

Association Between Depth of Neutropenia and Clinical Outcomes in Febrile Pediatric Cancer and/or Patients Undergoing Hematopoietic Stem-cell Transplantation

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Background: Infectious Diseases Society of America guidelines defines febrile neutropenia (FN) patients as high risk, if they have an absolute neutrophil count (ANC) ≤ 100 cells/ μL anticipated to last >7 days. However, data evaluating the clinical significance of the depth and duration of neutropenia are limited.

Methods: We conducted a retrospective cohort study of pediatric oncology patients presenting with FN to examine whether the effects of the depth and duration of neutropenia prior to presentation were predictive of blood stream infection (BSI), invasive fungal disease (IFD), pediatric intensive care unit (PICU) admission or length of stay.

Results: A total of 585 FN episodes (FNEs) were identified in 265 patients. ANC at the time of presentation was <100 in 411 (70%), 100–500 in 119 (20%), and >500 cells/ μL with subsequent decline to <500 cells/ μL in the next 48 hours in 55 (10%) of FNEs. In the group with ANC > 500 with subsequent decline in 48 hours, rates of IFD and BSI were higher when compared with ANC < 100 cells/ μL [odds ratio (OR) = 5.9, 95% confidence interval (CI): 0.7–29.6] and (OR = 2.35, 95% CI: 0.102–5.4), and patients in this group were more likely to be admitted to the PICU (OR = 5.1, 95% CI: 1.134–19.46). No difference in outcomes was identified when the groups of ANC < 100 and ANC of 100–500 cells/ μL were compared. Neutropenia >7 days prior to FNE was an independent risk factor for BSI (OR = 2.88, 95% CI: 1.55–5.35 and increased length of stay.

Conclusions: Clinicians should not be reassured when patients present with FN and initial ANC >500 cells/ mL after recent chemotherapy if continued decline is expected as patients in this group are at high risk of IFD, BSI and PICU admission.

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Febrile neutropenia (FN) is a common condition in children receiving chemotherapy and can be life-threatening.¹ Risk prediction rules based on clinical and laboratory parameters have been developed in a number of prospective pediatric studies.^{2–8}

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One important predictive measure that has been described is the depth and duration of neutropenia, as the relative risk of infection becomes apparent at an absolute neutrophil count (ANC) <100 cells/ μL (profound neutropenia).^{6,9} Both the Infectious Diseases Society of America guidelines and the International Pediatric FN Panel define patients as high risk if they have ANC < 100 cells/ μL anticipated to last >7 days. There are no clear definitions of severity of neutropenia that stratify infectious risk based on ANC levels, nor has the duration of neutropenia prior to presentation been assessed for an association with infectious complications and outcomes.

The present study evaluates the effect of the depth and duration of neutropenia prior to presentation of FN and the correlation with the following clinical outcomes: blood stream infection (BSI), invasive fungal disease (IFD) and pediatric intensive care unit (PICU) admission within 30 days of FN presentation or length of stay (LOS). This study does not aim to develop a risk prediction score for outcomes in pediatric patients with cancer. Instead, the goal is to determine predictive values of some laboratory parameters at the time of FN presentation including ANC depth and duration of neutropenia that may impact physician clinical decisions.

METHODS

Design

A retrospective cohort study was conducted at the University of Chicago Medical Center/Comer Children's Hospital, a 172-bed acute care facility serving a diverse pediatric patient population.

The study was approved by the Clinical Trials Review Committee and the UCM Institutional Review Board. To identify appropriate patients for inclusion, the UCM Clinical Research Data Warehouse was queried for hospital admissions from March 2009 to December 2016 with ICD-9 or ICD-10 codes for malignancy odds ratio (OR) stem cell transplant (SCT) diagnoses AND an ICD-9/ICD-10 code for neutropenia OR ANC < 1000 , AND fever $\geq 38.0^\circ\text{C}$ ($\geq 100.4^\circ\text{F}$) in a 24-hour period in children or adolescent patients 21 years of age or younger. Retrospective electronic medical record (EMR) review was performed to verify that FN episodes (FNEs) were appropriate for inclusion.

FNEs were excluded if not fulfilling the above mentioned criteria, including febrile non-neutropenic episodes. Importantly, FNEs with ANC > 500 cells/ μL (but <1000 cells/ μL) and decline in ANC over the subsequent 48 hours were included as FNEs for the purposes of this study; however, FNEs with ANC >500 cells/ μL without decline to ANC <500 cells/ μL were excluded (Fig. 1). When admission has >1 FNE, only the first FNE for each admission were included. For patients with >1 admission for FN, each admission was counted as a separate FNE, and the analysis accounted for the correlation between multiple admissions of the same patient.

Demographic data for each FNE was obtained through EMR review including age, sex, underlying diagnosis, any type of infection occurrence, chemotherapy administration in last 2 weeks, whether FNE occurred before or during SCT, length of hospitalization and discharge status.

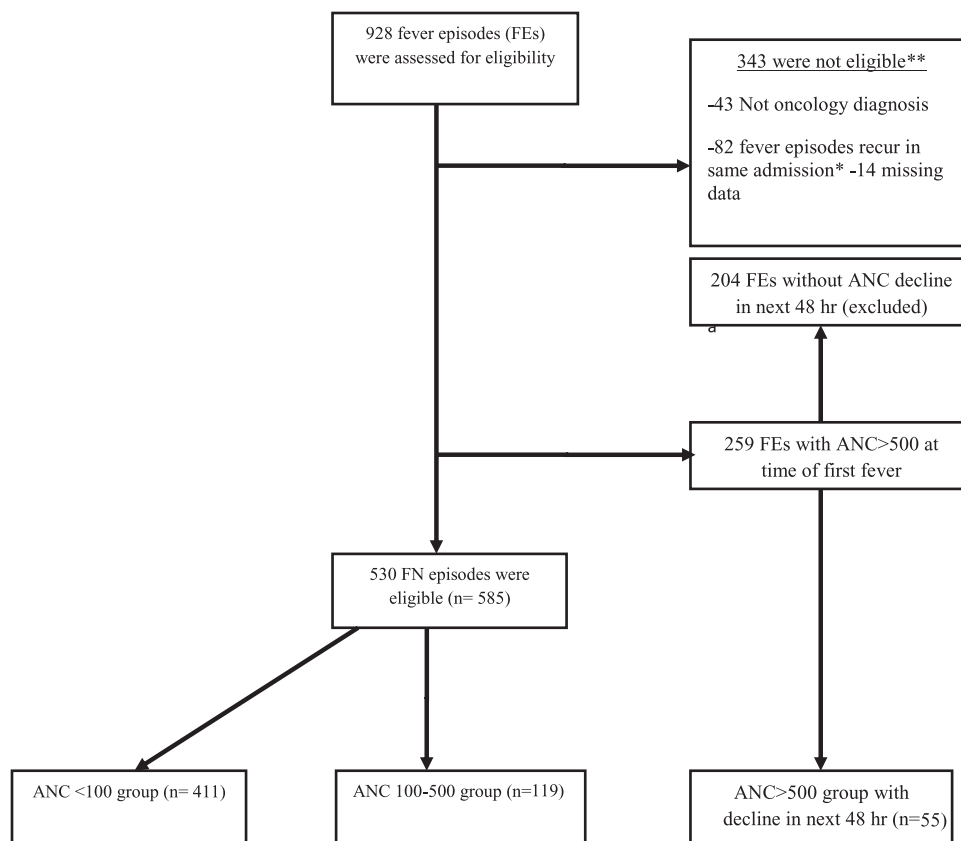


FIGURE 1. Study flow diagram. FNEs based on ANC value at time of presentation.

Six laboratory indices at the time of presentation for all FNEs were recorded, including ANC, the duration of neutropenia below 1000 prior to presentation, absolute monocyte count, absolute lymphocyte count (ALC), platelet count and hemoglobin level. In addition, the duration of neutropenia after fever onset was recorded.

Primary endpoints were BSI and/or IFD occurrence within 30 days of FN presentation, both of which were markers for invasive infections. Secondary endpoints were PICU admission and LOS, both which served as markers for severity of illness.

Definitions

Fever was defined as a single oral temperature of >38.3°C or temperature of >38.0°C sustained over a 1-hour period or on >1 occasion in a 24-hour period.⁶ Neutropenia was defined as an ANC < 500 cells/μL or an ANC of 500–1000 cells/μL with decline to <500 cells/μL during the next 48 hours.⁶ Organisms grown in blood cultures were determined to be a pathogen or a contaminant using the guidance of the National Health Safety Network for skin commensals. BSI was diagnosed when at least 1 blood culture collected during FN grew a true pathogen. Common commensal bacteria were included as “true pathogens” if identified from multiple culture sets, or if a single blood culture set was collected before start of antibiotic therapy and the result deemed clinically significant by the primary or infectious disease team.^{10,11} IFD was stratified as possible, probable, and proven according to the latest EORTC/MSG criteria (2008).¹² FNEs were categorized into 3 groups based on ANC depth at time of presentation into 3 groups, <100, 100–500 and >500 cells/μL with decline in ANC to <500 cells/μL over the subsequent 48 hours. Hereafter, the group with an ANC >500

cells/μL at presentation with subsequent drop in the next 48 hours after presentation will be designated as the “group with ANC >500 cells/μL.”

FNEs were also categorized into 3 groups based on duration of neutropenia (ANC < 1000 cells/μL) prior to presentation: ≤7 days, >7 days, or unknown based on at least 2 recorded ANCs in the 2 weeks prior to presentation. Unknown status was designated to FNEs that did not have any recorded ANC in the 7 days prior to presentation for FN. Similarly, FNEs were also dichotomized into 2 groups based on duration of neutropenia after the onset of fever: ≤ 7 days or >7 days. Duration of neutropenia after fever onset was defined as follows: the first day of fever and neutropenia through the day when ANC recovered to >500 cells/μL or the patient was discharged, whichever day came first.

FNE-related PICU admission was defined by the need for PICU admission within 30 days from presentation with FNE. Patients who were already located in the PICU prior to FNE were not counted as a PICU admission. LOS was defined by the number of days from the first day of FNE until the discharge date. For patients who stayed in the hospital for purposes other than FN management, the LOS was defined by the number of days from the first day of fever until the day antibiotics were discontinued or ANC recovered to ≥500 cells/μL, whichever was later.

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 (ie, concern for central venous catheter infection or septic shock). Cefepime was administered instead of ceftazidime for patients 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 >5–7 days. There were no major changes in FN management during study the period. Patients at high-risk for invasive bacterial infection were placed on prophylaxis (usually ciprofloxacin), or high risk for IFD [SCT, AML, relapsed acute lymphoblastic leukemia (ALL)] were on antifungal prophylaxis (fluconazole, micafungin) based on chemotherapy protocol recommendations

Patients presenting with non-neutropenic fever and stable vital signs to the emergency department or outpatient clinic usually

receive ceftriaxone IV after blood cultures are obtained with outpatient follow-up. If blood cultures turn positive, ANC declines to <500 cells/μL, or fevers persist with clinical changes, patients were admitted for further observation and management.

Data Analysis

The initial step in the analysis involved obtaining descriptive statistics on all dependent and independent variables. Mixed-effects logistic regression models were fit for the PICU, IFD, and BSI outcomes with the inclusion of a random subject effect to account for the multiple observations per patient. For LOS, median lengths of stay were estimated using Cox regression models were fit with robust standard errors to allow for correlation within patients. The initial model for each outcome included all the variables of interest, and then a backward elimination procedure was used to drop variables that were not at least trending towards statistical significance ($P < 0.10$). Plots were based on the final, most parsimonious models. Statistical significance was defined as $P < 0.05$. Analyses were performed using Stata Version 15 (StataCorp, College Station, TX).

RESULTS

A total of 585 FNEs were identified in 265 patients. The mean age was 11.0 (SD = 6.5) years. The majority of FNEs (437/585 or 75%) presented from an outpatient setting, either from the emergency department (ED) or directly from clinic. One-third of patients who had at least 1 FNE (93/265 or 35%) underwent SCT. Of all FNEs, there is (123/585, 21%) FNEs occurred in SCT recipients. ALL was the most common malignancy (173/585, 30%) in 87 patients, followed by neuroblastoma with 103 (18%) in 41 patients, AML with 84 (14%) in 38 patients and lymphoma with 66 (11%) in 34 patients.

FNEs were categorized into 3 groups based on the ANC at the time of presentation. The most common group was ANC < 100 cells/μL with 411 (70%) FNEs, followed by the group with ANC 100–500 cells/μL with 119 (20%), and by the group with ANC >500 cells/μL with 55 (10%). In the last group, ANC nadir to <100 cells/μL occurred in 49/55 (89%), and the majority of BSI (90%)

TABLE 1. Patient Characteristics (N = 585)

Characteristics	N (%)
Age <10 yr	260 (44)
Underlying Diagnosis	
ALL	173 (30)
AML	84 (14)
NB	103 (18)
Lymphoma	66 (11)
Other solid tumors	129 (22)
SCT	117 (20)
Depth of Neutropenia ANC	
0–100	411 (70)
100–500	119 (20)
>500 with drop	55 (10)
Duration neutropenia before FN	
≤7 d	430 (73)
>7 d	101 (17)
AMC < 100	440 (75)
ALC < 300	369 (63)
Platelet < 50	358 (61)
HB < 7	110 (19)
BSI	141 (24)
Invasive fungal disease	47 (8)
PICU admission	87 (15)
30-d mortality	8 (1.3)

NB, neuroblastoma; ; AMC, absolute monocyte counts; HB, hemoglobin level.

TABLE 2. Multivariable Analysis of Risk Factors for Outcomes (IFD, BSI, PICU Admission and LOS)

	IFD	BSI	PICU	LOS*
	OR (95% CI)	OR (95% CI)	OR (95% CI)	HR (95% CI)
Depth of ANC (cells/μL)				
<100 (Reference)	—	—	—	—
100–500	1.49 (0.47–4.72)	0.84 (0.45–1.56)	0.44 (0.14–1.32)	1.20 (0.95–1.51)
>500 with drop in 48	5.91 (1.18–29.65)	2.35 (1.02–5.40)	5.10 (1.34–19.46)	0.55 (0.38–0.81)
Depth of AMC (cells/μL)				
<100 (Reference)	—	—	—	—
>100	0.51 (0.13–1.94)	1.10 (0.57–2.10)	0.90 (0.30–2.69)	1.31 (0.97–1.79)
Depth of ALC (cells/μL)				
<300 (reference)	—	—	—	—
>300	0.35 (0.12–1.00)	0.70 (0.41–1.20)	0.69 (0.30–1.61)	1.21 (0.98–1.50)
Hemoglobin (g/dL)				
>7 (Reference)	—	—	—	—
<7	0.76 (0.25–2.32)	0.89 (0.51–1.56)	0.91 (0.35–2.35)	1.12 (0.93–1.34)
Platelet Count (x 10 ⁶ /μL)				
>50 (Reference)	—	—	—	—
<50	1.24 (0.45–3.44)	2.08 (1.21–3.59)	1.28 (0.53–3.07)	0.89 (0.73–1.08)
Neutropenia days before FN				
≤7 days (Reference)	—	—	—	—
>7 days	2.14 (0.60–7.61)	2.88 (1.55–5.35)	0.89 (0.29–2.71)	0.64 (0.49–0.82)

*Cox regression analysis on LOS. A HR < 1 indicates longer LOS for that group compared with the reference group. A HR > 1 indicates shorter LOS for that group compared with the reference group.

and IFD (80%) occurred in this group. Other hematologic laboratory results are shown in Table 1.

Of the 55 FNEs presenting with ANC >500 cells/μL, 78% (43/55) occurred in patients who received chemotherapy within 2 weeks of presentation versus 65% in the <100 group and 54% and in the 100–500 cells/μL group ($P < 0.05$). Rates of clinical outcomes over ANC groups are shown in Table, Supplemental Digital Content 1, <http://links.lww.com/INF/D804>.

An ALC of <300 cells/μL was identified in 369/585 (63%) of FNEs. In SCT patients, FNEs with ALC <300 were identified 92/369 (25%) of the time, while FNE in non-SCT (AML, ALL+ lymphoma and solid tumor) were identified 277/369 (75%) of the time.

Bivariate Analysis of Risk Factors for Outcomes

No significant difference in rates of IFD, BSI, PICU admission or LOS was found when patients presenting with fevers and ANC <100 cells/μL were compared with ANC 100–500 cells/μL (Table 2).

Higher rates of IFD and BSI were identified in the group with ANC > 500 cells/μL when compared with the group with ANC < 100 cells/μL, (OR = 5.9, 95% CI: 1.18–29.65 and OR = 2.35, 95% CI: 1.02–5.40, respectively). Patients with fevers and ANC >500 cells/μL at presentation were also significantly more likely to be admitted to the PICU (OR = 5.1, 95% CI: 1.34–19.46) and have an increase in LOS [hazard ratio (HR) = 0.55, 95% CI: 0.38–0.81] when compared with the group with ANC < 100 cells/μL (Table 2). Predicted probability of clinical outcomes based on ANC depth is illustrated in (Fig. 2) and Table, Supplemental Digital Content 2, <http://links.lww.com/INF/D805>. The impact of other laboratory indices on the clinical outcomes are shown in Table 2.

Multivariable Analysis of Risk Factors for Outcomes Including Clinical and Laboratory Variables

Invasive Fungal Disease

IFD complicated 47/585 (8%) of all FNEs. Eleven proven IFD were identified. Five patients had fungemia with *Candida* spp,³ *Fusarium* spp¹ and *Histoplasma*.¹ Four had mold infections with deep tissue involvement with *Aspergillus* sp,¹ *Fusarium* sp² and *Zygomycetes*.¹ Two additional patients had 2 disseminated candidiasis. In a multivariate logistic regression model on the basis of covariates laboratory variables assessable at time of presentation, rates of IFD were higher (OR = 3.1, 95% CI: 0.96–10.2) in the group with ANC >500 cells/μL compared with the group with ANC <100 cells/μL (Table 3). Further analysis was conducted after excluding the 25 IFD categorized as “possible,” resulting in 22 (4%) cases of probable and proven IFD in the 3 groups; 14 cases(3.4%) in the ANC < 100 group, 2 cases (1.6%) in the ANC 100–500 group was and 6 cases (10.9%) in the ANC > 500 cells/μL group. Even after excluding possible cases, IFD was still higher in the ANC > 500 cells/μL group (OR = 3.9, $P = 0.044$) (Table, Supplemental Digital Content 1, <http://links.lww.com/INF/D804>).

Additionally, severe lymphopenia ALC ≤ 300 cells/μL was noted to be an independent risk factor for IFD (Table 3).

Blood Stream Infection

BSI occurred in 141 (24%) of FNEs in 105 patients. The most common organisms were viridans group streptococci (21%), followed by coagulase-negative *Staphylococcus* spp. (13%), and *E. coli* (11%). Rates of BSI were higher (OR = 1.9, $P = 0.037$) in the group with ANC >500 cells/μL compared with the group with ANC < 100 cells/μL. There were no differences in rates of BSI

TABLE 3. Multivariable Logistic Regression Analysis on BSI, IFD and PICU

BSI	Odd ratio	Std. Err.	P	95% CI
ANC depth				
Ref ANC <100				
100–500	0.53	0.16	0.36	0.29–1.96
>500	1.94	0.45	0.037	1.07–4.59
Ref. platelet >50				
Platelet ≤50	2.23	0.58	0.02	1.33–3.72
Prior neutropenia				
≤7 d				
>7 d	2.88	0.89	0.01	1.56–5.29
Prior chemotherapy				
In last 2 weeks	2.80	0.41	0.011	1.14–4.84
Diagnosis				
ALL/ Lymphoma				
AML/mixed	2.94	1.06	0.003	1.45–5.97
SCT	1.50	0.32	0.08	0.58–1.91
Soild tumor	0.61	0.17	0.081	0.35–1.06
IFD				
ANC depth:				
Ref ANC <100				
ANC 100–500	0.43	0.28	0.20	0.12–1.54
>500	3.13	1.88	0.058	0.96–10.2
AMC depth:				
Ref AMC <100				
AMC >100	0.51	0.34	0.325	0.13–1.93
ALC depth:				
Ref ALC <300				
ALC >300	0.33	0.17	0.038	0.11–0.94
Prior neutropenia				
Ref ≤ 7days				
>7 days	1.30	1.47	0.589	0.42–3.05
Chemotherapy in last 2 weeks 				
Diagnosis	1.49	0.65	0.92	0.63–3.50
AML/mixed	6.70	5.18	0.014	1.47–30.5
SCT	3.68	2.28	0.035	1.09–12.4
Solid tumor	1.65	1.10	0.44	0.45–6.08
PICU 				
ANC depth				
Ref ANC <100				
ANC 100–500	0.22	0.13	0.01	0.071–0.7
>500	2.94	1.45	0.02	1.12–7.74
Prior neutropenia				
Ref ≤7 days				
>7 days	0.52	0.55	0.97	0.35–2.94
Chemotherapy in last 2 weeks 				
Diagnosis	1.34	0.47	0.40	0.66–2.68
AML/mixed	2.69	1.78	0.13	0.73–9.85
SCT	1.95	0.95	0.16	0.75–5.07
Soild tumor	0.95	0.48	0.92	0.35–2.56

between patients presenting with ANC < 100 when compared with ANC of 100–500 cells/μL (Table 3). Prior neutropenia >7 days, severe thrombocytopenia, chemotherapy in last 2 weeks and AML were independent risk factors for BSI (Table 3).

PICU Admission Within 30 Days

Eighty-seven (15%) FNEs required escalation of care and transfer to the PICU within 30 days of presentation. The majority (88%) occurred within 7 days of presentation. FNEs were significantly more likely to be admitted to the PICU (OR = 2.9, 95% CI: 1.12–7.74) in the group with ANC >500 compared with the group with ANC < 100 cells/μL (Fig. 1). The duration of prior neutropenia and other laboratory variables studied did not impact PICU admission (Table 3). The study lacked the power to perform multivariable analyses related to mortality as this outcome was rare, only occurring in 8/585 (1.3%) FNEs (Table, Supplemental Digital Content 1, <http://links.lww.com/INF/D804>).

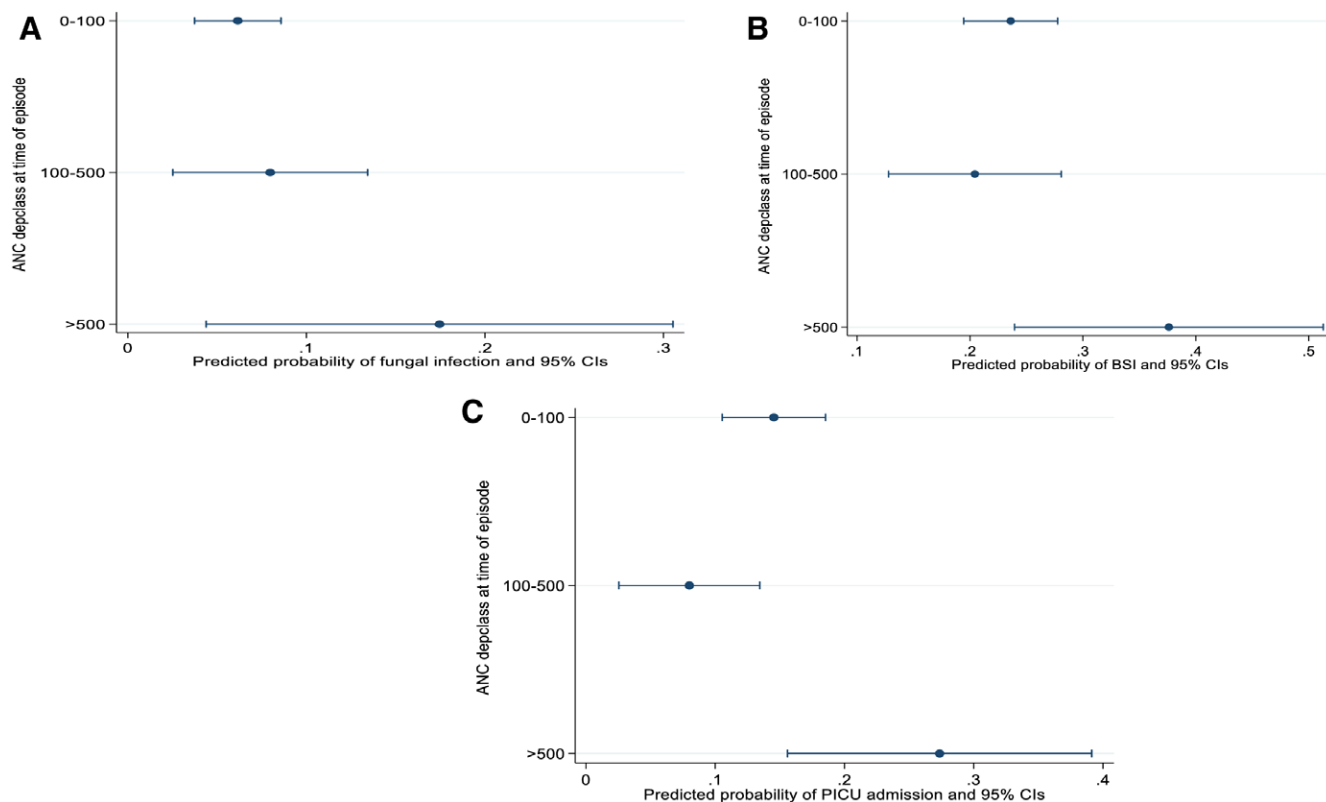


FIGURE 2. Predicted probability of IFD, BSI and PICU rate based on ANC depth at time of presentation on Multivariate analyses. A: Predicted probability of IFD for ANC groups (0–100), (100–500) and >500 are 6%, 8% and 17%, respectively. B: Predicted probability of BSI for ANC groups (0–100), (100–500) and >500 are 23%, 20% and 37%, respectively. C: predicted probability of PICU admission for ANC groups (0–100), (100–500) and >500 are 14%, 7% and 27%, respectively. Figure 1 shows that group presented with ANC >500 cells/μL with drop to <500 in next 48 h have higher risk probabilities developing IFD, BSI and more likely to be admitted in PICU when compared with other 2 groups (ANC<100, and 100–500 cells/μL)

Length of Stay

LOS was more prolonged in the group with ANC > 500 cells/μL group compared with other 2 groups: ANC < 100 (median 10 days vs. 6 days) (HR = 0.55, 95% CI: 0.38–0.81) and 100–500 cells/μL (median 10 vs. 4 days) (HR = 0.46, 95% CI: 0.32–0.67). The group presenting with an ANC ≤ 300 was admitted for 2 days longer when compared with groups presenting with ANC > 300 cells/μL (median 7 days vs. 5 days) (HR = 1.21, 95% CI: 1.00–1.56). These results are shown in Table 2.

DISCUSSION

The results of this large cohort study of pediatric FN demonstrate the impact of depth and duration of neutropenia on clinical outcomes. Our results highlight the risks of BSI, IFD and PICU admissions in the population of patients with an ANC > 500 with subsequent decline in 48 hours, independence of underlying diagnosis, which is not specifically highlighted in other guidelines. These findings provide important data that may be used to optimize current clinical practice guidelines.

The relationship of quantitative ANC and adverse outcomes was first described by Bodey et al after finding that patients with acute leukemia presenting with profound neutropenia (ANC ≤ 100 cells/μL) were more likely to have severe infections and conversely, that infection rates decreased when ANCs rose.¹³ Most research studies in the pediatric literature treat ANC as a dichotomous

variable, ANC ≤ 100 or with ANC > 100 cells/μL.^{2–4,14,15} There are couple studies that predict the likelihood of BSI in pediatric patients with cancer and fever without severe neutropenia^{16,17}; however, there are limited data to guide the optimal management and clinical outcomes for pediatric oncology patients with fever and an ANC > 500 cells/μL with a subsequent marked decrease.^{15,18} In clinical practice, when patient present to ED with fever and ANC > 500 cells/μL, most clinicians choose to give 1 dose of broad-spectrum antibiotics (often ceftriaxone) after obtaining blood cultures with close outpatient follow-up. However, our findings suggest that this group had a trend toward invasive infections and adverse outcomes, particularly patients who has ANC decline with recently received chemotherapy.^{19,20}

In our cohort, nearly 70% of FNEs in the group who had ANC > 500 cells/μL had a documented invasive infection, with 44% having a BSI and 18% having an IFD from all episodes in this group. These findings suggest that the ANC at the time of presentation is much less important than the actual decrease in and nadir of the ANC. Interestingly, when we conducted separate analysis treating ANC as a dichotomous variable with only 2 groups; ANC ≤ 100 or ANC > 100 cells/μL (merging group with ANC 100–500 and ANC > 500 in 1 category), findings showed no difference in outcomes (BSI, IFD, LOS) (data not shown).

Bodey et al¹³ also described the relationship between episodes of falling neutropenia and the occurrence of severe infection and higher morbidity and mortality.²¹ Studies focusing on the

relationship between ANC depth and PICU admission or LOS in pediatric FN are lacking.

Previous studies have shown that the longer the patient remains neutropenic after presentation, the higher the risk of developing a severe infection.^{13,22} There was no statistically significant difference in IFD rate between the 2 groups (longer and shorter neutropenia). The effect of neutropenia duration may have been blunted in our study given that we excluded secondary or recurrent fever episodes for patients in a single admission. Further analysis including these recurrent FNEs supported prior studies that longer durations of neutropenia increase the risk of IFD (OR=2.9, $P = 0.02$). We showed that neutropenia prior to presentation was associated with risk of BSI and LOS, but not of IFD and PICU admission.

Previous studies showed that the monocyte nadir is a possible indicator for neutrophil nadir during cancer chemotherapy²³ and can be used as a tool for predicting severe infection and poor outcomes.^{2,24} We found, in contrast, that absolute monocyte count ≤ 100 did not impact of any outcomes of interest, including BSI. Additionally, lymphopenia has been identified as a risk factor for IFD in adult hematopoietic SCT recipients,²⁵ but has not been assessed in pediatric studies. In our study, multivariate analysis of the group with $ALC \leq 300$ cells/ μ L at the time of presentation had higher incidence of IFD (OR = 3.3) when compared with patients who had $ALC > 300$ cells/ μ L.

Consistent with other studies,^{4,18} we found that severe thrombocytopenia (< 50 /mL) at presentation, prolonged duration of neutropenia and diagnosis of AML were all predictors for BSI in multivariate analysis.

The current study has several important limitations. First, it is a retrospective, single-center analysis, and results may not be generalizable to other institutions with different practices of antimicrobial prophylaxis and different empiric management of FN. Second, the ANC groups at time of presentation were selected to represent upper and lower boundaries, and we did not investigate the impact of ANC dynamics or antimicrobial prophylaxis on clinical outcomes. Our goals were to determine the impact of depth and duration of neutropenia on outcomes regardless of underlying diagnosis or clinical presentation. However, given that subjective clinical variables were not analyzed and most of our data are quantitative, the potential for informational bias and error in abstracting clinical variables are minimal. To decrease observer bias, risk factors and the outcomes of interest were recorded by different investigators (M.A, L.A.P, T.S) to blind associated variables in each FNE. Data pulled from our data warehouse were supplemented by manual review of the EMR.

In conclusion, our study finds that pediatric patients presenting with FN and initial ANC > 500 cells/mL with decline over the subsequent 48 hours had a higher incidence of BSI, IFD, and 30-day morbidity. Although the overall risk of severe infection and morbidity is greatest with the lowest ANC nadir, clinicians must remain vigilant when caring for patients presenting with fever and initial ANC > 500 cells/mL after undergoing recent chemotherapy if continued decline is expected.

Prospective studies of FN among children enrolled in large multicenter trials may be beneficial in evaluating these risk factors to further guide clinical care and may be incorporated into current risk prediction models.

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