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OBM Transplantation

Research Article

Febrile Neutropenia in Children: Etiologies, Outcomes, and Risk Factors with Prolonged Fever

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Academic Editor: Dora Ho

Special Issue: Infectious Complications in Hematopoietic Stem Cell Transplantation

OBM Transplantation
2020, volume 4, issue 1
doi:10.21926/obm.transplant.2001102

Received: November 27, 2019
Accepted: February 06, 2020
Published: February 21, 2020

Abstract

Most studies of children with prolonged fever and neutropenia (PFN) have focused on invasive fungal disease (IFD) as the etiology of fever and not on other causes. Data are lacking regarding risk factors and adverse outcomes in pediatric cancer patients with PFN compared with those whose fevers resolve more rapidly. Retrospective medical record

review was performed for all cancer patients with febrile neutropenia (FN) in the pediatric oncology unit at University of Chicago Medicine Comer Children's Hospital from March 2009 to July 2016. Resolving febrile neutropenia (RFN), lasting less than 96 hours, and PFN episodes (≥ 96 hours) were compared to identify risk factors and outcomes associated with PFN. A total of 572 FN episodes were identified in 265 patients. PFN occurred in 119 (21%) FN episodes (50 patients) and RFN occurred in 453 (79%) FN episodes (215 patients). In multivariable analysis, autologous stem cell transplant (odds ratio [OR] 6.5, P <0.001), fever >39°C at the time of presentation (OR 2.4, P<0.01) and absolute monocyte count (AMC) <100 cells/m^3 (OR 2.7, P=<0.01) were independently associated with PFN. Pneumonia, neutropenic enterocolitis and IFD were more common etiologies of fever in PFN compared with RFN. Patients with PFN were more likely to be admitted to the pediatric intensive care unit [OR 3, (95%CI, 1.66%-5.28%), P<0.001] and had a trend toward higher 30-day mortality [OR 3.8, (95%CI, 0.52%-29.32%), P=0.07]. Patients with PFN are at increased risk for serious illness and death. A better understanding of the etiologies of PFN other than IFD is needed to be able to appropriately diagnose and treat this high-risk group.

Keywords
Prolonged neutropenic fever; infections; pediatric cancer and stem cell transplant

1. Introduction

Chemotherapy-induced neutropenia is a common complication in pediatric cancer patients, rendering them extremely vulnerable to life-threatening infections [1-3]. With longer durations of neutropenia and increasing patient complexity, the uncertainty surrounding a possible infectious etiology of FN increases and formulating a generalizable approach becomes more challenging. The clinical approach of diagnostic studies, selecting appropriate antibiotics and duration of therapy in patients with prolonged fever and neutropenia (PFN) may vary widely depending on the patient's underlying disease and presenting symptoms. Inability to diagnose an infection or selection of therapy that does not cover the offending pathogen may result in poor patient outcomes, while unnecessary antibiotic therapy may have effects including the emergence of drug-resistant microorganisms *C. difficile* infection, drug toxicity leading to prolonged length of stay (LOS), and increasing use of healthcare resources [4, 5].

The goal of this study was to identify risk factors, etiologies, and outcomes associated with PFN beyond IFD in children at one academic medical center.

2. Methods

2.1 Design

A retrospective cohort study was conducted at University of Chicago Medicine (UCM) Comer Children's Hospital, a 172-bed acute care hospital located on Chicago's south side that serves a diverse pediatric population. The medical center offers highly specialized cancer care, including stem cell transplant (SCT) [6].

Study protocols were approved by the Clinical Trials Review Committee (CTRC) and the UCM Institutional Review Board (IRB). To identify appropriate patients for inclusion, the UCM Clinical Research Data Warehouse was queried for hospital FN episodes from March 2009 to July 2016 with a) ICD-9 or ICD-10 codes for malignancy OR SCT diagnoses AND b) an ICD-9/ICD-10 code for neutropenia OR absolute neutrophil count (ANC) <1,000 cells/μL, AND c) fever ≥38.0°C (≥100.4°F) in a 24-hr period in children or adolescent patients 21 years of age or younger. ICD-10 codes were used to identify FN episodes after October 2015 and ICD-9 codes before this month. Retrospective electronic medical record (EMR) review was performed to verify that FN episodes were appropriate for inclusion based on the above characteristics. The study flow diagram is shown in Figure 1.

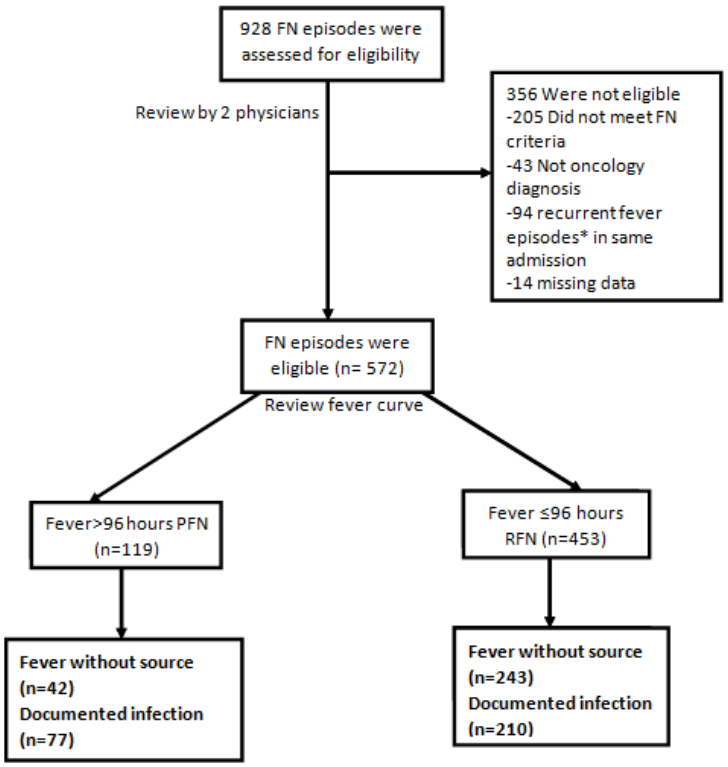

Figure 1 Study flow diagram. Febrile neutropenia (FN) episodes and etiology of resolving (RFN) and prolonged febrile neutropenia (PFN). * recurrent fever episodes without recovery from first FN episodes.

All episodes not meeting the above-mentioned criteria, including febrile non-neutropenic episodes, were excluded. For patients with more than one admission for FN, each admission was counted as a separate episode. Recurrent fever episodes in the same admission which were substantively separated from a prior episode with marrow recovery were included, but recurrent fever episodes without recovery from a first FN episodes was excluded.

2.2 Data Collection

Study data (demographic, clinical, laboratory and outcomes) were collected by EMR review and managed using REDCap (Research Electronic Data Capture) [7]. Encounters were classified by type

of FN including RFN or PFN. Data collected included, but was not limited to, patient demographics (age, gender, oncologic diagnosis, history of and type of SCT), clinical features at presentation of FN episode, and laboratory data (white blood cell [WBC] count, ANC, absolute monocyte count [AMC], absolute lymphocyte count [ALC], platelet count and hemoglobin at time of presentation, and microbiological data).

Data related to any antibacterial prophylaxis at the time of FN episodes, granulocyte-colony stimulating factor (G-CSF) use, clinical outcomes including pediatric intensive care unit (PICU) admission, and 30- day mortality were reviewed.

2.3 Definitions

Fever was defined as a single oral temperature of >38.3°C or temperature of >38.0°C sustained over a 1-h period or on more than one occasion during a 24-hour period [8]. Neutropenia was defined as ANC<500 cells/µL or ANC that was expected to decrease to <500 cells/µL during the next 48 hours. FN episodes were classified based on fever duration and response to antibiotics into 2 groups: 1) RFN: an episode that resolved within 96 hours, 2) PFN: an episode that failed to resolve after at least 96 hr of antibacterial therapy [9]. Patients were all observed in the inpatient setting until fever resolved and ANC recovered.

FN episodes were classified based on fever source as clinically documented infections (e.g., cellulitis, pneumonia, neutropenic enterocolitis), microbiologically documented infections (MDI) (i.e., blood stream infections [BSI]; *C. difficile* infection [CDI]; upper respiratory tract infection [URTI]); or fever without source, defined as those associated with neither a pathogen nor a candidate infectious focus) [10]. In SCT recipients each FN episode was followed from the day of transplant (day 0) until 12 months post-transplant, or until the patient was lost to follow-up or died, whichever occurred first.

Positive blood culture results were determined to be a pathogen (i.e., BSI) or a contaminant using the National Healthcare Safety Network (NHSN) criteria for skin commensals and the clinical team's decision to treat as a pathogen [8]. IFD was stratified into categories of possible, probable and proven according to the latest EORTC/MSG criteria of 2008 [11]. Pneumonia (bacterial, viral) was defined using clinical, microbiological and/or imaging findings. Fungal pneumonia was classified as IFD for the purposes of this study. It was difficult to differentiate CDI from *C. difficile* colonization in immunocompromised patients in whom chemotherapy often results in diarrhea, so CDI was defined as *C. difficile* test positivity in a patient who was symptomatic. Neutropenic enterocolitis was defined by characteristic computed tomography (CT) findings of colitis in a neutropenic patient presenting with fever and abdominal pain and tenderness. PICU admission was defined as admission to the PICU within 30 days after the first day of an FN episode. 30-day mortality was defined as any inpatient death within 30 days after the first day of an FN episode.

2.4 Patient Management

Institutional practice is to use ceftazidime as the initial empiric antimicrobial for FN patients with addition of vancomycin ± gentamicin based on clinical presentation (i.e., concern for central venous catheter infections or septic shock). Cefepime was administered instead of ceftazidime for selected patients with high-risk FN such as those with acute myelogenous leukemia (AML). Empiric antifungal therapy (usually liposomal amphotericin B) was added if the patient remained febrile on

day 5 of antibiotics and if neutropenia was expected to last longer than 5 to 7 days. Patients at high risk for invasive bacterial or fungal infections were placed on prophylaxis (typically ciprofloxacin or levofloxacin and fluconazole, respectively) based on chemotherapy protocol recommendations [6].

The standard of care and diagnostic testing during the study period followed Infectious Diseases Society of America (IDSA) and International Pediatric Fever and Neutropenia (IPFNP) guidelines. Individualized patient care varied based on the case and clinical presentation particularly for episodes with fever without source >96 hours.

2.5 Statistical Analyses

Demographic, risk factor, clinical, laboratory, and outcome variables for each type of clinical encounter were presented as frequencies and percentages for categorical variables and means, and standard deviations for continuous variables. Differences in characteristics between FN types were computed using chi-square or Fisher's Exact tests for categorical variables and the Mann-Whitney U test for continuous variables. For each characteristic, bivariate tests were also computed using generalized linear mixed models (GLMMs) to obtain odds ratios for PFN while clustering by patient. To identify risk factors with independent effects on the odds of prolonged FN, a multivariable GLMM was conducted for all risk factor variables found with $p<0.10$ in the bivariate GLMMs. Many characteristics and outcomes had $n<10$, which requires penalized likelihood logistic regression models. However, penalized likelihood models assume independence of the observations. To explore the effects of the choice of method, for the PICU and mortality outcomes, bivariate GLMMs were compared with penalized likelihood logistic regression models which do not account for clustering by patient. Bivariate tests were conducted for risk factor, clinical, and laboratory data, as well as for outcomes. P-values <0.05 were considered statistically significant. Analyses were conducted using SAS 9.4 (Cary, NC, 2012). To minimize the bias of correlations between episodes of patients with multiple episodes, we used GLMMs with patients as random effects to account for the correlations.

3. Results

3.1 Patients and Episodes Characteristics for the Entire FN Cohort

A total of 572 FN episodes were identified in 265 patients, among whom 45.3% were female. One third of patients (91/265, 34%) underwent SCT. Of all FN episodes, 24.2% occurred in SCT recipients. We found that among patients with FN, children >10 years of age and children <5 years of age were almost 1.8 times more likely to develop PFN than those 5-10 years of age, although no significant difference was evident when the three groups were compared (p=0.11). Acute lymphoblastic leukemia (ALL) was the most common malignancy, accounting for 170 (30%) of all episodes followed by neuroblastoma, 110 (19.2%); acute myeloid leukemia (AML), 91 (16%); lymphoma, 70 (12.2%); and other solid tumors, 123 (21.5%). BSI was present in 133 (23.2%) of all FN episodes, IFD in 30 (5.2%), and fever without source was seen in almost half of all cases. The majority of FN episodes, 453 (79%), were RFN, and 119 (21%) were PFN.

3.2 Bivariate and Multivariate Analysis of Risk Factors Associated with PFN versus RFN

Demographic factors between PFN and RFN patients did not differ by age or sex (Table 1). Parameters that were associated with an increased risk of PFN on bivariate analysis when compared with RFN included: SCT recipients (OR=2.73, P <0.0001), particularly autologous SCT (OR=7.4, P=<0.0001), fever >39ºC at the time of presentation (OR=2.75, P<0.0001), hypotension at time of presentation (OR= 2.2, P=0.007), receiving antibacterial prophylaxis at the time of the FN episode (OR=2, P=0.04), receipt of G-CSF (OR=2, P=0.008), ANC <100 cells/mm^3 (OR=2.2, P =0.003), AMC <100 cells/m^3 (OR=2.7, P=0.002), ALC <300 cells/mm^3 (OR=2.4, P<.001), and severe thrombocytopenia < 50 G/L (OR=1.55, P=0.04). When the data were fit in a multivariate logistic regression model on the basis of covariates, we found that only autologous SCT (odds ratio [OR] 6.5, P <0.0001), fever >39°C at the time of presentation (OR 2.4, P<0.01), and AMC <100 cells/mm^3 (OR 2.7, P=<0.01) were independently associated with PFN (Figure 2). Administration of chemotherapy in the previous 2 weeks, gastrointestinal symptoms, mucositis or rigors at presentation, presence of a central line, history of BSI, and duration of neutropenia before the FN episode were not associated with PFN. Additional patient's characteristics are shown in Table 1.

Table 1 Characteristics of risk factors for and outcomes of PFN compared with RFN in children aged 0-21 years (n= 572).

	RFN N (%)	**PFN N (%)**	**Total N (%)**	**P-value**	**PFN vs. RFN OR (95% CI)**
Total	453 (79.2)	119 (20.8)	572 (100.0)		
Age				0.11	
0-4	96 (21.2)	28 (23.5)	124 (21.7)		Reference
5-9	118 (26.1)	20 (16.8)	138 (24.1)		0.59 (0.31-1.13)
>10	239 (52.8)	71 (59.7)	310 (54.2)		1.02 (0.61-1.71)
Gender					
Female	209 (46.1)	52 (43.7)	261 (45.6)	0.63	0.92 (0.60-1.41)
Diagnosis				0.31	
ALL	136 (30.0)	32 (26.9)	168 (29.4)		Reference
AML/Mixed leukemia	53 (11.7)	23 (19.3)	76 (13.3)		1.82 (0.95-3.49)
Lymphoma	50 (11.0)	14 (11.8)	64 (11.2)		1.22 (0.59-2.53)
Neuroblastoma	80 (17.7)	22 (18.5)	102 (17.8)		1.16 (0.61-2.17)
Other	29 (6.4)	5 (4.2)	34 (5.9)		0.74 (0.26-2.11)
Solid tumor	105(23.2)	23 (19.3)	128 (22.4)		0.94 (0.51-1.74)
NO-SCT	383(84)	79(66)	462 (60)		Reference

SCT	71 (15.7)	40 (33.6)	111 (19.4)	**<0.0001**	2.73 (1.71-4.38)
Autologous SCT	18 (4.0)	27 (22.7)	45 (7.9)		7.41 (3.81-14.42)
Allogeneic SCT	52 (11.5)	13 (10.9)	65 (11.4)		1.17 (0.59-2.31)
Chemotherapy in last 2 weeks	348 (76.8)	95 (79.8)	443 (77.5)	0.48	1.19 (0.71-1.97)
Fever ≥39.0ºC	92 (20.3)	49 (41.2)	141 (24.7)	**<0.0001**	2.75 (1.77-4.28)
Gastrointestinal symptoms	143 (31.6)	44 (37.0)	187 (32.7)	0.26	1.27 (0.82-1.95)
Mucositis	104 (23.0)	32 (26.9)	136 (23.8)	0.37	1.21 (0.76-1.94)
Chills	25 (5.5)	5 (4.2)	30 (5.2)	0.57	0.75 (0.28-2.03)
ANC ≥100	147 (32.5)	21 (17.7)	168 (29.4)	**0.002**	0.45 (0.27-0.75)
Platelet <50	266 (58.7)	82 (68.9)	348 (60.8)	**0.04**	1.54 (0.99-2.39)
AMC ≥100	113 (24.9)	13 (10.9)	126 (22.0)	**0.001**	0.37 (0.20-0.68)
ALC ≥100	304 (67.1)	56 (47.1)	360 (62.9)	**<0.0001**	0.41 (0.27-0.63)
History of bacteremia	117 (25.8)	37 (31.1)	154 (26.9)	0.25	1.28 (0.81-2.01)
On antibacterial prophylaxis	33 (7.3)	16(13.5)	49 (8.6)	**0.03**	1.97 (1.03-3.79)

On G-CSF	72 (15.9)	32 (26.9)	104 (18.2)	**0.008**	1.96 (1.20-3.20)
Hypotension	42 (9.3)	22 (18.5)	64 (11.2)	**0.005**	2.21 (1.25-3.92)

ALL: Acute lymphoblastic leukemia, ALC: absolute lymphocyte count, AMC: absolute monocyte counts, AML: acute myeloid leukemia, ANC: absolute neutrophil count, G-CSF: granulocyte-colony stimulating factor, OR, odds ratio, PFN: prolonged neutropenic fever, RNP: resolving neutropenic fever, SCT: stem cell transplant.

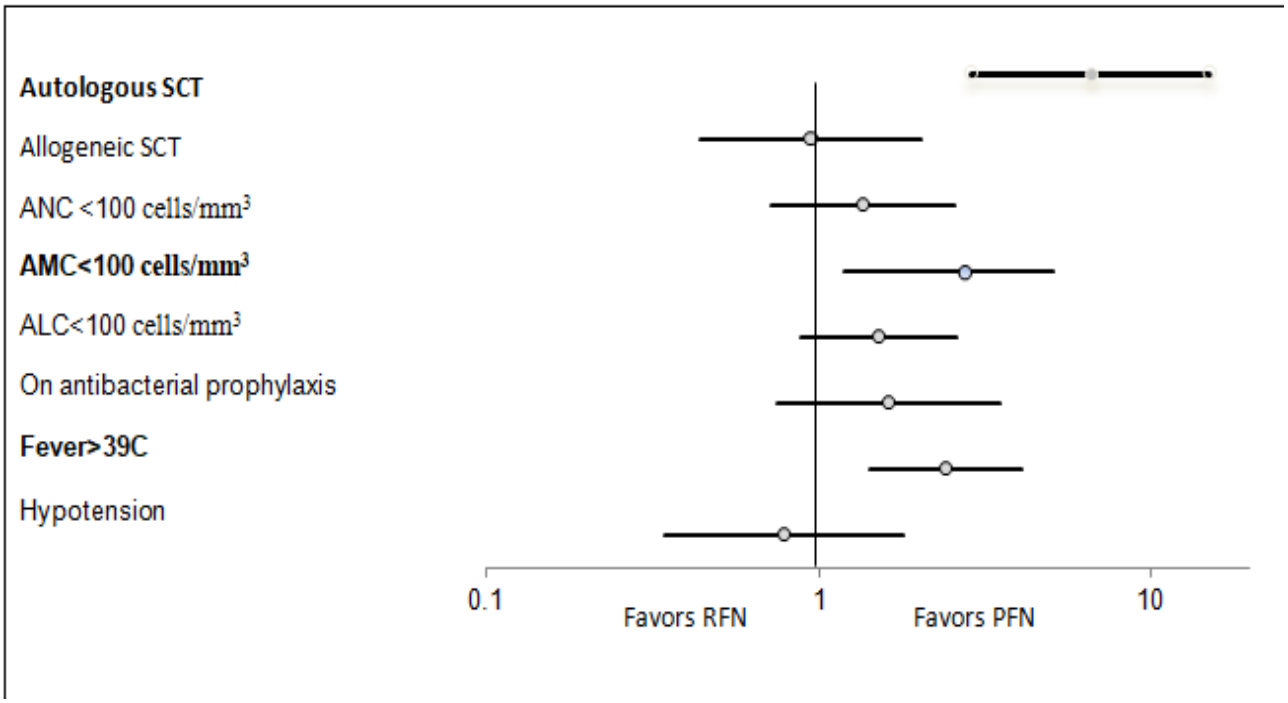

Figure 2 Multivariate analysis of risk factors for prolonged neutropenic fever in children in 572 episodes. ALC: absolute lymphocyte count, AMC: absolute monocyte counts, ANC: absolute neutrophil count, PFN: prolonged neutropenic fever; RFN: resolving neutropenic fever, SCT: stem cell transplant.

3.3 Clinical Etiologies and Outcomes

In patients with PFN, BSI occurred in 30%, URTI confirmed by respiratory multiplex PCR panel in 18.5%, CDI in 7.6%, pneumonia in 8.4%, and neutropenic enterocolitis in 5%. IFD was identified in 21 (17.7%) of PFN episodes and categorized as proven in 2, probable in 4, and possible in 15 cases. In contrast, IFD was recorded in only 9 cases (2%) of RFN. Of the 9 cases, one was proven, one was probable and 7 were possible cases (Table 2). There was no difference in URTI rate in PFN compared with RFN (P=0.83). However, we found IFD (P<0.0001), pneumonia (bacterial/viral) (P=0.0001), and neutropenic enterocolitis (P=0.002) were more likely diagnosed in PFN compared with RFN. Fever without source was less common in PFN (49 episodes, 41%) compared with RFN (250 episodes, 55%) (OR=0.4, P= 0.001) (Table 2). Odds ratios of potential etiologies in PFN were compared with RFN, as illustrated in Figure 3. A sub-analysis of BSI episodes based on type of pathogens (Table 3) revealed that *Streptococcus* species BSI are more likely (OR=1.8) in PFN than RFN, though this finding was not statically significant (P=0.06). The distribution of respiratory pathogens in PFN and RFN is shown in Table 4.

PICU transfer and mortality at 30 days were compared in the 2 groups. Patients with PFN were more likely to be admitted to the PICU than were RFN patients (OR=3, P =0.0003) (Table 5). There was no difference in mortality between the 2 groups (Table 5).

Table 2 Clinical etiologies of PFN compared with RFN in children.

	RFN (N=453) N (%)	**PFN (N=119) N (%)**	**P-value**	**OR (95% CI)**
Fever without source	250 (55.2)	42 (35.3)	0.0001	0.45 (0.29-0.68)
Fungal	9 (2.0)	21 (17.7)	<0.0001	10.51 (4.61-23.92)
BSI	97 (21.4)	36 (30.3)	0.05	1.57 (0.99-2.48)
PNA	5 (1.1)	10 (8.4)	0.0001	8.18 (2.67-25.00)
VURTI	80 (17.7)	24 (18.5)	0.83	1.08 (0.631.84-)
Neutropenic enterocolitis	8 (1.8)	7 (5.9)	0.02	3.48 (1.19-9.97)
CDI	19 (4.2)	9 (7.6)	0.06	1.79 (0.78-4.14)

CDI: *C. difficile* infection, VURTI: viral upper respiratory tract infection, FUO: fever of unknown origin, BSI: blood stream infection, PNA: pneumonia, PFN: prolonged neutropenic fever; RFN: resolving neutropenic fever.

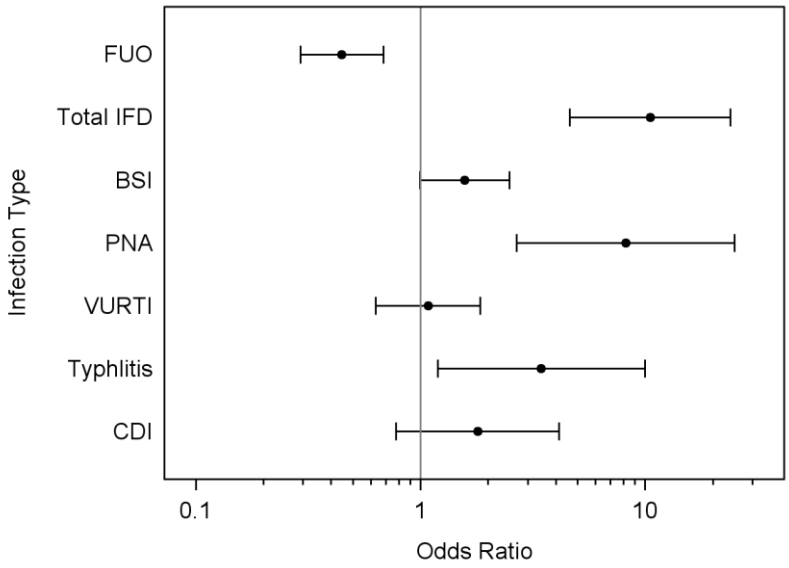

Figure 3 Odds ratios for categories of infection in pediatric PFN compared with RFN. BSI: bloodstream infection, CDI: *C. difficile* infection, FUO: fever of unknown origin, BSI: blood stream infection, PNA: pneumonia, PFN: prolonged neutropenic fever; RFN: resolving neutropenic fever, VURTI: viral upper respiratory tract infection (detected by multiplex PCR panel).

Table 3 Etiology of microbiologically documented bloodstream infection in PFN compared with RFN in children.

	RFN (N=97) N (%)	**PFN (N=36) N (%)**	**Total (N=133) N (%)**	**P-value**	**OR (95% CI)**
Streptococcus spp	23 (23.7)	13 (36.1)	36 (27.1)	0.06	1.83 (0.74-4.55)
S. aureus	12 (12.4)	3 (8.3)	15 (11.3)	0.21	0.63 (0.15-2.67)
CoNS+Bacillus spp	21 (21.7)	6 (16.7)	27 (20.3)	0.16	0.73 (0.25-2.10)
Others*	17 (17.5)	6 (16.7)	23 (17.3)	0.20	0.94 (0.33-2.72)
NDR-GNB	32 (33.0)	11 (30.6)	43 (32.3)	0.16	0.88 (0.36-2.11)
DR-GNB	9 (9.3)	4 (11.1)	13 (9.8)	0.24	1.22 (0.34-4.46)

CoNS: Coagulase-negative staphylococci, DR-GNB: drug-resistant Gram negative bacteria, NDR-GNB: non drug-resistant Gram negative bacteria, OR: odds ratio, PFN: prolonged neutropenic fever, RFN: resolving neutropenic fever. *Others: includes all other Gram positive bacteria not listed in the table, most of which were anaerobic species.

Table 4 Pathogen distribution in upper respiratory panel of PFN compared with RFN in pediatric FN.

Pathogen	RFN (N=85)	PFN (N=24)
Rhinovirus/Enterovirus	50	14
Adenovirus	1	2
Coronavirus	9	2
Human Metapneumovirus	4	1
Influenza A+B	8	1
Para influenza	7	4
RSV	8	3
Bordetella pertussis	1	0
Chlamydophila pneumoniae	0	0
Mycoplasma pneumoniae	4	0

PFN: prolonged neutropenic fever, RFN: resolving neutropenic fever, RSV: respiratory syncytial virus, RVP: respiratory viral panel.

Table 5 Clinical outcomes PFN compared with RFN in children.

	RFN (N=453) N (%)	**PFN (N=119) N (%)**	**P-value**	**OR (95% CI)**
PICU admission	36 (8.0)	24 (20.2)	0.0001	2.96 (1.66-5.28)
30-day mortality	2 (0.4)	2 (1.7)	0.15	3.89 (0.52-29.32)

PICU: pediatric intensive care unit, PFN: prolonged neutropenic fever, RFN: resolving neutropenic fever

4. Discussion

The results of this large retrospective cohort study of pediatric FN provide contemporary data about the burden, risk factors, etiology, and outcomes of PFN in pediatric patients with cancer and SCT. Based on our review, PFN occurred in 21% (119/572) of all FN episodes. SCT recipients, particularly patients with autologous SCT, those with fever >39°C, and with AMC <100 cells/mm^3 at the time of presentation were independently associated with PFN. Additionally, our findings highlight other infectious etiologies associated with PFN (pneumonia, neutropenic enterocolitis) in addition to IFD.

To date, the literature has focused on IFD in studies of PFN [8], generally, IFD is a common cause of PFN [12], accounting for approximately 5-20% of PFN [13, 14]. Our primary aim was to explore other infectious etiologies associated with PFN and risk factors that may allow a clinician to discriminate between patients with FN that resolves within 96 hr after starting the empiric antibiotic therapy (RFN) versus patients who would remain febrile and neutropenic for more than 96 hr (PFN). Studies aimed at identifying such variables in pediatric patients are lacking [3] and knowledge of these predictors may be helpful in guiding management of FN.

In comparison to ALL, a diagnosis of AML was associated with a 1.8-fold increased risk of PFN. Most studies of FN in pediatric cancer patients have found that those with solid tumors had a lower risk for invasive infections and better overall outcomes compared with hematological malignancies (ALL, AML) [15, 16]. When we evaluated neuroblastoma as a separate category, we found that ALL and neuroblastoma patients had the same risk of developing PFN (Table 2). A possible reason for this is that current neuroblastoma protocols include intensive chemotherapy followed by autologous SCT [17].

In the present study, SCT recipients had a higher risk of developing PFN. In a secondary analysis based on type of SCT, interestingly, autologous SCT recipients were more likely to develop PFN when compared with allogeneic SCT. Our results are unexpected because allogeneic SCT recipients usually receive more intensive chemotherapeutic regimens than do recipients of other autologous SCT [18]. One possible explanation is that the majority of PFN episodes in autologous SCT recipients have neuroblastoma as the underlying diagnosis.

Studies of the utility of G-CSF in reducing infection-related complications in children with chemotherapy-related neutropenia have had conflicting results [19, 20]. We found that FN episodes among patients receiving G-CSF at the time of presentation were more likely to develop PFN though this finding was not significant in multivariable analysis. It has been previously reported that G-CSF may cause drug fever or fever without source [21], and because most autologous SCT regimens require G-CSF by protocol, this may be a confounder in the strong association of autologous SCT with risk of PFN [22, 23].

Having AMC<100 cell/mm^3 was a predictor for PFN in our study, consistent with previously identified correlations among high infection risk, prolonged duration of NF, and worse FN outcomes [24, 25]. Previous studies showed that the monocyte nadir is a possible indicator for neutrophil nadir during cancer chemotherapy [26] . This relationship may serve as a prognostic factor in the management of FN episodes. Although profound neutropenia (ANC<100 cell/mm^3) and lymphopenia (ALC< 100 cell/mm^3) were both risk factors for PNF on bivariate analysis, they were not independent risk factors in our multivariable regression model.

Our multivariable analysis indicated that fever >39°C at presentation was significantly associated with a higher incidence of PFN. Temperature >39°C at presentation has been previously reported as a predictor of BSI and clinical complications for FN in children [27, 28]. A prospective FN pediatric study identified hypotension as a predictor of invasive bacterial infection [29], but hypotension was not an independent risk factor in our multivariable model.

Prior studies have shown that pneumonia (bacterial/viral) in FN patients is associated with an 8-fold increased the risk of death (OR=8, P<0.0001) [16, 30]. Our findings suggest that FN patients with pneumonia were more likely to have PFN compared with RFN. This result supports current clinical practice guidelines which recommend obtaining a chest x-ray (or repeating a prior chest x-ray or computed tomography scan of the chest) when fever has persisted >96 hr even if the patient remains without symptoms.

The overall incidence of neutropenic enterocolitis was 2.6% in the entire cohort and occurred more commonly in patients presenting with PFN than RFN (6% vs 1.8%; P=0.02), though diagnostic bias due to timing of routine testing could drive this conclusion. There was a trend toward a higher rate of CDI in PFN (OR =1.8, P=0.06), however differentiation of *C. difficile* infection from colonization in symptomatic patients in this population was difficult [31] and results should be interpreted with caution.

In the present study, patients with PFN were more likely admitted to the PICU than RFN (9% vs. 2%; OR= 3, p < 0.0003). Mortality in pediatric studies of FN has ranged from 0.7% to 3.9% [25, 29, 32, 33]. Our findings are consistent with this range, with an overall mortality of 2.3%.

There were no significant differences in PFN occurrence in our study between the group that received antibacterial prophylaxis and the group that did not. Recent studies showed that antibacterial prophylaxis (i.e., levofloxacin) was effective in preventing bacteremia in children receiving intensive chemotherapy or undergoing SCT. In our study, we didn't investigate effect antibacterial prophylaxis on preventing invasive bacterial infection [34, 35] since our cohort was inclusive of a heterogeneous group of FN events while patients at higher risk for complications are more likely to have antibacterial prophylaxis prescribed, e.g., for AML. Furthermore, there were few patients on levofloxacin at time of study.

The current study has several limitations. First, it is a retrospective analysis at a single academic medical center. Second, results may not be generalizable to other institutions with different practices of antimicrobial prophylaxis and different empiric management of FN. Third, the study lacked the power to perform some subgroup of autologous SCT and association with increased risk of PFN. Fourth, there is diagnostic testing bias as some tests were not routinely performed in both PFN and RFN groups based clinical variation in patient care. To minimize these limitations, data gathering was not only based on administrative data, but the patient EMR was reviewed as well by a physician. Notably, the neuroblastoma population was atypically large in our cohort because there is a large Neuroblastoma Program at UCM Comer Children's Hospital.

5. Conclusions

Children undergoing autologous SCT, having a fever ≥39.0°C or AMC <100 cells/mm^3 at the time of presentation were at risk for development of PFN. Patients having these characteristics with persisting fever for 72-96 hr after starting broad spectrum antibiotics need reevaluation. Pneumonia, neutropenic enterocolitis, and IFD were more common etiologies of fever if

prolonged in these patients. Patients with PFN were at increased risk for serious illness. A better understanding of the etiologies of PFN beyond IFD is needed to be able to appropriately diagnose and manage this high-risk group of patients. Prospective studies of PFN among children enrolled in large cohorts may be beneficial in evaluating these risk factors further, which may enable the reduction of mortality and the improvement of outcomes.

Author Contributions

These authors contributed equally to this work.

Competing Interests

The authors have declared that no competing interests exist.

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