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ORIGINAL ARTICLE

MICROBIOLOGIC PROFILE AND PREDICTORS OF SEVERE OUTCOME OF PEDIATRIC CANCER WITH FEBRILE NEUTROPENIA ADMITTED AT A TERTIARY MEDICAL CENTER

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The authors declare that the data presented are original material and has not been previously published, accepted or considered for publication elsewhere; that the manuscript has been approved by all authors, and all authors have met the requirements for authorship.

ABSTRACT

Background: The treatment of pediatric cancer has advanced dramatically. With the discovery of newer, more potent chemotherapeutic agents, patients are confronted with severe and prolonged degrees of neutropenia, which has inherent consequences.

Objective: The study aimed to determine common microbial isolates and predictors of severe outcome of pediatric cancer patients with febrile neutropenia aged 0-18 years old admitted at a tertiary hospital.

Methods: This was a cross-sectional study on pediatric cancer patients with febrile neutropenia admitted at the Philippine Children's Medical Center from March 1, 2017 to September 30, 2017. The clinical presentations of subjects were noted. Patients were categorized as to the presence or absence of severe outcomes. Common microbial isolates were noted. Predictors of severe outcome were identified using stepwise logistic regression analysis.

Results: Out of 105 enrolled patients, 32 developed severe outcomes. The most common isolates were *Klebsiella pneumoniae* followed by *Escherichia coli* and Candida species. Univariate analysis showed that acute myelogenous leukemia (p-value: 0.0195), treatment relapse (p-value: 0.0131), ANC on admission </= 100 cells/mm3 (p-value: 0.0001), fever of >7 days during admission (p-value: 0.0001), non-response to empiric antibiotics (p-value:0.0001), microbiologically-defined infection (MDI, p-value: 0.0001), fever without a focus (p-value:0.001), bloodstream infection (p-value: 0.0192), unknown focus of infection (p-value: 0.0058), and a positive culture (p-value: 0.0001) were related to a severe outcome. None of these predictive variables, however, were statistically significant on multivariate logistic regression analysis.

Conclusion: *K. pneumoniae*, *E. coli* and Candida were the predominant organisms identified in febrile neutropenic cancer patients in our institution. Although AML, treatment relapse, profound neutropenia, fever of >7 days during admission, non-response to empiric antibiotics, MDI, fever without a focus, bloodstream infection, unknown focus of infection and a positive culture were related to a severe outcome, multivariate regression analysis did not show these to be significant.

KEYWORDS: *Microbiologic profile, Fever, Neutropenia, Predictors*

INTRODUCTION

Febrile neutropenia refers to the occurrence of fever in a neutropenic patient undergoing cytotoxic treatment, commonly with uncontrolled neoplasm of the bone marrow [1]. Infection occurs as a consequence of immunosuppression due to the underlying disease, or from the use of cytotoxic treatment, and possibly in association with invasive procedures [2].

Clinicians handling pediatric patients with cancer are often faced with the challenge of managing episodes of febrile neutropenia. While aggressive chemotherapy improves survival of children with hematologic disorders, it carries the risk of infection, which is a major cause of morbidity and mortality in this patient population [3,4]. Epidemiologic studies demonstrate a high incidence of sepsis in pediatric patients receiving chemotherapy, in approximately 12.8% of children aged 1-9 years and 17.4% of children aged 10-19 years. This underscores febrile neutropenia as a significant complication in the treatment of childhood cancer [4].

At the Cancer and Hematology Center of the Philippine Children's Medical Center (PCMC), there were 300 febrile neutropenia cases out of 2,500 admissions in 2016. This accounted for 12% of all cases seen during this period. There were three local studies which looked into the microbiologic data of febrile neutropenia patients admitted at PCMC [5,6,7]. However, these were retrospective researches. This is the first prospective study on the microbiologic profile and predictors of severe outcome of febrile neutropenia patients in our institution. Information on identified pathogens will aid in the selection of appropriate antimicrobials for empiric therapy and promote judicious use of these agents. Insights gained on factors shown to be associated with unfavorable outcomes can influence improvements in the provision of care for this population and contribute in decreasing morbidity, mortality, and cost-related hospitalization.

MATERIALS AND METHODS

We conducted a cross-sectional study to determine microbial isolates and predictors of severe outcome of pediatric cancer patients aged 0 to 18 years with febrile neutropenia, admitted at the Philippine Children's Medical Center from March 1, 2017 to September 30, 2017.

Approval from the Institutional Review Board (IRB) and Research Ethics Committee of the Philippine Children's Medical Center were obtained prior to the conduct of the study. Informed consent and assent were sought prior to subject enrollment. Potential conflicts of interest were disclosed and patient's identities were kept confidential at all times.

The minimum sample size of 105 was calculated using power analysis by G*Power software as indicated by the returned values of the A Priori analysis. A logistic regression of a binary response variable (Y) on a binary independent variable (X) with sample size of 105 observations achieves 95% power at 0.05 level of significance.

All cancer patients 0-18 years old, undergoing chemotherapy/combination therapy and admitted due to fever and neutropenia were included in the study. Excluded are patients where chemotherapy has not started, newly-diagnosed malignancies admitted for the first time, those with existing severe infection prior to the onset of neutropenia, those with healthcare associated infections on admission, and patients on palliative care.

Patients who withdrew from the study and those who were initially enrolled but were later discharged against medical advice were considered dropouts.

Recruitment was done by the investigators upon admission at the Emergency Department. As soon as informed consent was obtained, history taking and a thorough physical examination were performed. The investigators had no direct involvement in the evaluation and management of cases. Daily observation of subjects was done

during the entire course of hospital stay until discharge. Data pertinent to the study were recorded using a case report form.

Patients were classified as belonging to either the "complicated group" if they developed a severe outcome or the "non-complicated group" if without severe outcome. Severe outcome was defined as having any of the following: hypotension (BP below the 5th percentile or below two standard deviations (SDs) of the mean for age and gender, respiratory failure (arterial oxygen pressure < 60 mmHg on room air or need for mechanical ventilation), congestive heart failure, uncontrolled arrhythmia, intensive care unit admission, and death.

Numerical variables were expressed as means or standard deviation. Clinical and microbiologic data were expressed as frequencies and percentages. Odds ratios and their 95% confidence intervals were computed and a p-value of <0.05 was considered significant. Stepwise logistic regression with backward selection strategy was employed on specific variables. The significance of the main effects of different independent variables on the outcome was determined by Multivariate analysis to establish strength of each independent variable and outcome variable. SPSS (Statistical Package for the Social Sciences) software was utilized to analyze the data.

RESULTS

A total of 105 cancer patients with febrile neutropenia were included, with 73 patients classified under the non-complicated group (70%) and 32 patients under the complicated group (30%). Table 1 shows the demographic and clinical profile of patients. More than half of patients in each group were males. The mean age of subjects was 6.9 years. The most common underlying disease in both groups was acute lymphocytic leukemia, with 56% of cases in the complicated group and 60.3% in the non-complicated group. More than half of patients in both groups were on induction chemotherapy when they developed febrile neutropenia. Profound neutropenia (defined as an absolute neutrophil count of <100 cells/mm^3) was seen in a higher percentage of patients in the complicated group (73%) than in the non-complicated group (58%). Ninety-seven percent of patients in the complicated group and all patients in the non-complicated group had fever of less than 7 days duration before admission but during hospitalization, most of the patients in the complicated group had prolonged fever lasting >7 days (78.1%) but none of those in the non-complicated group developed prolonged fever. Piperacillin-Tazobactam was the most common empiric antibiotic used for patients in both groups. Most of the patients in the complicated group did not respond to the initial empiric antibiotic (68.8%) while all but one patient in the non-complicated group responded to treatment. Most of the patients in the complicated group had Microbiologically-Defined Infection (MDI) while most patients in the non-complicated group had fever without a focus (60.3%), or Clinically-defined Infection (CDI, 35.6%). Bloodstream infection was the most common infection seen in more than half of patients in the complicated group. Unknown focus of infection (45.2%), followed by respiratory infection (23.3%) characterize most of the patients in the non-complicated group. Organisms were isolated from most of the patients in the complicated group while a majority of patients in the non-complicated group had negative culture results. All of the patients in the non-complicated group were discharged improved while only 68.8% of patients in the complicated group improved and 31.2% died. The overall mortality rate was 9.5%.

Table 1. Demographic and Clinical Profile of Pediatric Cancer Patients with Febrile Neutropenia Stratified to Non-Complicated or Complicated Group

	Outcome Frequency (%)			
Clinical Parameters		**Non-complicated Group n= 73 (70)**	**Complicated Group n= 32 (30)**	**Total n= (105)**
Age				
	Mean (SD)	6.8 (4.7)	7.3 (5.7)	6.9 (5.0)
	Median	5	5	5
	Range	1-18	2-18	1-18
Sex				
	Male	51 (69.9)	22 (68.8)	73 (69.5)
	Female	22 (30.1)	10 (31.3)	32 (30.5)
Primary Underlying Disease				
	Leukemia			
	Acute Lymphocytic Leukemia	44 (60.3)	18 (56)	62 (59.0)
	Acute Myelogenous Leukemia	7 (9.6)	9 (28.1)	16 (15.2)
	Chronic Myelogenous Leukemia	2 (2.7)	0	2 (1.9)
	Lymphoma	3 (4.1)	0	3 (2.9)
	Solid-organ Tumors	17 (23.3)	5 (15.6)	22 (21)
Type of treatment				
	Chemotherapy	72 (98.6)	32 (100)	104 (99)
	Combination	1 (1.4)	0	1 (1.0)
Status of treatment				
	On treatment			
	Induction	39 (53.4)	19 (59.4)	58 (55.2)
	Intensification	0	3 (9.4)	3 (2.9)
	Consolidation	12 (16.4)	2 (6.3)	14 (13.3)
	Maintenance	14 (19.2)	2 (6.3)	16 (15.2)
	Re-induction	4 (5.5)	0	4 (3.8)
	Remission	0	0	0
	Relapse	3 (4.1)	6 (18.8)	9 (8.6)
ANC on admission				
	</= 500 cells/mm3	31 (42.5)	9 (28.1)	40 (38.1)
	</= 100 cells/mm3	42 (57.5)	23 (71.9)	65 (61.9)
Duration of fever prior to admission				
	</= 7 days	73 (100)	31 (96.9)	104 (99.0)
	> 7 days	0	1 (3.1)	1 (1.0)
Duration of fever during admission				
	</= 7 days	73 (100)	7 (21.9)	80 (76.2)
	>7days	0	25 (78.1)	25 (23.8)
Empiric Antibiotic Used				

	Ceftazidime +/ - aminoglycosides	14 (19.2)	2 (6.3)	16 (15.2)
	Cefepime	4 (5.5)	2 (6.3)	6 (5.7)
	Piperacillin-tazobactam	55 (75.3)	25 (78.1)	80 (76.2)
	Meropenem	0 (0)	3 (9.4)	3 (2.9)
Response to antibiotic therapy				
	Responders	72 (98.6)	10 (31.3)	82 (78.1)
	Non-Responders	1 (1.4)	22 (68.8)	23 (21.9)
Infection Type				
	Microbiologically-Defined Infection (MDI)	3 (4.1)	22 (68.8)	25 (23.8)
	Clinically-Defined Infection (CDI)	26 (35.6)	8 (25.0)	34 (32.4)
	Fever of Without a Focus	44 (60.3)	2 (6.3)	46 (43.8)
Site of infection				
	Oral Cavity	12 (16.4)	3 (9.4)	15 (14.3)
	Respiratory tract	17 (23.3)	4 (12.5)	21 (20.0)
	GI/Intra-abdominal Tract	7 (9.6)	3 (9.4)	10 (9.5)
	Genito-urinary tract	1 (1.4%)	2 (6.3)	3 (2.9)
	Skin and Soft Tissue	2 (2.7)	0	2 (1.9)
	Bloodstream	0	17 (53.1)	17(16.2)
	Unknown	33 (45.2)	2 (6.3)	35 (33.3)
	Others	1 (1.4)	1 (3.1)	2 (1.9)
Isolated Organisms				
	Without	69 (94.5)	10 (31.3)	79 (75.2)
	With	4 (5.5)	22 (68.8)	26 (24.8)
Primary Outcome				
	Discharged/ Improved	73 (100)	22 (68.8)	95 (90.5)
	Expired	0	10 (31.3)	10 (9.5)

A total of 30 pathogens were isolated from 26 patients. Table 2 summarizes the isolates in both groups. More than half of the organisms were isolated from the blood (n=20, 66.7%). Four isolates were from 4 patients in the non-complicated group (5.5%) and 26 isolates were from 22 patients in the complicated group (68.8%). Most patients with positive isolates were on induction chemotherapy (54%), while some were in relapse (19%). Four patients had more than one organism which grew from different sites. Gram negative Multi-drug resistant organisms (MDROs) *Klebsiella pneumoniae, Escherichia coli, Enterobacter cloacae,* and *Pseudomonas aeruginosa*, were the predominant isolates (n=12, 40%), followed by gram negative non-Multidrug-resistant organisms (non-MDROs; n=12, 40.0%). Three *Klebsiella pneumoniae* were found to be Extensively Drug-Resistant Organisms (XDROs) and were sensitive only to amikacin and/or colistin. *Klebsiella pneumoniae* was the most common isolated organism (n=10, 33%), followed by *Escherichia coli* (n=9, 30%) and Candida species (n=5, 17%). Eight of 10 *K. pneumoniae* isolates and 5 of 9 *E. coli* isolates were Extended Spectrum Beta-lactamase-producing (ESBL-producing) bacteria. A summary of the distribution of isolates is summarized in Table 3.

Table 2. Microbiologic Profile of Patients with Febrile Neutropenia

		Non-complicated Group n: 4 (%)	**Complicated Group** n: 26 (%)	**Total** n: 30 (%)
Isolated Organisms				
	Gram positive bacteria, *Non-MDRO	0	0	0
	Gram positive bacteria, **MDRO	1 (25.0)	2 (7.7)	3 (10.0)
	Gram negative bacteria, Non-MDRO	2 (50.0)	5 (19.3)	7 (23.3)
	Gram negative bacteria, MDRO	1 (25.0)	11(42.3)	12 (40.0)
	Gram negative bacteria, ***X-DRO	0	3 (11.5)	3 (10.0)
	Fungus	0	5 (19.2)	5 (16.7)

(Four patients had 2 organisms isolated from different sites)
**Non-MDRO- Non multidrug-resistant organism*
***Multidrug-resistant organism*
****Extensively drug-resistant organism*

Table 3. Distribution of Microbial Isolates Based on Specimen Site

Specimen Site	ISOLATED ORGANISMS											
	K. pneumonia		*E. coli*		*P. aeroginosa*		*E. cloacae*		COPS**	CONS***	Candida	TOTAL
	(+)ESBL*	(-)ESBL	(+)ESBL	(-)ESBL	(+)ESBL	(-)ESBL	(+)ESBL	(+)ESBL	(+)MRSA			n:30(%)
Blood	7	1	2	2	-	1	1	-	1	1	4	20(66.7)
Urine	1	1	-	1	1	-	-	-	-	-	1	5 (16.6)
Stool	-	-	2	1	-	-	-	-	-	-	-	3 (10.0)
Wound	-	-	1	-	-	-	-	-	1	-	-	2 (6.7)
TOTAL n:30	10		9		2		1		2	1	5	
Percentage (%)	30		30		7		3		7	3	17	

**ESBL- Extended Spectrum Beta Lactamase*
**COPS- Coagulase Positive S. aureus*
****CONS- Coagulase Negative Staphylococcus MRSA- Methicillin-Resistant S. aureus*

Tables 4, 5, and 6 show the resistance patterns of isolated organisms. *Klebsiella pneumoniae* showed in vitro resistance to major antimicrobial drugs used in the treatment of febrile neutropenia as follows: Ceftazidime (80% resistance), Cefepime (80%), Piperacillin-tazobactam (70%), Meropenem (40%), Gentamicin (50%), and Amikacin (10%). *Escherichia coli* in vitro resistance to Ceftazidime, Cefepime, Piperacillin-tazobactam, Meropenem, Gentamicin and Amikacin were 89%, 78%, 78%, 22%, 44%, and 33% respectively. *Pseudomonas aeruginosa* showed no resistance to major antimicrobial drugs used in the treatment of febrile neutropenia. *Enterobacter cloacae* had 100% in vitro resistance to Ceftazidime, Piperacillin-tazobactam and Gentamicin, but was susceptible to Cefepime, Amikacin, and Meropenem. All of the isolated gram-negative organisms showed no resistance to Colistin. *Staphylococcus aureus* and coagulase negative

Staphylococcus showed 100% in vitro resistance to Oxacillin. The Candida isolates showed no in vitro resistance to major antifungal drugs such as Amphotericin, Flucytosine, Fluconazole and Voriconazole.

Table 4. Resistance Rates of Gram-Negative Organisms in Patients with Febrile Neutropenia

	K. pneumonia **n: 10**	***E. coli*** **n: 9**	***P. aeruginosa*** **n: 2**	***E. cloacae*** **n: 1**
Ceftriaxone	8 (80)	6 (67)	2 (100)	1 (100)
Ceftazidime	8 (80)	8 (89)	0	1 (100)
Cefepime	8 (80)	7 (78)	0	0
Piptazobactam	7 (70)	7 (78)	0	1 (100)
Gentamycin	5 (50)	4 (44)	0	1 (100)
Amikacin	1 (10)	3 (33)	0	0
Ciprofloxacin	6 (60)	7 (78)	0	1 (100)
Levofloxacin	1 (10)	7 (78)	0	1 (100)
Imipenem	5 (50)	2 (22)	0	0
Meropenem	4 (40)	2 (22)	0	0
Colistin	0	0	0	0

[n= Total number of isolates (% Resistance)]

Table 5. Resistance Rates of Gram-Positive Organisms in Patients with Febrile Neutropenia

	Coagulase Positive *S. aureus* *MRSA **n: 2**	**Coagulase Negative Staphylococcus** **n: 1**
Oxacillin	2 (100)	1 (100)
Clindamycin	0	0
Vancomycin	0	0
Linezolid	0	0

[n= Total number of isolates (% Resistance)]
**MRSA- Methicillin-Resistant S. aureus*

Table 6. Resistance Rates of Candida Species in Patients with Febrile Neutropenia

	Candida Species **n: 5**
Amphotericin	0
Flucytosine	0
Fluconazole	0
Voriconazole	0

[n= Total number of isolates (% Resistance)]

Table 7 shows the univariate analysis of predictive factors related to severe outcome in patients with febrile neutropenia. Variables that were determined to be related to severe outcome include: Acute myelogenous leukemia (p-value: 0.0195), treatment relapse (p-value: 0.0131), ANC on admission of </= 100 cells/mm3 (p-value: 0.0001), fever of >7 days during admission (p-value: 0.0001), microbiologically-defined infection (p-value: .0001), non-response to empiric antibiotic therapy (p-value:0.0001), fever without a focus (p-value:0.001), bloodstream infection (p-value: 0.0192), unknown focus of infection (p-value: 0.0058), and a positive culture or presence of isolated organisms (p-value: 0.0001).

Table 7. Predictive Factors Related to Severe Outcome Based on Univariate Analysis

Variables		**O.R. (95% CI)**	***p*- value (<.05)**
Age		2.26 (0.04-11.48)	0.6849
Sex			
	Male		
	Female	0.95 (0.38-2.33)	0.9092
Primary Underlying Disease			
	Leukemia		
	Acute Lymphocytic Leukemia	0.80 (0.34-1.86)	0.6038
	Acute Myelogenous Leukemia	3.69 (1.23-11.03)	<0.0195
	Chronic Myelogenous Leukemia	0.44 (0.02-9.42)	0.5995
	Lymphoma	0.31 (0.02-6.18)	0.4428
	Solid-organ Tumors	0.61 (0.20-1.83)	0.3775
Type of treatment			
	Chemotherapy	1.34 (0.05-33.91)	0.8572
	Combination		
Status of treatment			
	On treatment		
	Induction	1.27 (0.55-2.96)	0.5728
	Intensification	17.44 (0.87-348.17)	0.0613
	Consolidation	0.34 (0.07-1.61)	0.1738
	Maintenance	0.28 (0.06-1.32)	0.1074
	Re-induction	0.31 (0.02-6.18)	0.4428
	Remission	2.26 (0.04-114.48)	0.6849
	Relapse	8.19 (1.55-43.18)	<0.0131
ANC on admission			
	</= 500 cells/mm3		
	</= 100 cells/mm3	1.89 (0.77-4.64)	<0.0001
Duration of fever prior to admission			
	</= 7 days		
	> 7 days	0.14 (0.01-3.60)	0.2374
Duration of fever during admission			
	</= 7 days		
	>7days	0.0 (0.00-0.04)	<0.0001
Response to Antibiotic Therapy			
	Responders		
	Non-responders	0.01 (0.00—0.05)	<0.0001
Infection Type			

	Microbiologically-Defined Infection (MDI)	51.33 (12.96-203.29)	<0.0001
	Clinically-Defined Infection	0.60 (0.24-1.53)	0.2871
	Fever of Without a Focus	0.05 (0.01-0.21)	<0.0001
Site of infection			
	Oral Cavity	0.53 (0.14-1.53)	0.3472
	Respiratory tract	0.47 (0.14-1.53)	0.2105
	GI/Intra-abdominal Tract	0.98 (0.24-4.04)	0.9726
	Genito-urinary tract	4.80 (0.42-54.96)	0.2073
	Skin and Soft Tissue	0.44 (0.02-9.42)	0.5995
	Bloodstream	62.49 (3.5-1116.8)	<0.0192
	Unknown	0.02 (0.00-0.32)	<0.0058
	Others	2.32 (0.14-38.33)	0.5558
Isolated Organisms			
	Without		
	With	37.95 (10.82-133.11)	<0.0001

Table 8 shows the Multivariate Logistic Regression Analysis to identify predictors of severe outcome. The model was statistically significant $\chi 2$ (32) = 129.117, p <.000. This explained 70.8% (Cox & Snell R2) of the variance in severe outcome in patients with febrile neutropenia and correctly classified 100% of cases. However, none of the variables that were determined to be related to severe outcome on univariate analysis reached statistical significance on multivariate regression analysis.

Table 8. Multivariate Logistic Regression Analysis Predicting Likelihood of Developing Severe Outcome

		Odds Ratio	**95% CI for Odds ratio**		***p*-value (<.0000)**
			Lower	**Upper**	
Primary Underlying Disease					
	Acute Myelogenous Leukemia	0.000	0.000	-	0.999
Status of treatment					
	Relapse	1.497	0.000	-	1.000
ANC on admission					
	< 100 cells/mm^2	105926.326	0.000	-	0.999
Duration of fever during admissiion					
	> 7 days	3.179E+16	0.000	-	0.998
Empiric Antibiotic Therapy					
	Non-responders	8.811E+14	0.000	-	0.998

Infection type					
	Microbiologically-identified Infection				
	Fever without a focus	0.000	0.000	-	1.000
Site of infection					
	Bloodstream				
	Unknown	0.000	0.000	-	0.999
Isolated organisms					
	With	0.000	0.000	-	1.000

DISCUSSION

Life-threatening infection is a common consequence of febrile neutropenia which develops among pediatric cancer patients receiving chemotherapy. Our study showed that 30% of our subjects developed severe outcome that resulted to mortality in 9% of those in the complicated group. Mortality rate in patients with febrile neutropenia documented in other studies ranged from 5 to 21%. [8-10]

The most common primary underlying disease noted in this study was leukemia, similar to findings in other studies [8,11]. The nature of hematologic malignancy and intensity of myelosuppressive treatment predispose these leukemic patients to develop neutropenia to a higher degree compared to patients with solid tumors [12,13]. Most patients in our study developed febrile neutropenia during the induction phase of chemotherapy, similar to the study of Karanwal [13]. The high incidence of neutropenia with early cycles of chemotherapy may be explained by the high doses of drugs used during induction, while the lower incidence in subsequent cycles is likely due to dose modification and hematopoietic cell adaptation that occur at a later time [14]. The greater degree of myelosuppression during induction may also explain why most patients have positive cultures.

Fever without a focus was most common at the time of presentation in 43.5% of subjects. In both groups of patients, MDI was found in 23.8 % of subjects and most of them belonged to the complicated group. Similarly, high rates of fever without a focus were found by Karanwal in 47%, and Shamsi in 60% of their patients. Taj's report however, showed that this finding was seen in only 18.58% of subjects [15]. A local study involving adult febrile neutropenic patients showed MDI in 27.83% of subjects, close to the frequency of MDI in our study. The study of Padua involving pediatric patients with febrile neutropenia, however, found that CDI (63.8%) was more common than MDI (12.7%)[7]. In our study, bloodstream infection (BSI) was the primary site seen in 53.1% of patients in the severe group. Similar rates of BSI have been documented in other studies [3,15,37]. Of 105 febrile neutropenic patients included in our study, a positive blood culture was seen in 26 patients (24.8%). In other studies, positive cultures were observed in only 7-18% of cases [17,18,19]. The low yield of blood culture in pediatric patients with febrile neutropenia is well-recognized and can be attributed to multiple factors: volume of blood taken, choice of culture media, number of inoculated culture bottles and frequency in performing the procedure [20].

Gram-negative organisms *K. pneumoniae* followed by *E. coli,* were the predominant isolates in

our investigation. Padua's study[7], as well as those done in other countries such as India, Turkey, Brazil, and Japan, reported gram negative bacteria as common isolates in febrile neutropenia patients [13,18,21,22,23]. *E. coli* has been cited as one of the most frequently isolated organisms in other investigations [15,24,25]. Twenty three percent of gram-negative isolates in our study were multi-drug resistant. Manglicmot-Gumboc et. al. noted a similar frequency of gram-negative MDROs occurring in febrile neutropenia patients (20.92%) [6]. A study performed in Italy reported a 13.7% incidence of MDROs associated with bacteremia in their subjects [26]. A study on cancer patients done in Spain showed the following variables to be associated with the acquisition of multidrug resistant gram-negative bacteria: presence of other co-morbidities, antibiotic use in the previous month, urinary catheterization, use of parenteral nutrition, previous intensive care unit admission, mechanical ventilation, previous blood transfusion, and a previous episode of bacteremia. Of these, independent risk factors for developing MDR infection were prior antibiotic exposure and urinary catheterization [26].

In addition to being multi-drug resistant, most of the gram-negative isolates in our study were ESBL-producers. ESBLs are highly diversified enzymes that hydrolyze beta-lactams in the periplasmic space, preventing penicillin-binding. [27] One study on *E. coli* and *K. pneumoniae* bacteremia in patients with neutropenic fever revealed that hospital stay of > 2 weeks within 3 months prior to the onset of bacteremia and use of broad-spectrum cephalosporins 4 weeks prior to the onset of bacteremia were significantly related to the acquisition of ESBL [28].

Three XDROs were documented in our study, a finding that was not seen in earlier studies on febrile neutropenia done in this institution [5,6,7]. A study done by Reddy et al in India showed that extreme drug resistance was seen in 32%, and pan drug resistance in 16% of Gram-negative bacterial infections in their review of sensitivity of bloodstream isolates in children with malignancy [29].

Staphylococcus aureus was the most common gram-positive isolate in our study. Bhatti's study showed that 33.9% of isolates in febrile neutropenic children were gram positive organisms, of which *S. aureus* was the most frequent (9.8%)[30].

Candida organisms were isolated in 16.7% of our patients. In a study in Malaysia, candidemia occurred in 23% of patients [31]. Rates of candidemia varied from 1 to 13.6% in other studies [32,33].

High rates of resistance of isolates to major antimicrobials used in the treatment of febrile neutropenia were evident in this study. *K. pneumoniae* showed high resistance to Ceftazidime (80%), Cefepime (80%), Piperacillin-tazobactam (70%), Meropenem (40%), Gentamicin (50%) and Amikacin (10%). The 2016 Antimicrobial Resistance Surveillance Program (ARSP) reports lower resistance rates to Ceftazidime (13.5%), Cefepime (30.4%), Piperacillin-tazobactam (22.7%), Meropenem (11.4%), Gentamicin (24.0%) and Amikacin (5.5%)[34]. Among the gram-positive organisms, *Staphylococcus aureus* showed 100% resistance to Oxacillin, higher than what was reported by ARSP (61.6%)[34].

Univariate analysis showed that patients with acute myelogenous leukemia, treatment relapse, ANC of ≤ 100 cells/mm3 on admission, fever of >7 days during admission, non-response to empiric antibiotics, MDI, fever without a focus, bloodstream infection, unknown focus of infection, and a positive blood culture were related to severe outcome. Several studies likewise showed AML, fever of more than 5 days, and presence of known isolated organisms, as factors predictive of developing severe outcome on univariate analysis [16,18,35]. There were a few studies which showed profound neutropenia, significant focus of infection, fever of more than 5 days, previous documented infection, and isolation of a known pathogen in cultures [6,18,25] as significant predictive factors associated with severe outcome on multivariate

analysis. Our study, however, showed that the above findings were not significantly associated with a severe outcome on multivariate analysis. Of note was that the studies cited above involved more subjects compared to our investigation. Nevertheless, significant variables found on univariate analysis can still be of value to the clinician to identify those at risk of developing severe outcomes.

CONCLUSIONS

Gram-negative bacteria were the most common pathogens isolated in febrile neutropenic patients. ESBL-producing *K. pneumoniae* was most common followed by *E. coli* and Candida species.

Although results of logistic regression analysis on predictors of severe outcome did not reach statistical significance, Univariate analysis showed that severe outcome was more likely to develop in the presence of the following factors: Acute myelogenous leukemia, treatment relapse, ANC on admission of </= 100 cells/mm3, fever of >7 days during admission, non-response to empiric antibiotics, microbiologically-defined infection, fever without a focus, bloodstream infection, unknown focus of infection and presence of known isolated organisms. These findings can help identify patients at increased risk of developing severe outcome, to promote timely and aggressive medical management and prevent complications and death.

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