbreviation: IQR, interquartile range.

where antimicrobials were not ceased prior to neutropenic fever onset (median, 16 days; 7/17 [41%] escalation) compared to those where it was ceased (median, 11 days; 1/7 [14%] escalation).

DISCUSSION

In this first study dedicated to examining patterns and etiology of PNF, we found the rate of PNF to be high, but the rate of infectious etiology was low. Importantly, antimicrobial prescribing in the setting of PNF had significant implications for overall exposure to and escalation of empiric therapy across the treatment journey. Crucially, 82% of PNF was not infection-associated, and the association between known fever-inducing treatments and noninfectious PNF was strong. This suggests that empiric preneutropenic therapy should be reviewed early for cessation, particularly in those receiving cytarabine, antithymocyte globulin, and haploidentical transplants.

Only 5 instances of PNF had a confirmed infectious etiology. The spectrum of infections encountered in the preneutropenic period were different to those typically seen in neutropenic patients [17]. This is logical, as pathogens typically encountered in neutropenic fever often relate to invasion of endogenous flora through the mucosa, which is due to the significant mucositis and enterocolitis that occur as a result of chemotherapy or conditioning and a lack of cellular repair and defense at the mucosal barrier. Conversely, line infections and community-acquired infection would logically play a larger role in PNF due to new central line insertion and being early in their admission to hospital. This was evidenced in our cohort by *Staphylococcus aureus* and *Salmonella* bacteremias, and rhinovirus URTI. These findings

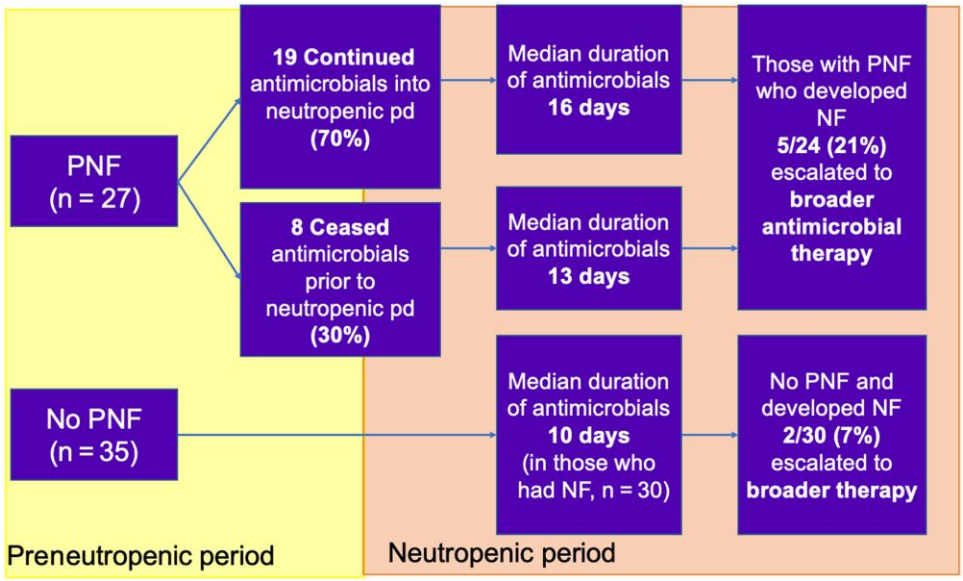

Figure 3. Impact of preneutropenic fever on antimicrobial duration and escalation. Abbreviations: NF, neutropenic fever; pd, period; PNF, preneutropenic fever.

suggest that management of patients with PNF need not necessarily mimic that of patients with neutropenia. Certainly, early review of empiric antibacterial therapy is warranted in the setting of a low likelihood of an infective cause.

The finding of 44% PNF in AML chemotherapy recipients is consistent with the limited published literature (43%–80% occurrence of cytarabine-related fevers) [9]. Importantly, this is the first study to look specifically at the likelihood of infection in PNF among this cohort, where 63% of PNF was not infection-associated in those receiving cytarabine. Given cytarabine forms the backbone of most AML induction regimens, this represents a sizeable proportion of patients at risk of developing noninfective PNF and highlights a key target for AMS intervention. While our sample was not adequately powered to assess the relationship between cytarabine dose and likelihood of fever, higher doses may be related to higher rates of fever in other studies [9]. Future work with a larger sample comparing rates according to cytarabine dose and/or phase of chemotherapy would be of value in helping clinicians predict the likelihood of noninfective PNF.

Thymoglobulin-related PNF was strikingly high in our study (82%) with very low incidence of infection (7%), which has not been previously reported in the allo-HCT group. A 2012 study found that fever developed in 18%–25% of those receiving thymoglobulin for renal transplant induction, and in 63% for renal transplant rejection [10]. Our study suggests that thymoglobulin-related fever occurs early postinfusion and resolves by a median of 46 hours, or approximately 2 days, which is helpful detail for clinicians. Further studies examining the timing of these fevers would be of clinical utility, to better characterize thymoglobulin-related PNF and provide reassurance of the low likelihood of infection. Again, the very high rate of noninfective fever described among patients receiving thymoglobulin represents a previously underinvestigated area for AMS programs.

Our study finding of 80% PNF in haplo-HCT, all of which were noninfective in nature, is consistent with the limited literature. A retrospective case series of 40 haplo-HCT recipients found 83% of patients experienced fever, a median of 25.5 hours after cell infusion [11]. This study also found all fevers to be noninfectious; 91% of fevers resolved in response to cyclophosphamide and fever subsided within 7 days of cell infusion. Our study provides further evidence of the high rate of PNF among recipients of haplo-HCT and the low likelihood of infectious etiology. Interestingly, we found that fever in the context of haplo-HCT can occur postconditioning but prior to cell infusion, as well as post–cell infusion. As hydrocortisone was prescribed in the setting of fever post–cell infusion, this fever was relatively short-lived. Given the increasing utilization of haplo-HCT [12], this information will be helpful in adequately managing these patients at high risk of noninfective fever, and guidelines on how to manage PNF would be useful.

Adverse outcomes from prolonged antimicrobial therapies in patients with hematological malignancies are well documented. Trubiano et al identified hematological malignancy as a risk factor for infection with multidrug-resistant gram-negative organisms, vancomycin-resistant enterococci, and *Clostridioides difficile* [13]. Infection with these organisms is likely driven, at least in part, by prior exposure to broad-spectrum antimicrobials [19–21]. Furthermore, patients with hematological malignancies infected with resistant organisms

experience poor outcomes, including mortality, intensive care unit admission, and prolonged hospital length of stay [22, 23]. AMS programs aimed at reducing the use of broad-spectrum antimicrobials have been shown to be beneficial in improving antimicrobial sensitivity, patient outcomes, and reducing healthcare costs [24, 25]. Hence, there is a strong argument for reducing unnecessary antibiotic exposure where possible in these patients.

Our study found that those who were commenced on empiric antimicrobial therapy due to PNF often had empiric therapy unnecessarily continued into the neutropenic period, where antimicrobials were then further escalated when neutropenic fever ensued. This type of spiraling empiric prescribing could have been avoided with early review of antimicrobial therapy after PNF onset. The low rate of infection, the early diagnosis of these infections (within 48 hours), and high rates of predictable noninfectious etiologies of fever demonstrated in this study should reassure clinicians that early review and de-escalation of antimicrobials is appropriate in PNF. De-escalation of antimicrobials in the preneutropenic period will preserve broad-spectrum agents for use during neutropenia, when they are of greater importance. In addition, the potential downstream effects of PNF antimicrobial use on our ability to identify infectious etiologies in neutropenic fever are potentially considerable, and therefore studying and addressing this clinical entity of PNF further could have positive impacts not only for AMS, but for neutropenic fever management as well.

Limitations

Data on timing and duration of fever were limited by the frequency of temperature measurement, and as the standard-of-care frequency of observation assessment at our center is every 4 hours, this is the margin of error for such estimates. Reassuringly, differences observed between groups were significantly greater than 4 hours, suggesting there is a real difference between the different noninfectious fever etiologies. While the ANC of patients may have been above the threshold of 0.5 cells/μL and hence not considered severely "neutropenic," it is quite possible that patients, particularly with acute leukemia, may not have functional neutrophils and be similarly vulnerable to infection. Nonetheless, the actual rates of infection identified in this group were very low, suggesting that this is not a significant issue. Furthermore, the definition of PNF used in this study would deliver some overlap with those considered to have neutropenic fever, if the patient's counts were expected to drop below 0.5 cells/μL within 48 hours. However, even with the potential overlap with what could be classified as neutropenic fever, the rate of infections were low and not with typical pathogens seen in neutropenic sepsis. It is worth noting that even in the setting of neutropenia, an infectious etiology is often not identified [26], and hence, a lack of microbiologically defined infection does not absolutely rule out infection, so careful individualized clinical review should be encouraged prior to antimicrobial cessation in this population.

This is a small single-center study, which may affect generalizability to other settings and is likely to lack power to detect differences and relationships between some patient groups. In addition, there are other possible causes of fever that were not examined, such as blood transfusion–related fever or drug-related fevers other than those listed. A large, multicenter study of PNF is warranted to further explore this area and is being undertaken by our study group.

CONCLUSIONS

This is the first study to our knowledge that looks specifically at PNF in patients with hematological malignancy. Nearly half of the patients included in the study experienced PNF and the rate of infection in PNF was remarkably low, particularly among those receiving treatments with high fever potential, namely cytarabine, thymoglobulin, or haploidentical HCT. Antimicrobial prescribing during PNF, and particularly a lack of cessation of empiric antimicrobials prior to developing neutropenia, had significant impacts on overall duration and escalation of broad-spectrum antimicrobial therapy. PNF is a clinical scenario which would benefit from targeted AMS interventions and further prospective studies.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. A. P. D., M. A. S., and J. C.-R. designed the study. A. P. D. and S. Y. T. recruited patients. J. C.-R., A. P. D., S. Y. T., and G. N. collected data. A. P. D. performed statistical analyses. All authors interpreted the data. J. C.-R. and A. P. D. wrote the manuscript. M. A. S., S. Y. T., G. N., A. B., and K. A. T. provided critical review and commentary on the manuscript.

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