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ORIGINAL ARTICLE

PROFILE OF NOSOCOMIAL INFECTIONS AMONG CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA

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

ABSTRACT

Objectives: The study aimed to determine the frequency and clinical profile of nosocomial infections among pediatric patients with Acute Lymphoblastic Leukemia (ALL) admitted at the Philippine General Hospital from January 2010 to December 2011.

Methodology: This is a descriptive cross sectional study involving the review of medical records of pediatric patients with ALL under the charity service of the Section of Pediatric Hematology and Oncology of Philippine General Hospital (PGH). The frequency, clinical presentation, outcome, causes of death and isolated organisms from sterile sites were determined. Fischer's Exact test was used to assess correlation between variables with Gram-negative bacterial infection and mortality.

Results: There were 80 documented nosocomial infections among 45 pediatric patients with ALL. The incidence was 9.22 per 100 admissions. The majority presented initially with fever (50%) and 37 (82%) had neutropenia. Blood stream infections were present in 33 (73%) out of 45 pediatric ALL patients. Gram-negative organisms (76%), particularly *Pseudomonas putida (33%)*, *Pseudomonas aeruginosa (12%)* and *Burkholderia pseudomallei (12%)* were isolated in majority of patients. About 42.2% of the 45 patients had resolution of the infection and 26.7% resulted to death primarily caused by septic shock in 7 (58.3%) of the 12 patients identified. Presence of fever (p-value 0.011, RR 2.1094) was associated with presence of Gram-Negative bacteria at 5% level of significance and with 2.109 times more risk to having a gram-negative infection. There was no significant correlation between mortality and symptoms of infection.

Conclusion: Nosocomial infections remain to be a significant cause of morbidity and death among pediatric patients with ALL. Gram negative infections were the most common cause of sepsis in these patients. One fourth of the patients with nosocomial infections died.

KEYWORDS:
Nosocomial Infection, Acute Lymphoblastic Leukemia, Gram negative infections, Pseudomonas infections, Burkholderia infections

INTRODUCTION

Nosocomial infections are an important complication leading to morbidity and mortality in pediatric cancer patients[1]. Despite progress in treatment, such as the increased use of chemotherapy drugs, broad spectrum antibiotics and white blood cell stimulants, patients still experience prolonged infection when they are immunocompromised and remain admitted in hospitals for longer periods[2]. Acute Leukemia is the most common pediatric malignancy with acute lymphoblastic leukemia (ALL) accounting for 75%-80% of childhood acute leukemia[3]. These patients have increased risk of developing infection partly because of immunosuppression and increased exposure to health care setting with higher risk for contracting infection particularly during chemotherapy. Infection still remains a major cause of therapy-associated morbidity and death among patients with malignant diseases[4].

Attempts had been made to identify causes of morbidity and mortality during chemotherapy for ALL but there are few local studies that explored infection, its complications and outcomes during hospital admission. The results of a forthcoming retrospective study on the outcome of children with ALL at the charity service at the Philippine General Hospital (PGH) from 2003-2007 showed that out of the 210 ALL patients identified for the five year review, only 46 (21.9%) are still living with ongoing chemotherapy, 71 (33.8%) had abandoned therapy and 93 (44.2%) died in the hospital or at home[5]. In another five year retrospective study done on the common microbial isolates and sensitivity pattern of blood culture from pediatric cancer patients admitted the same hospital for febrile neutropenia, 6 of the 90 patients had growth on initial blood culture, 50% had Gram-negative bacteria, 33% had Gram positive bacteria and 17% had fungal isolates[6].

This study aimed to describe the profile of nosocomial infections among ALL patients during their admission at a tertiary hospital. In addition, the study aimed to evaluate the impact of the different risk factors on the infectious episodes and use the data gathered to set the suitable guidelines for the prevention and management of infections.

METHODOLOGY

This descriptive, cross-sectional study reviewed all medical records of admitted patients with B-cell Acute Lymphoblastic Leukemia (ALL) who were diagnosed with nosocomial infections during hospital admission with at least 3 days of hospital stay from January 2010 to December 2011 in a tertiary hospital. Pediatric patients (0 to 18 years old), diagnosed with ALL, undergoing chemotherapy while admitted at the pediatric ward under the section of Hematology and Oncology, Department of Pediatrics at PGH and developed infection on third day of admission or later were included in the study. The following were excluded from the study: those with incomplete charts**,** had active viral infection, and were admitted for less than 48 hours. The list of ALL patients who were included in the study was obtained from the annual census data of the Section of Pediatric Hematology and Oncology of the Department of Pediatrics of a tertiary hospital.

Upon enrollment to the study, the patients' charts were reviewed and the following information was obtained: age (in years and months), sex, anthropometric measurements (weight, height), nutritional status based on WHO growth charts, treatment group risk, length of hospital stay, baseline laboratory results upon

admission including complete blood count (CBC), presence or absence of neutropenia, associated symptoms of infection (e.g. cough, fever, abdominal pain, etc), laboratory procedures done when suspected of having nosocomial infection including CBC with white blood cell count and absolute neutrophil count, hospital day when nosocomial infection was acquired, and site of infection. Also determined were results of microbiologic cultures from blood, sputum, wound discharge and any suspected focus of infection (cultures done both in the hospital laboratory and other laboratories recognized by the section) and outcome (resolved infection, re-infection, mortality and abandoned treatment).

Statistical Analysis

Descriptive analysis was used to determine the overall frequency of developing nosocomial infection among pediatric patients with ALL while admitted in the hospital. Percentages and mean were computed for qualitative and quantitative variables, respectively. Nosocomial infection was classified using the criteria of the Infectious Disease Section of the Department of Pediatrics at the Philippine General Hospital. The Fisher's Exact Test was used to assess correlation between presence of Gram-negative bacteria and the following variables: gender, nutritional status, risk group, length of hospital stay, chemotherapy protocol and symptoms of infection.

RESULTS

There were a total of 193 admissions with 88 episodes of nosocomial infections identified in 53 ALL patients (ALL). Only 45 (84.9%) medical charts were available for review from the 80 documented episodes of nosocomial infection.

Table 1. Demographic Profile of patients with pediatric ALL (N=45)

Demographics	Frequency	Percentage (%)
Age in Years		
0 - 2 years	6	13.3
3 - 5 years	14	31.1
6 - 9 years	10	22.2
10 -14 years	11	24.4
15 -18 years	4	0.1
Gender		
Male	30	66.7
Female	15	33.3
Nutritional Status		
Length / Height for Age		
• **Normal**	39	86.7
• **Stunted**	4	8.9
• **Severely Stunted**	2	4.4
Nutritional Status		
Weight for Age (Birth to 5 years)	17	37.8
• **Normal**	3	6.7
• **Underweight**	0	
• **Severely Underweight**		
BMI for Age		
(>5 years to 18 years)		
• **Normal**	20	44.4
• **Obese**	0	0
• **Overweight**	1	2.2
• **Wasted**	3	6.7
Severely Wasted	1	2.2
Treatment Group		
• **High Risk**	23	51.1
• **Standard Risk**	22	48.9

The characteristics of patients who developed nosocomial infections are shown in Tables 1 and 2. The incidence of admitted patients developing nosocomial infection is 9.22 per 100 admissions. All the patients were being administered Low Income Country (LIC) Regimen 1 Chemotherapy within the study period.

Table 2. Presenting Symptoms and Laboratory Characteristics of Pediatric ALL patients with Nosocomial Infections in 2010 to 2011(N= 45).

Characteristics	Frequency	Percentage (%)

Presenting complaint		
Fever	34	75.6
Cough	6	13.3
Difficulty Breathing	3	6.7
Bleeding	2	4.4
White Blood Cell Count		
< 1,000/cm	42	93.3
> 1,000/cm	3	6.7
Absolute Neutrophil Count		
< 500/cm	37	82.2
> 500/cm	8	17.8

Table 3. Episodes of Nosocomial Infection and Length of Hospital Stay

Length of Hospital Stay	Number of patients with New onset Nosocomial Infection	Total Number of ALL Patients with Nosocomial Infection	Total Number of episodes of Nosocomial Infection
< 7 days	19	19	19
< 14 days	16	35	42
< 21 days	6	41	57
< 28 days	4	45	67
≥ 28 days	0	45	80

Symptoms of infection and the corresponding laboratory results on initial nosocomial infection were identified (Table 2). Fever is the most common presenting symptom. Majority of patients (93.3%) had white blood cell counts less that 1,000/cm. There were 37 (82.2%) ALL patients who had neutropenia at the time of infection.

The mean length of stay for ALL patients was 28 days. Table 3 shows that the longer the hospital stay, the higher is the incidence of nosocomial infection. There was notable increase in the number of episodes of nosocomial infection as the length of hospital stay increases.

Table 4. Classification of Nosocomial Infection among ALL patients (N=45)

Classification of Nosocomial Infection	Frequency
Sepsis - Signs and symptoms with Positive Blood Culture - Signs and symptoms with Negative Blood Culture	 26 (58%) 0
Respiratory Infection LRTI + new infiltrates on chest radiograph with negative blood culture - LRTI with positive ETA and negative Blood culture	 7 (16%) 3 (7%)
Bacteremia - with Positive Blood Culture but no focus of infection - with Infective Endocarditis	 7 (16%) 0
Fever of Unknown Origin	3 (7%)
Urinary Tract Infection - colony counts > 100,000/mL with Positive Urine culture - colony counts > 100,000/mL with Negative Urine culture	 1 (2%) 0
Total	45

Nosocomial infection was classified according to the criteria of the Infectious Disease Section of the Department of Pediatrics of a tertiary hospital in Table 4 and also shows the distribution of patients according to classification of nosocomial infection.

There were 33 patients (73.3%) who had microorganisms seen on blood (Table 5). Mixed infections (polymicrobial) were detected in four (12.1%) patients while 29 (87.9%) patients had single isolates from the blood culture. Majority were Gram-negative infections (75.8%), the most common of which was *Pseudomonas putida* followed by *Pseudomonas aeruginosa* and *Burkholderia pseudomallei.* Gram-positive organisms (12.1%) identified were *Staphylococcus aureus* and Methicillin-resistant *Staphylococcus aureus.*

Table 5. Distribution of pathogens isolated from bloodstream infections among ALL patients admitted at a tertiary hospital from 2010-2011.

Causative Organism	Species	TOTAL (n=33)
Gram-negative		**25 (75.8%)**
	Pseudomonas putida	11
	Pseudomonas aeruginosa	4
	Burkholderia pseudomallei	4
	Acinetobacter baumanii	2
	Bacillus species	1
	Klebsiella ozanae	1
	Acinetobacter spp	1
	Alcaligenes faecalis	1
Gram-positive		**4 (12.1%)**
	Methicillin-resistant Staphylococcus aureus	2
	Staphylococcus aureus	2
Mixed Isolates		**4 (12.1%)**
	Pseudomonas putida & Flavobacterium spp.	3
	Pseudomonas putida & Klebsiella ozanae	1
TOTAL		**33**

Table 6 shows the sensitivity pattern of common microorganisms isolated among the patients. Results showed that for Gram-negative, *Pseudomonas putida* and *Pseudomonas aeruginosa* was highly sensitive to Amikacin, Ceftazidime, Cefipime and Meropenem. The study also determined that *Staphylococcus aureus* isolated was sensitive to Vancomycin and Clindamycin.

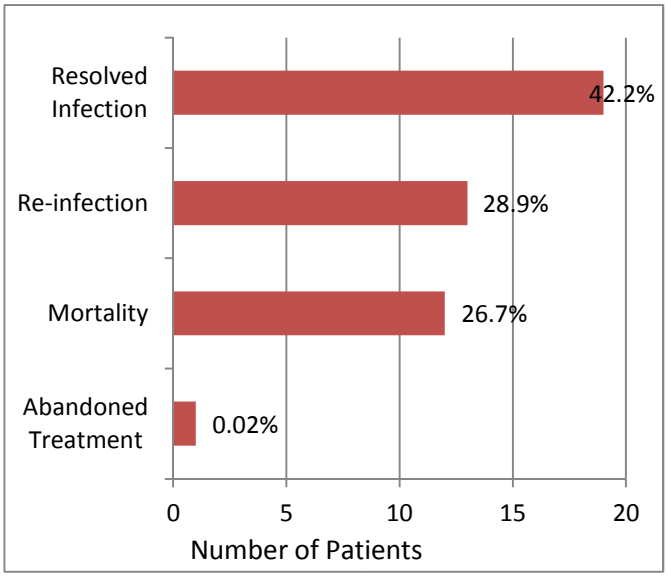

Figure 1. Outcome of Nosocomial Infection among ALL patients in a tertiary hospital from 2010 to 2011.

The outcome of nosocomial infection among ALL patients is shown in Figure 1. This shows that majority of patients had resolution of infection (42.2%). About 14 (28.9%) patients had re-infection, and 12 (26.7%) died. There were 12 mortalities during the two year study period comprising 26.7% of the 45 cases. The top three leading causes of death were septic shock [7 (58.3%)], disseminated, intravascular coagulopathy [2 (16.7%)], and respiratory failure [2 (16.7%)].

The causes of death among ALL patients with nosocomial infection have also been identified (Table 7). Results show that the 12 patients who died were all neutropenic and were hospitalized for more than seven days. For the seven patients (58.3%) who died of septic shock, study showed that blood culture isolates were all Gram-negative organisms and three of the seven patients had *Pseudomonas putida.* One of the

Table 6. Sensitivity Pattern of Common Microbial Isolates.

Antibiotics	*Pseudomonas putida*			*Pseudomonas aeruginosa*			*Burkholderia mallei*			*Burkholderia pseudomallei*			*Acinetobacter baumanii*			*Staphylococcus aureus*		
	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R
Amikacin	5		1	4						1					1			
Ampicillin									1	1								
Ampicillin Sulbactam									1	1					1			
Ceftazidime	6			4			1					1	2					
Cefipime	5		1	2		1	1			1								
Cefuroxime	3																	
Ceftriaxone				1		1	1						1					
Ciprofloxacin	1					1				1								
Clindamycin																2		
Co-Amoxiclav						1				1								
Gentamicin	1		3	3		1							1		1	1		
Imipenem	2		2	3		1	1			1			2					
Meropenem	5			4			1						2					
Piperacillin-Tazobactam	1			2		1												
Vancomycin																2		

Table 7. Causes of Death among ALL patients diagnosed with Nosocomial Infection admitted in January 2010 to December 2011

Causes of Death	Number of Patients	Percentage (%)
Septic Shock	7	58.3
Disseminated Intravascular Coagulopathy (DIC)	2	16.7
Respiratory failure	2	16.7
Intracranial Bleeding	1	8.3
TOTAL	**12**	**100.0**

two (16.7%) patients who died of respiratory failure had an isolated organism from endotracheal tube aspirate (ETA), *Acinetobacter baumanii*, while the other one showed no growth in ETA.

The Fisher's Exact Test was used to assess correlation between presence of Gram negative bacteria and the following variables: gender, nutritional status, risk group, length of hospital stay, chemotherapy protocol and symptoms of infection. Results showed that only fever (p-value 0.011, RR 2.1094) was associated with presence of Gram-Negative bacteria at 5% level of significance. There was no significant correlation between mortality and symptoms of infection.

DISCUSSION

Nosocomial infections is a common and burdensome complication in pediatric patients with neoplastic diseases specifically those with B Cell-ALL. This research reviews the causes and patterns of infections in pediatric leukemia that can help determine the factors governing these nosocomial infections particularly in a tertiary hospital.

There were 80 documented infections among 45 ALL patients. The incidence rate of nosocomial infections among patients with ALL was 9.22% This value is higher than studies previously done in Thailand on nosocomial infections (NI) by Oberdorfer et al. which showed that the

incidence of NI's was 6.5/100 admission and in Germany by Simon et al which had a rate of 5.2 cases per 100 admissions[1,7]. This may be because the study centered on patients with ALL, the most common form of neoplastic disease. This is supported by study of Oberdorfer et al which stated that patients with ALL represented 59% of the subjects with neoplastic disease and had the highest NI rate (41.3%)[1].

In this study, blood stream infections were present in 33 (73.3%) pediatric ALL patients, which percentage is higher when compared to other studies by Simon et al (52.5%) and Urrea et al. (55.5%)[7,8] .This result, however, is comparable to the study done by Siddiqui where 90% of the patients had blood stream infections[2]. Local studies done by Isais-Agdeppa and Celiz-Pascual among febrile neutropenic cancer patients contradicts these results with an outcome of only 7% of patients showing growth in blood culture from Philippine General Hospital and 8% from Makati Medical Center, respectively[6,9].

The study showed that 25 patients (75.8%) were identified with Gram-negative isolates and four (12.1%) with Gram-positive isolates. In terms of etiologic agents, there is a variable trend per institution. Studies from European countries reported Gram-positive bacteria to be more common such as in the study by Urrea et al which reported 78.6% Gram-positive bacteria while the study of Simon found up to 83.3% Gram-positive and 11.1% Gram-negative bacteria[8, 7]. In a study by El-Mahallawy in Egypt, Gram-positive cocci were the predominant cause of blood stream infections in pediatric cancer patients constituting 68.9% of organisms isolated over a six-month study period[10]. Looking at the trend, there is predominance of Gram-positive organisms in blood cultures from hospitals outside the Philippines. This being the case, the use of broad spectrum antibiotics that would cover both gram-negative and gram-positive organisms is still recommended in tertiary hospitals.

Study results show the sensitivity pattern of the isolated common Gram-negative organisms to Ceftazidime, Cefipime, Meropenem and Amikacin. Over the past decades, trends in bacterial isolates in cancer patients showed a predominance of Gram-negative organisms.

The investigation of infectious causes and complications in patients with cancer are crucial to early treatment[3]. In this study, there were 4 (21%) cases of mixed infection which can be attributed to the patient's low immunity after chemotherapy thereby increasing propensity for infection. This study showed that the presence of fever had significant correlation with Gram-negative infections but has no correlation with mortality. Results showed a decrease in mortality rate with only 26.7% compared to the study of Lubaton[10]. It is important to note that nosocomial infection resolved in 42.2% of the patients while re-infection occurred in 28.9% of the patients. Unfortunately, septic shock (58.3%) was still the leading cause of death among the patients. The mortality is high compared to other international researches but similar to local research values.

CONCLUSION

Nosocomial infections remain to be a significant cause of morbidity and death among pediatric patients with Acute Lymphoblastic Leukemia. The elevated rates of sepsis and bacteremia caused by Gram-negative microorganisms among immunocompromised pediatric patients showed that the patients were at risk for mortality. Re-infection was common and occurred in 28.9% of the patients Mortality occurred in 27% of the patients.

RECOMMENDATION

Understanding the vulnerability of the host can allow planning of more rigorous management and infection-control practices for susceptible populations such as the patients with acute lymphoblastic leukemia. However, further researches have to be done to identify the risk factors associated with high mortality rate among pediatric oncology patients especially in developing countries such as the Philippines. Microbial isolates and sensitivity patterns should be monitored and the trend identified for the application of suitable antibiotic therapy. Improvement in recording the patient's information, as well as recording of the symptoms in the chart is suggested. Improvement of a Leukemia patient's database is recommended for easy filing and accessibility for future researchers. Based on the results of the present study, it is recommended that physicians should collect specimens for culture when microbiologic infection is considered among pediatric patients with oncologic conditions. It is also recommended that clinical trials be conducted to determine appropriate treatment regimen for nosocomial infection. Risk factors for infection may be studied in a retrospective study which may include 5 to 10 years of review. Further, a prospective study may be conducted at tertiary hospitals to determine changes in the prevalent microorganisms as well as antibiotic susceptibility not just among leukemia patients but among other oncologic diseases or in other immunocompromised groups.

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