Frequency and Culture Sensitivity for Bacteremia During Febrile Neutropenia in Children with Acute Lymphoblastic Leukemia. Do Age and Gender Matter?

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ABSTRACT

Objective: To determine the frequency of bacteremia and its association with age and gender in febrile neutropenic children suffering from acute lymphoblastic leukemia and identify the commonest pathogens and their antibiotic susceptibility identified on blood cultures.

Study Design: Cross-sectional analytical study.

Place and Duration of Study: Pediatrics Inpatient Department, Shifa International Hospital, Islamabad Pakistan, from Sep 2018 to Mar 2019.

Methodology: Children with acute lymphoblastic leukemia aged 1-12 years, presenting with temperature >100^{o}F and absolute neutrophil count of <500 cells/µL were enrolled. An automated blood culture system was used and Clinical and Laboratory Standards Institute Guidelines 2017 were used for susceptibility testing. Antibiotics were started empirically in all cases and changed after susceptibility testing.

Results: A total of 62 children were enrolled. The mean age was 8.6 ± 2.4 years. Majority of the children i.e., 32 (51.6%) were females. The frequency of bacteremia was 16 (25.8%) and there was no significant association with age or gender (p=0.475 and p=0.881 respectively). Majority of the isolates were gram-positive. The organism isolated in the highest frequency was Methicillin-Resistant Staphylococcus Epidermidis (MRSE) 5 (31.25%). Susceptibility to Vancomycin was present in 10 isolates while seven isolates were sensitive to penicillins/cephalosporins.

Conclusion: Bacteremia, primarily caused by gram-positive bacteria was found in 25.8% of our sample and was uninfluenced by age or gender. MRSE was the most frequent isolate. The bacterial isolates were susceptible primarily to vancomycin and penicillins/cephalosporins.

Keywords: Antibiotic susceptibility, Bacteremia, Blood cultures, Children, Febrile neutropenia.

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INTRODUCTION

Neutropenia is one of the most widely recognized complications in children suffering from leukemia. The generally accepted definition of neutropenia is the absolute neutrophil count (ANC) below the value specific for a race and age group. The lower limit of ANC at the time of birth is 6000/mm^3, which falls to 1500/mm^3 after the age of one year.[1] In people of African origin, the acknowledged lower limit is 1200/mm^3. Neutropenia is a major and common complication in children receiving anticancer chemotherapy. Neutropenic episodes may get complicated by life threatening bacterial infections that may necessitate prompt and aggressive antibiotic treatments. Trying the alternative options i.e., a delay in chemotherapy or reducing the dosages of chemotherapeutics leads to longer hospitalizations, increased health care costs, and higher mortality rate in cancer patients.[2]

In the recent medical literature, bacteremia has been found in 16-25% of pediatric oncology patients who become febrile.[3] The bacteria responsible for bacteremia are from both categories of bacteria i.e., gram-positives and gram-negatives. The spectrum of bacteria causing febrile episodes in such patients has displayed a changing pattern over the decades. Largely, the gram -negative bacteria particularly Entero-bacteriaceae (including *Escherichia coli, Klebsiella species*, and *Enterobacter species*) and Pseudomonas aeruginosa, were isolated from blood of pediatric oncology patients in the early years when cytotoxic chemotherapy was introduced.[4] Then, there was an increased contribution of gram-positive microorga-nisms such as coagulase-negative *Staphylococci* and *Viridans* group *Streptococci*, in causing bacteremia. More recently, there has been re-emergence of gram-negative bacteria, in pediatric oncology patients.[5] Inonestudy, in a pediatric oncology unit, 74 (58%) cultures yielded Gram-negative bacilli, 51 (40%) were positive for Gram-positive cocci, and 3

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(2%) grew fungi.[3] Another study found 69% positive blood cultures caused by gram-negative bacteria, 28.8% by gram-positive organisms, and 2.2% by fungi.[6] Some studies have depicted an increasing prevalence of multidrug-resistant (MDR) gram-negative as well as gram-positive pathogens in pediatric oncology patients. The risk factors for the acquisition of MDR pathogens are prior exposure to antibiotics and urinary catheterization.[7,8]

In Pakistan, very little is known about the pediatric oncology patients and the statistics concerning bacteremia in such children are rarely explored. A study at Institute of Nuclear Medicine and Oncology Lahore has studied the bacterial spectrum & anti-microbial susceptibility pattern of cephalosporins, aminoglycosides, carbapenems, and fluoroquinolones against gram-negative bacterial strains in multiple types of pediatric oncology patients.[7] Another study from Pakistan Institute of Medical Sciences Islamabad has focused on Acute Lymphoblastic Leukemia (ALL) but had a small sample size (n=37) of children with febrile neutropenia.[8] They did not correlate the frequency of bacteremia with age or gender. The spectrum of antibiotics used in sensitivity analysis was also small. Our study had focused on children with ALL recruited in a relatively larger sample size and investigated the relationship of age and gender with bacteremia frequency. Studying the type of isolated organisms and the susceptibility trend of the identified bacteria were secondary goals. More antibiotics were added to the spectrum in sensitivity analysis. The study helped us recognize the common pathogens isolated on blood cultures obtained from children with ALL presenting with febrile neutropenia and identify the antibiotics that were needed to be administered to these children, which would result in deescalation of antibiotics and a judicious decrease in the use of antibiotics.

METHODOLOGY

It was a cross-sectional analytical study carried out at the Pediatrics Inpatient Department, Shifa International Hospital Islamabad from September 2018 to March 2019. We calculated a sample size of 62 with the use of World Health Organization sample size calculator. The anticipated population proportion of 20%[9], absolute precision of 10%, and confidence level of 95%were used in the calculation.

After approval from the hospital ethical committee (IRB number 884-159-2017), through non-probability consecutive sampling.

Inclusion Criteria: Children of ages 1-12 years who were receiving anticancer therapy for ALL, and had fever and neutropenia were included from the study.

Exclusion Criteria: Children already on antibiotics for more than one week were excluded from the study.

Fever was defined as a solitary oral temperature estimation ≥101°F, or a temperature ≥100°F for one hour constant lyor at two times with a base interim of 12 hours.[10] Neutropenia was defined as an ANC of <500/µL, or <1000/µL with an anti-cipated decline to less than 500/µL in the next 48-hour period.[11]

Informed consent was taken from the parents and/or guardians of the included children. Pre-designed questionnaires regarding demographic and laboratory characteristics of the children were filled in using electronic medical records. All children were evaluated clinically at the time of admission. Venous samples were sent for culture and antibiotics were started empirically. For culture, two samples were taken, preferably from two different veins. When a central venous catheter was set up, one sample was taken from it, and another was taken from a peripheral vein. Each sample had 2-5 ml of venous blood.[12,13] Two-sample strategy was adopted because the yield for a positive blood culture is 97% as compared to 86% for one sample. Trained nurses or phlebot-mists obtained blood specimens at the bedside. The skin was disinfected with 2% chlorhexidine. The veins in the antecubital fossa were the preferred sampling sites using a needle and syringe, however, any reasonably accessible or easily visible peripheral vein was utilized.

The samples were preserved in blood sampling bottles and then sent to Shifa Laboratory for evaluation. An automated blood culture system "BD BACTEC™ 9050" (Becton and Dickinson Microbiology System, Sparks, MD, USA)" was used for the detection of bacterial growth.[14] The BD BACTEC™ Automated Blood Culture System utilized fluorescent technology in detecting the growth of organisms in the blood culture vials. The sample to be tested was inoculated into one or more BACTEC blood culture vials producing a blood to broth ratio of 1:50 to 1:100.[15] Each vial contained a chemical sensor, which could detect an increase in carbon dioxide (CO) produced by the growth of micro-organisms. The instrument monitored the sensor every 10 minutes for an increase in its fluorescence, which was proportional to the amount of CO present. A positive reading indicated the presumptive presence of viable micro-organisms in the vial. The vials were incubated until signal-positive or until the

end of day five, which ever was earlier.[16] Bacteremia was registered in the case of any organism isolated in two blood cultures from different samples or from the same sample if two blood samples could not be retrieved from the patient. When positive signal was observed, bottles were unloaded from instrument and Gram's stain and culture sensitivity were performed by disc diffusion technique as perthe Clinical and Laboratory Standards Institute (CLSI) Guidelines 2017. Sensitivity was tested on Mueller-Hinton agar plates by interpreting the zones of inhibition after in oculations. The cultured organisms were labelled either susceptible, resistant, or intermediate to each drug tested. Strains showing "intermediate" antimicrobial susceptibility profiles were considered to be resistant. The antibiotics used were penicillins, cephalosporins, carbapenems, aminoglycosides, vancomycin, fluoroquinolones, and miscellaneous other antibiotics e.g., sulfamethoxazole/trimethoprim, chloramphenicol, linezolid, and doxycycline. The quantity of antibiotics in each antibiotic disc used WAS given in Table-I.

Table-I: Antibiotic quantity in each disc used for culture sensitivity.

Antibiotic Group	Antibiotics	Quantity per antibiotic disc
Penicillins	Ampicillin	10 µg
	Amoxicillin-Clavulanate	20-10 µg
	Piperacillin-Tazobactam	100-10 µg
Cephalosporins	Cefixime	5 µg
	Ceftriaxone	30 µg
	Ceftazidime	30 µg
	Cefipime	30 µg
	Cefazolin	30 µg
Carbapenems	Imipenem	10 µg
	Meropenem	10 µg
	Ertapenem	10 µg
Aminoglycosides	Amikacin	30 µg
	Gentamycin	10 µg
Glycopeptides	Vancomycin	30 µg
Miscellaneous	Doxycycline	30 µg
	Ciprofloxacin	5 µg
	Levofloxacin	5 µg
	Linezolid	30 µg
	Trimethoprim-Sulfamethoxazole	1.25-23.75 µg
	Chloramphenicol	30 µg

The quantity of antibiotic used for sensitivity analysis was altered for all bacterial isolates according to the CLSI guidelines. Blood cultures and blood counts were done again every 48-72 hours in children with unrelenting fever.[17] Other laboratory investigations were performed during the hospital stay according to the child's clinical condition.

The collected data were analyzed accordingly using SPSS version 19. For qualitative variables (gender, organisms, and antibiotics) frequencies and percentages were calculated. For the quantitative variable i.e. age, means and standard deviations were calculated. Effect modifiers like age and gender were controlled through stratification. After stratification, chi-square test was applied and the *p*-value ≤0.05 was viewed as significant.

RESULTS

Sixty-two children were finally enrolled. The mean age of the children was 8.6 ± 2.4 years. Thirty-four (54.8%) children were ≤9 years of age while 28 (45.2%) were >9 years of age. Thirty-two (51.6%) children were female while 30 (48.4%) were male. Bacteria were isolated from blood cultures of 16 (25.8%) children while 46 (74.2%) had negative blood cultures. The bacterial isolates were compared with age and gender of the children (Table-II). These results depicted that the organisms isolated in the blood cultures had no significant association with age and gender (*p*=0.475 and *p*=0.881 respectively).

Table-II: Comparison of organism isolated with baseline characteristics (n=62).

Variables	Organism Isolated		Total	χ^2	*p*-value
	Yes, n (%)	No, n (%)			
Age in years					
≤9	10 (29.4)	24 (70.6)	34 (100)	0.511	0.475
>9	6 (21.4)	22 (78.6)	28 (100)		
Gender					
Male	8 (26.7)	22 (73.3)	30(100)	0.022	0.881
Female	8 (25)	24 (75)	32 (100)		

Amongst these 16 isolates, 11 (68.75%) were gram positive organisms while five (31.25%) were gram-negative organisms. Of,[16] bacterial isolates, frequency of *Methicillin-Resistant Staphylococcus Epidermidis* (MRSE) was found to be the highest 5 (31.25%), followed by *Methicillin-Susceptible Staphylococcus* epidermidis (MSSE) n=3, (18.75%), Pseudomonas aeruginosa n=3, (18.75%), and other organisms e.g., *Escherichia coli*, *Micrococcus, Enterococcus, Streptococcus* and *Methicillin*-resistant *Staphylococcus aureus* (MRSA) 1 (6.25% each).

The sensitivities of different antibiotics were recorded based on the culture sensitivity report received from the Shifa Laboratory. The susceptibility pattern has been shown in Table-III.

Table-III: The reported sensitivities for different antibiotics.

Antibiotics Tested for Sensitivity	Bacterial Isolates with Sensitivity or Resistance	Sensitive Isolates n (%)	Resistant Isolates n (%)
Penicillins/ Cephalosporins.	13	7 (53.85)	6 (46.15)
Aminoglycosides	6	4 (66.67)	2 (33.33)
Carbapenems	4	3 (75)	1 (25)
Vancomycin	10	10 (100)	-
Fluoroquinolones	3	3 (100)	-
Doxycycline	2	1 (100)	-
Trimethoprim/ Sulfamethoxazole	2	2 (100)	-
Chloramphenicol	1	1 (100)	-
Linezolid	2	2 (100)	-

DISCUSSION

This study was conducted on febrile neutropenic children who were diagnosed with ALL. Bacteraemia was present in 25.8% children. Similar findings were also observed in previous studies. In a Pakistani study, positive blood cultures were identified in 25% of febrile neutropenic children.[8] A South African Study recognized that 13.8% children with cancer who were admitted with fever had positive blood cultures.[10] An Indian study attributed 39.8% cases of all febrile episodes in neutropenic patients to positive blood cultures.[16] A Turkish study concluded that amongst 96 children with ALL who had 299 episodes of febrile neutropenia, 25% of the episodes were bacteremic infections.[17] The reasons for higher risk of bacteremia in children with oncological malignancies are neutropenia and immuno suppression secondary to the disease as well as chemo-therapy.[16,18]

In our study, majority of the children (54.8%) were less than nine years of age. The gender proportion showed that 51.6% were females. Data analysis showed that the age and gender had no correlation with the type of organisms that were isolated. We could not find any other study exploring similar association.

Majority (68.75%) of the isolates in our study were gram-positive bacteria. In one study, gram-positive bacteraemia was present in 73%of all blood cultures where as 27% accounted for miscellaneous gram-negative organisms.[18] Kjellander *et al*,[19] observed gram-positive bacteremia in 53.1% and gramnegative bacteremia in 46.9 % in a Swedish study from 2002 to 2008. In Pakistan, Irfan *et al,*[20] inspected the bacterial segregates of febrile neutropenic children and found 53% as gram-positive and 42% as gram-negative organisms. The gram-positive bacteremia has been linked with excessive utilization of indwelling venous catheters, oral mucositis, and poor hygiene of the patients.[18] Other studies have observed higher frequencies of gram-negative bacteremia in pediatric oncology patients. A Pakistani study by Akhtar *et al*,[8] found gram-negative bacteria responsible for bacteremia in 77.8 % cases and gram-positive bacteria responsible in 22.2% cases. Another study depicted 57.3% of the isolated bacteria as gram-negative organisms, whereas, 40.8% were gram-positive organisms.[21] A Turkish study observed gram-negative organisms in 47.2% blood cultures, gram-positive organisms in 38.2%, and fungal agents in 9.1% blood cultures.[22] A review of 27 articles has concluded that gram-negative bacteria were the most numerous pathogen isolated.[23] Potential reasons for this difference could be the lesser use of central catheters and ports, as well as avoidance of quinolone prophylaxis.[24]

The commonest pathogens isolated in our study were MRSE (31.25%), MSSE (18.75%), and Pseudomonas aeruginosa (18.75%). However, no MDR organism was isolated. In another Pakistani study, Irfan *et al,*[20] explored the typeof bacteria isolated from blood of febrile neutropenic children and found that the most common isolated micro-organisms were *Staphylococcus* species (55.2%), *Escherichia coli* (36.6%), *Acinetobacter species* (14.8%), *Klebsiellap neumoniae* (11.6%), *Bacillus species* (9.7%), and *Pseudomonas aeruginosa* (9.7%). Akhtar *et al,*[8] realized that, overall, the most common bacterial isolates were *Klebseilla* species with a frequency of four (44.4%), *Pseudomonas* with a frequency of three (33.3%) and *Staphylococcus aureus* with a frequency of two (22.2%). Kjellander *et al*,[19] noticed that the leading bacterial isolates were *Escherichia coli* (17.8%), *Staphylococcus* (14.7%), viridans *Streptococci* (14%), and *Klebsiella species* (9.8%).

Furthermore, we studied the antibiotic susceptibility patterns of the isolated organisms. We found that vancomycin had the highest number of sensitive isolates (n=10) whereas sensitive isolates to penicillins /cephalosporins, aminoglycosides, carbapenems, and fluoroquinolones were seven, four, three, and three respectively. Considering the resistance pattern, we found that theres istant isolates topenicillins/cephalosporins were six, whereas two isolates were resistant to aminoglycosides and one was resistant to carbapenems. Irfan *et al,*[20] found an increase in resistance against fluoroquinolones in *Entero-bacteriaceae* (27.3-49.5%, p=0.0003) and *Pseudomonas aeruginosa* (13.3-29.4%, p=0.3) while comparing the data collection time

periods of 1999–2000 and 2001–2006. Similar emerging resistance has been reported from Japan where an increase in fluoroquinolone resistance from 37.4% in 2015 to 38.3% in 2016 was noted among *Escherichia coli* when quinolones were extensively used as prophylaxis.[24] The mirrored results were observed in Spain when the quinolone prophylaxis was stopped.[25] The resistance against quinolones dropped from 71-37% (p<0.001). Thus, there is an emergent need for a country wide rational antibiotic policy to prevent the development of MDR organisms in Pakistan. It is also recommended that leukemia centers should be established separately in hospitals to minimize exposure of immuno compromised patients. Further more, antibiotic therapy ought to be individualized for all patients, and supervision of anti-microbial treatment should be made compulsory to anticipate the rise and spread of MDR strains in the medicinal services' settings. In addition to this, guidelines need to be developed to identify low-risk patients that can be dealt with at out patient clinics with or without antibiotics. This would diminishthe spread of hospital-associated infections and the emergence of MDR strains.

LIMITATIONS OF STUDY

The findings of this study could be observed in the light of limitation that this was a single center study with a small sample size being observed. In addition, we did not include information regarding indwelling catheter and hygienic condition of the patient as they are linked to gram-positive bacteremia. Future studies, involving multiple centers in Pakistan with a broad range of antimicrobials for culture sensitivity testing and inclusion of confoundersare hence recommended.

CONCLUSION

Bacteremia, primarily caused by gram-positive bacteria was found in 25.8% of our sample comprising of febrile neutropenic children. MRSE was the most frequent isolate. The bacterial isolates were susceptible primarily to vancomycin and penicillins/cephalosporins. There was no association of age and gender with bacteremia in the sampled children.

Conflict of Interest: None.

Authors' Contribution

RUBM: Conception, data collection, manuscript writing, AA: Conception, manuscript writing, analysis, SBA: Manuscript writing, review, analysis, SC: Manuscript writing, review, SJ: Manuscript writing, KA: Manuscript writing, review.

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