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Ngai JNL, Masacupan KDT, Racho ARR, Del Rosario MLU, Lagaya-Arañas LMO, Luna IA. Clinical and Microbiological Profile and Factors Affecting Outcome among Pediatric Febrile Neutropenic Patients with Hematologic Malignancies.
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ORIGINAL ARTICLE

CLINICAL AND MICROBIOLOGICAL PROFILE AND FACTORS AFFECTING OUTCOME AMONG PEDIATRIC FEBRILE NEUTROPENIC PATIENTS WITH HEMATOLOGIC MALIGNANCIES

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ABSTRACT

Objective: To evaluate the clinical and microbiological profile and factors affecting outcome among pediatric febrile neutropenic (FN) patients with hematologic malignancies (HM)

Methodology: This was a cross-sectional study which looked into medical records of Filipino children 0-18years old diagnosed with FN and HM and admitted from June 2016 up to June 2022 at the St. Luke's Medical Center, Quezon City (SLMC-QC). Data on age, sex, underlying malignancy, stage of treatment, site of infection, presence of central line, initial antibiotic therapy, culture positivity and isolates were retrospectively evaluated. Incomplete records were excluded. The relationship between clinical & microbiologic profile and outcomes were analyzed using T-test and Chi-square test. Significance was set at $p<0.05$.

Results: This study included 267 episodes of FN. Patients had a mean age of 8.3 years with male preponderance (59%). The most frequent underlying malignancy was acute lymphoblastic leukemia (61%). Episodes occurred primarily during the induction (40%) and consolidation phases (28%) of chemotherapy. Most (65%) had an absolute neutrophil count (ANC) of $<100/mm^3$. Central line catheter was present in 59% of episodes and 52% had an implanted port. There was no identifiable focus of infection in 52% of cases. Gram-negative bacteria, specifically *Klebsiella pneumoniae* (13%) and *Escherichia coli* (11%) were the most common isolates. Most patients (88%) recovered. Age >10years, male sex, diagnosis of acute myelogenous leukemia, relapse disease, ANC $<100/mm^3$, presence of a central line, and central line associated bloodstream infection were significantly associated with duration of hospital stay. Presence of central venous line was the most significant factor associated with mortality.

Conclusions: Several clinical and microbiological factors, specifically age >10years, male sex, diagnosis of acute myelogenous leukemia, relapse disease, ANC $<100/mm^3$, presence of a central line, and central line associated bloodstream infection, were documented to significantly affect outcome in Filipino pediatric FN patients with HM.

KEYWORDS: *Pediatric, Febrile Neutropenia, Hematologic Malignancies, Leukemia, Philippines*

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INTRODUCTION

Febrile neutropenia (FN) is a medical emergency posing a high mortality rate if not treated promptly and aggressively.[1] The most effective empirical antimicrobial regimen must be rapidly administered to patients as delay in treatment may result in septicemic shock and increase mortality.[2] FN has been observed to be much more common in hematologic malignancies.[3] Mortality has been associated with several factors such as duration and degree of neutropenia, bacteremia, isolation of resistant organisms, identifiable focus, performance status, comorbidities, and type of underlying malignancies.[4]

Treatment practices for FN vary between centers and depend on institutional policies, hospital isolates, and physician preferences. Governing bodies recommend the use of empiric agents that specifically cover for invasive gram-negative bacteria, especially *Pseudomonas aeruginosa,* but defer to the physician's best judgment to suit the situation and needs of the patient.[5] A high prevalence of infections in the community and antibiotic resistance due to the unrestricted and rampant use of broad-spectrum antibiotics further complicates disease management.[6]

It is worthwhile to evaluate the clinical profile, pathogenic organisms, pattern of antibiotic sensitivity, and outcome of treatment among high risk hematologic malignancies with febrile neutropenia. While there are innumerable studies from Western countries on febrile neutropenia and its etiology, choice of empiric antibiotic and outcome, literature on febrile neutropenia patients in developing countries is gradually evolving.[6] In the Philippines, local data remain sparse and there is absence of local standard protocols established for the management of febrile neutropenia in pediatric patients with hematologic malignancies thus, this study looked into the clinical and microbiological profile and factors affecting outcome among pediatric febrile neutropenic patients with hematologic malignancies.[7-9]

MATERIALS AND METHODS

Study Design

A cross-sectional analytic study design was utilized which included records of Filipino patients 0 to 18 years old diagnosed with hematologic malignancies who were admitted for and/or developed febrile neutropenia during their admission from June 2016 to June 2022 at St. Luke's Medical Center, Quezon City (SLMC-QC). For the purpose of this study, hematologic malignancies refer to the three main types, specifically: leukemia, lymphoma, and multiple myeloma.

Inclusion Criteria

Filipino children aged 0 to 18 years and 354 days admitted at SLMC-QC between June 2016 to June 2022 and diagnosed with hematologic malignancy and admitted for or developed febrile neutropenia during the period of admission were included.

Exclusion Criteria

Patients with the following conditions were excluded: (1) fever attributed to malignancy, blood transfusion, or medications; (2) concurrent COVID-19 infection; and (3) those with incomplete data.

Sample Size and Sampling

To estimate the sample size, Cochran's formula was used where the margin of error (e) was set at ±5% (95% confidence). In a study by Anirban and Amit, prevalence was estimated at 12.8%.[10] Based on this, the computed sample size for this study was 171. Patients were screened for eligibility until a total of 267 unique episodes of FN in 96 distinct patients were obtained.

Data Collection

Convenience sampling of charts at the medical records of SLMC-QC was performed and documents were screened for eligibility using the set criteria. No randomization was done since all patients were assigned under one group and no blinding procedures on patients, investigators, and study staff was implemented.

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Clinical and microbiological profile of pediatric patients with febrile neutropenia and hematologic malignancies admitted from June 2016 to June 2022 was obtained. The following data were collected: age, sex, underlying malignancy, stage of treatment, absolute neutrophil count (ANC), site of infection, presence of central venous catheter, initial antibiotic therapy, culture positivity and culture isolate. Charts with incomplete data were excluded.

Outcomes noted were mean duration of hospital stay, recovery from infection, and status upon discharge whether recovered or expired.

Data Analysis

Data encoding utilized Microsoft Excel 2018. EpiInfo 3.5.3 software was used in processing and analyzing the data gathered. Descriptive statistics were generated for all variables using mean and standard deviation. Frequencies and percentages were computed for nominal data. T-test for numerical data and Chi-square test for nominal data were used to determine whether there were significant differences between factors. Clinical and microbiologic profiles of pediatric febrile neutropenia were analyzed using frequency and percentage for categorical profiles and mean and standard deviation for continuous profiles. Determination of the relationship between duration of hospital stay with the clinical and microbiologic profile was analyzed using T-test and Chi-square test. Level of significance was set at $p < 0.05$.

Ethical Issues

The study abided by the Principles of the Declaration of Helsinki and was conducted following the Guidelines of the International Conference on Harmonization-Good Clinical Practice (ICH-GCP). The Clinical Protocol and all relevant documents were reviewed and approved by the SLMC-QC Institutional Ethics Review Committee. Only the investigator was allowed to view the patient's files within the vicinity of the medical records section. Patient confidentiality was respected by ensuring anonymity of records. Each patient document was coded and did not contain any identifying information to ensure confidentiality.

All study data were recorded and investigators were responsible for the integrity of the data (i.e. accuracy, completeness, legibility, originality, timeliness and consistency).

RESULTS

Clinical Profile

There were 267 episodes of FN documented in this study. Table 1 shows the clinical profile of subjects. Average age was 8.3 years old with 64% belonging to the <10 years age group. Male-female distribution showed a male preponderance at 59%.

Acute lymphoblastic leukemia (ALL, 61%) was most frequent among the hematologic malignancies, followed by acute myelogenous leukemia (AML, 36%). Majority of febrile neutropenia episodes developed during the induction phase (40%) and consolidation phase (28%) of chemotherapy. Most (65%) had an ANC <100/mm^3 upon diagnosis of febrile neutropenia.

Central line catheter was present in 157 episodes (59%) with 139 (52%) having a central venous access device (CVAD). Most did not have an identifiable focus of infection (52%), while in those with a focus, the most common were pulmonary (17%), gastrointestinal (14%), and catheter-associated (10%).

Table 1. Clinical profile of pediatric febrile neutropenia patients with hematologic malignancies

Parameter	N= 267
Age (years)	8.25±4.986
Less than 10	171 (64%)
10 or more	96 (36%)
Sex	
Male	158 (59%)
Female	109 (41%)
Malignancy	
ALL	164 (61%)
AML	97 (36%)
Lymphoma	3 (1%)
Chronic myelogenous leukemia	3 (1%)

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Table 1 continued. Clinical profile of pediatric febrile neutropenia patients with hematologic malignancies

Parameter	N= 267
Treatment Phase	
Induction	107 (40%)
Consolidation	75 (28%)
Relapse	52 (19%)
Maintenance	33 (12%)
ANC (/mm^3)	
Less than 100	174 (65%)
>100-500	58 (22%)
>500-1000	35 (13%)
Presence of Central Line	
Central Access Venous Device	
None	139 (52%)
Peripherally Inserted Central	110 (41%)
Catheter	16 (6%)
Internal Jugular	2 (1%)
Identified Site of Infection	
None	138 (52%)
Pulmonary	46 (17%)
Gastrointestinal	38 (14%)
Catheter-associated	27 (10%)
Skin and Soft tissue	14 (5%)
Genitourinary	4 (1%)

Microbiological Profile

Most episodes of febrile neutropenia had negative cultures with only 29% culture positivity. Overall, 93 culture isolates were identified. Majority were gram-negative bacteria (63.4%), followed by gram-positive (25.8%), and fungal isolates (10.8%). The most common gram-negative isolate was *Klebsiella pneumoniae*. The most common gram-positive isolate was *Staphylococcus epidermidis*.

Table 2. Microbiological profile of pediatric febrile neutropenia patients with hematologic malignancies

Culture Profile	Values
Culture Positivity	N=267
No growth	190 (71%)
Growth	77 (29%)

Table 2 continued. Microbiological profile of pediatric febrile neutropenia patients with hematologic malignancies

Culture Isolate	N=93
Gram-negative	**59 (63.4%)**
Klebsiella pneumoniae	13 (4.9%)
Escherichia coli	11 (4.1%)
Escherichia coli ESBL+	8 (2.6%)
Pseudomonas putida	5 (1.9%)
Klebsiella pneumoniae ESBL+	3 (1.1%)
Acinetobacter baumannii	3 (1.1%)
Aeromonas hydrophila	2 (0.7%)
Salmonella spp.	2 (0.7%)
Bacillus cereus	1 (0.4%)
Bacillus megaterium	1 (0.4%)
Enterobacter cloacae	1 (0.4%)
Enterococcus faecalis	1 (0.4%)
Enterococcus faecium	1 (0.4%)
Enterococcus spp.	1 (0.4%)
Kingella kingae	1 (0.4%)
Neisseria flava	1 (0.4%)
Proteus penneri	1 (0.4%)
Pseudomonas aeruginosa	1 (0.4%)
Sphingomonas paucimobilis	1 (0.4%)
Stenotrophomonas maltophilia	1 (0.4%)
Gram-positive	**24 (25.8%)**
Staphylococcus epidermidis	11 (4.1%)
Streptococcus oralis	3 (1.1%)
Staphylococcus aureus	2 (0.7%)
Staphylococcus capitis	2 (0.7%)
Micrococcus luteus	1 (0.4%)
Staphylococcus cohnii	1 (0.4%)
Staphylococcus haemolyticus	1 (0.4%)
Staphylococcus hominis	1 (0.4%)
Streptococcus mitis	1 (0.4%)
Streptococcus viridans	1 (0.4%)
Fungal	**10 (10.8%)**
Candida parapsilopsis	3 (1.1%)
Candida tropicalis	3 (1.1%)
Candida albicans	2 (0.7%)
Candida norvegensis	1 (0.4%)
Candida spp.	1 (0.4%)
Rhodotorula mucilaginosa	1 (0.4%)

Table 3 shows that the most common antibiotics administered were cefepime (66%) and meropenem (9%). Fifteen (6%) were given metronidazole and thirteen (5%) given fluconazole.

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Table 3. Antibiotics used during for febrile neutropenia

Antibiotics	Frequency of Use
Cefepime	175 (66%)
Meropenem	24 (9%)
Metronidazole	15 (6%)
Fluconazole	13 (5%)
Piperacillin Tazobactam	11 (5%)
Vancomycin	9 (3%)
Cefuroxime	7 (3%)
Clindamycin	7 (3%)
Ceftazidime	6 (2%)
Amikacin	5 (2%)
Amoxyclav	5 (2%)
Cefixime	3 (1%)
Acyclovir	2 (1%)
Amphotericin B	2 (1%)
Levofloxacin	2 (1%)
Azithromycin	1 (0%)
Ceftriaxone	1 (0%)
Ganciclovir	1 (0%)
Micafungin	1 (0%)

Of 93 isolates identified, 17 were documented to be resistant to 3rd and 4th generation cephalosporins (i.e. ceftriaxone, ceftazidime, and cefepime) and of these, 11 were ESBL-positive, comprising a mixture of *E. coli* and *K. pneumoniae*.

Outcome

The average duration of hospital stay was 30.1 days. Of 267 episodes, 235 (88%) were discharged alive and improved while 32 (12%) expired (Table 4).

Table 4. Duration of hospital stay and outcome

Outcome	
Duration of hospital stay (days)	30.10±34.04
Status upon discharge	N=267
Alive	235 (88%)
Expired	32 (12%)

Factors Affecting Outcome

Age >10 years old (31.3 vs 28, p=0.01) and male sex (35.63 vs 22.08, p=0.01) were identified to have significantly longer duration of hospitalization.

The type of malignancy was identified to affect duration of hospital stay, with AML having a significantly longer duration of hospital stay (39.9 days, p=0.01) compared with other hematologic malignancies. Those who were on relapse had longer hospitalization (40.56 days, p=0.01) compared with those who were on standard phases of chemotherapy. Having an ANC of <100/mm^3 had significantly longer duration of hospital stay at 34.5 days (p=0.01).

Presence of CVAD and PICC had significantly longer hospital stay at 38.5 days and 35.9 days, respectively (p<0.01 for both). Among all the factors studied, having catheter-associated infection was associated with the longest duration of hospital stay at 67.2 days (p<0.01). The presence or absence of growth in culture was not associated with significant differences in duration of hospital stay.

Table 5. Correlation of clinical and microbiologic factors with duration of hospital stay

Factor	N= 267	Duration of hospital stay (days)	p-value
Age (years)			
10 or more	**171**	**31.27**	**0.01***
Less than 10	96	28.00	
Sex			
Male	**158**	**35.63**	**0.01***
Female	109	22.08	
Malignancy			
AML	**97**	**39.87**	
CML	164	26.00	**<0.01***
ALL	3	24.67	
Lymphoma	3	15.00	
Treatment Phase			
Relapse	**52**	**40.56**	
Induction	107	31.04	**0.01***
Consolidation	75	28.55	
Maintenance	33	14.09	
ANC (/mm^3)			
Less than 100	**174**	**34.51**	**0.01***
>100-500	58	24.78	
>500-1000	35	16.97	
Presence of Central Line			
CVAD	**139**	**38.48**	
PICC	**16**	**35.88**	**<0.01***
None	110	18.90	
IJ	2	17.00	
Site of Infection			**<0.01***
Catheter-associated	**27**	**67.15**	
Pulmonary	46	35.28	
Gastrointestinal	38	25.84	
Skin and Soft tissue	14	25.14	
None	138	23.08	
Genitourinary	4	20.25	
Culture	77	36.30	0.051
Growth	190	27.58	
No growth			

*Significant at p-value <0.05

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As for status upon discharge (Table 6), the only variable correlated with outcome was the presence of central venous catheters. Specifically, having a CVAD was identified to have a 6 times higher (OR=6.277, 95% CI 1.890-20.851, p=0.003) likelihood of death while for PICC, there was a 9 times higher likelihood of death (OR=9.106, 95% CI 1.652-50.181, p=0.011).

Table 6. Correlation of clinical and microbiologic factors with status upon discharge

Factor	Odds Ratio	95% Confidence Interval	p-value
Age	2.815	0.964-8.225	0.058
Sex	1.336	0.521-3.43	0.546
Malignancy	0.109	0.004-3.031	0.191
ALL			
AML			
Lymphoma			
CML			
Treatment Phase	3.093	0.289-33.072	0.350
Relapse			
Induction			
Consolidation			
Maintenance			
ANC (/mm^3)	0.189	0.007-5.139	0.323
Less than 100			
>100-500			
>500-1000			
Central Line			
PICC	**9.106**	**1.652-50.181**	**0.011***
CVAD	**6.277**	**1.89-20.851**	**0.003***
Identified site of Infection	0.748	0.214-2.614	0.649
Gastrointestinal			
Catheter-associated			
Pulmonary			
None			
Skin and Soft tissue			
Genitourinary			
Culture Growth	1.622	0.153-17.21	0.688
Growth			
No Growth			

*Significant at p-value <0.05

DISCUSSION

This study identified that among the different hematologic malignancies, ALL was the most common underlying malignancy followed by AML. A similar incidence was also seen in other studies.[11] Febrile neutropenia was more common in diseases treated with dose-intensive therapies and bone marrow involvement such as ALL and AML. On the other hand, the higher incidence of ALL compared to AML could be attributed to the fact that ALL is more common in children with a lower incidence of childhood AML compared to adults.

In our study, the frequency of febrile neutropenia was highest in patients on the induction and consolidation phases of chemotherapy, consistent with findings across literature.[12-14] Induction and consolidation are considered as intensive chemotherapy while CNS consolidation and maintenance are considered as non-intensive phases.[12] Chemotherapy regimens administered during these intensive phases are of higher dose and considered to be myeloablative resulting in significant bone marrow suppression and consequently may cause longer neutropenia.[13,14]

Similar to other studies, the risk of developing febrile neutropenia was greater in patients with ANC <500/mm^3 and increases dramatically in those with ANC <100/mm^3.[1] In a study by Oderoi et al., ANC <100/mm^3 was identified as an independent predictor for febrile neutropenia.[12]

Most episodes of febrile neutropenia did not have an identifiable focus of infection. However, the absence of clinical signs or symptoms of infection in a great proportion of febrile neutropenic episodes does not exclude its presence.[15] Granulocytopenia markedly alters the host's inflammatory response making the classic signs and symptoms of infection undetectable. In addition, children with febrile neutropenia are less likely to have a clinically apparent site of infection compared to adults.[11]

We observed that the culture positivity rate in our study was only 29%. In general, the causative agent was not demonstrable in 60 to 70% of cases of febrile neutropenia episodes even with the best laboratory conditions.[16] This finding is consistent with various studies from both developed and developing countries reporting similar rates from 13 to 34%.[17-19] These results were also comparable with the study of Zahid et al. who reported microbiologically documented infection in only 31% of febrile neutropenic episodes.[20]

This study also demonstrated that gram-negative organisms are still the most predominant pathogens in febrile neutropenia as is observed among other developing countries.[16] In a study by Malabagi et al. in India of febrile neutropenia in hematologic malignancies, the most common organisms isolated were gram-negative bacilli.[3] A surveillance study at the pediatric oncology unit of the University Hospital in Kuala Lumpur showed that gram-negative bacteria comprise majority of isolates and identified these as the etiology of bacteremia in this group of patients.[21] Although there is a rising incidence of gram-positive bacteremia in febrile neutropenic patients this is observed more commonly among developed countries and have attributed this to the increasing use of indwelling catheters.[15]

On review of our institutions own and most recent hospital antibiogram (based mostly on cultures from adult patients), *K. pneumoniae* remains to be one of the top 3 bacterial isolates as a cause of infection in different organ systems cultured, consistent with what was shown in our study. The spectrum of bacterial isolates in our study was similar to what has been reported internationally.[22] This finding is congruent with the study of Harrifin et al. in Thailand, where *K. pneumoniae* was consistently the most common bacterial isolate in cancer patients, accounting for up to 20% of blood-culture isolates yearly.[23] In a study in Taiwan where they examined bacteremia in hematological and oncological children with febrile neutropenia, the most common isolates were Gram-negative bacteria, including *K. pneumoniae*.[24] In addition, it has been reported that there is an alarming increase in the isolation of extended-spectrum β-lactamase (ESBL)–producing bacteria. A recent study identified ESBL-producing isolates in 51.6% of *K. pneumoniae* bacteremia in children with hematologic/oncologic disease.[23-25] The rate of ESBL-producing isolates in this study was 11.82%, similar to findings which peg the incidence at 12 to 44% globally.[24,26] Factors responsible for the acquisition of ESBL-producing bacterial infections are prolonged hospital stay and prior use of broad-spectrum cephalosporins. Some consider the use of antimicrobial prophylaxis, specifically fluroquinolones to have some association with the development of ESBL production in *E. coli* and *K. pneumoniae,* although the mechanisms behind this association has yet to be elucidated on.[25] No patients in this study was given fluroquinolones as antibacterial prophylaxis for FN.

The first line antibiotic therapy used in this study was cefepime. It provides good activity against most Gram-negative bacteria and has been extensively studied for febrile neutropenia with good control of the disease.[27,28] Due to its good gram-negative, as well as gram-positive coverage, including coverage for methicillin-sensitive *S. aureus* and penicillin-non-susceptible alpha-streptococci, cefepime is a good candidate for use as empiric treatment for neutropenic fever.[27] In addition, this agent offers the advantage of Gram-positive coverage similar to that of cefotaxime and ceftriaxone, as well as good activity against *Pseudomonas aeruginosa* and many enteric bacilli that are resistant to third generation cephalosporins, including clinical isolates of *Enterobacter spp*. and *Citrobacter freundii*.[29] According to the IDSA guidelines, among the cephalosporins, cefepime can be used as a single agent for treating febrile neutropenic patients.[30]

Among the different identified clinical and microbiological parameters, it was found that age >10 years, male sex, diagnosis of AML, relapse state, having ANC <100/mm^3, presence of central line, and having catheter-associated infections had a significantly longer hospital stay.

With regard to age, younger children have a better prognosis and outcome for both ALL and AML. Holmes et al. rationalized that in malignancies like ALL, tumor cell type significantly influenced survival, with older children 10-19 years at diagnosis, being more likely to be diagnosed with T-cell ALL as opposed to B-cell ALL. They also showed that children in the 10-19 years age group were two times as likely to die compared to younger children.[31] In general, younger children respond better to treatment which may be related to the previously described good risk features. In a study by Hann et al.

comparing outcomes from febrile neutropenic episodes in children, they observed that the younger group also had a less defined site of infection.[11]

To our knowledge, there are no studies available directly correlating sex and outcome, specifically male sex and duration of hospital stay in febrile neutropenic patients. In a study done by Sulivan et al., in patients with hematologic malignancies, male sex was a risk factor for the development of perianal infections.[32] The pathogenesis of perianal infection in the neutropenic patient is similar to that in the immunocompetent patient. Male sex was a statistically significant predictor for early mortality among patients with chemotherapy-induced febrile neutropenia.[33] Although not well understood, the above findings may contribute to the longer duration of hospitalization and poorer outcomes in males given the difficulty of management and high rate of recurrence of anorectal complications.[34]

Cytogenomic subtypes may play a role in affecting the prognosis of hematologic malignancies. In ALL, the T-cell immunophenotype is reportedly twice as common in males and associated with poorer outcomes when compared to the B-cell immunophenotype which may contribute to the observation of increased likelihood of mortality in males.[31,35]

The type of hematologic malignancy affected outcomes, with this study identifying AML as having a longer duration of hospital stay. In a study by Ylmaz et al., they identified that AML was generally associated with significantly longer duration of neutropenia, fever resolution, and antibiotic administration.[21] In another study, they attributed this to the high dose Ara-C (cytarabine) regimen of AML which is also associated with high infectious mortality.[36]

In terms of relapse, it is known that the risk of febrile neutropenia is higher in children with cancer who have relapsed and who have advanced disease regardless of treatment. Additionally, as a consequence of receiving higher doses of chemotherapy for treatment of advanced disease, the risk for febrile neutropenia increases.[37] In a similar study, they identified that a greater percentage of acute leukemia patients in relapse tended to have longer febrile episodes and would require antibiotic changes than leukemia patients in remission, resulting in significantly longer hospital stay.[38]

The severity of febrile neutropenia, as reflected in the ANC, has consistently been correlated with morbidity, mortality and treatment delays in malignancies.[1] Children hospitalized for fever and neutropenia who have persistent fever and an ANC of <100/mm^3 are at high risk for morbidity and more likely to require antibiotic changes and antifungal therapy.[39] This is because the risk of clinically important infection rises as the neutrophil count falls.[40] On the other hand, children with ANC of 100/mm^3 who are classified as low risk would be candidates for early hospital discharge. This includes those with a diagnosis of ALL, non-progressive/relapse disease, not in the intensive phase of chemotherapy for ALL, and clinical stability that would otherwise not require inpatient care.[13]

In our study, the presence of central line and catheter-associated infection, among all the factors identified, was the one shown to be associated with the longest duration of hospital stay. Furthermore, the presence of PICC or CVAD was the only factor identified to be associated with a higher likelihood of mortality at 9 and 6 times higher, respectively.

In general, studies have identified central line associated blood stream infection (CLABSI) as a serious event. Although there is a large body of published evidence regarding CLABSI attributed to morbidity and mortality in adult populations with malignancies, information is still lacking in the pediatric population.[41]

Studies have shown that CLABSI results in prolonged hospital stay, increased mortality, and substantial costs to the healthcare system.[42] In a study by Roger et al. on CLABSI in children with AML, there is a significant increase in morbidity and admission to the pediatric ICU and a trend toward increased mortality.[43] Important consequences of CLABSI aside from extended hospital stay also include

interruption of chemotherapy or other treatment, catheter removal, intravascular thrombosis, endocarditis, and sepsis.[41] Prevention of CLABSI during episodes of febrile neutropenia is essential to further improve the long-term outcomes in pediatric patients with hematologic malignancies.

The major limitation of this study was its retrospective nature and single center experience. Although we only included pediatric febrile neutropenic patients with hematologic malignancies, complexities of the underlying malignancies makes the patient population heterogenous which may cause bias. This however may be remedied in future studies by increasing the sample size. Other clinical and microbiologic factors that have been shown to affect outcome (i.e. race, risk stratification, serial monitoring of ANC, duration of neutropenia, type of chemotherapy used, duration from last chemotherapy, cause of death) were also not included in this study. These may be addressed in a more systematic and comprehensive manner in future studies.

This study serves as a snippet of the microbiologic epidemiology of febrile neutropenic patients with hematologic malignancies, from a single medical center in a resource limited country. It is hoped that findings in this study may help improve practices to prevent infection-related outcomes in pediatric cancer patients.

CONCLUSION

This study showed that several clinical and microbiological factors significantly affect outcomes in Filipino pediatric febrile neutropenic patients with hematologic malignancies. Age >10 years old, male sex, AML diagnosis, relapse state, ANC <100/mm^3, presence of central line, and catheter-associated infection had significantly longer duration of hospital stay. Specifically, those with catheter-associated infection was identified to have the longest duration of hospital stay. Presence of PICC or CVAD were the only factors associated with a higher chance for mortality.

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CONFLICT OF INTEREST

None declared.

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