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Original Article

Bacteremia in Pediatric Oncology Patients; A Single-Center Experience

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ABSTRACT

Objective: To study organisms causing bacteremia and their outcome in cancer children with febrile neutropenia (FN) admitted at our centre.

Study Design: Retrospective longitudinal study.

Place and duration of study: Department of Pediatric Oncology, Shaukat Khanum Memorial Cancer Hospital, Lahore, from Feb to Dec 2017.

Methodology: All pediatric oncology patients with febrile neutropenia admitted to the inpatient department were included. Data fields included age, diagnoses, demographics, organism types, time to positivity, multi-drug resistance, antibiotics, and *outcome.*

Results: A total of 391 episodes of febrile neutropenia were documented among 86 patients. The mean age was 4.7±2.7 years. Twelve (14.0%) patients had intensive care admission, and 9(10.5%) of them died. Fifty-four (63.0%) children had primary diagnoses of haematological malignancies. Sixty-five percent had mucositis, central catheter, or both as risk factors. Thirty-nine isolates were cultured in 391 febrile-neutropenic episodes. *Escherichia coli* was the most frequently isolated organism in 16(41.0%) cultures, followed by *Pseudomonas* and *Streptococcus pneumoniae* in 4(10.3%) each. Poly-microbial isolates were seen in 6(15.4%) cultures. Multi-drug resistance was found in 12(30.8%) isolates. Thirty-four (87.0%) patients with positive cultures received appropriate antibiotics. Majority organisms were sensitive to Piperacillin/Tazobactam (14,35.9%) followed by Meropenem (10, 25.6%) and Colistin (6, 15.4%).

Conclusions: Rapid identification of organisms from positive blood cultures combined with antimicrobial stewardship can have improved antibiotic treatment and outcomes.

Key Words: Antimicrobial Stewardship, Bacteremia, Escherichia coli, Febrile neutropenia, Mucositis

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INTRODUCTION:

Children with malignancies are known to have an increased risk of bloodstream infections. This can result from multiple hosts and therapy-related risk factors like immunosuppression, mucositis or indwelling central venous lines.[1] Despite significant improvements in preventing and treating infectious complications in pediatric cancer patients, bacteremia leading to septicemia remains a major cause of mortality and morbidity, especially in developing countries like Pakistan.[2] Recent studies have documented the predominance of gram-negative bacteremia in pediatric cancer patients.[3] Among Gram-negative organisms isolated in cancer patients, *Escherichia coli (E. coli)* is the most frequently seen organism. Moreover, the detection rate of multi-drug resistant (MDR) gram-negative isolates is rising. Injudicious use of broad-spectrum antibiotics to treat bloodstream infections has led to the emergence of these MDR organisms.[4] Increased resistance to commonly prescribed antibiotics like Amoxicillin/ Clavulanic Acid, Trimethoprim/ Sulfamethoxazole, third-generation Cephalosporins, and quinolones has been detected.[3] Bacteremia leading to sepsis in the pediatric cancer population is associated with dismal clinical outcomes with delayed administration of chemotherapy, suboptimal treatment, prolonged hospital stays, higher mortality rates and increased overall healthcare cost.[5,6]

Organism-directed antibiotic therapy is a key factor affecting the survival of patients with septicemia. Nevertheless, conventional identification of organisms using blood cultures takes days, which can lead to delays in appropriate antibiotic administration; hence, multidrug-resistant organisms can lead to significant morbidity and mortality in those patients. In this study, we aimed to find organisms prevalent in our febrile neutropenic patients requiring admission, isolate characteristics, and time to positive blood cultures, which impact the timely administration of appropriate antibiotics and the outcome of patients with bacteremia.

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METHODOLOGY

We conducted this study at Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, Pakistan. It was a retrospective longitudinal analysis. After approval by the Institutional Review Board [EXMPT-25-09-18-01]. The in-house Electronic Hospital Information System (HIS) database was used to identify the patients from January 2017 to December 2017.

Inclusion Criteria: All febrile neutropenia (FN) episodes in pediatric cancer patients requiring admission per departmental febrile neutropenia guidelines were included in the study.

Exclusion Criteria: Febrile neutropenia (FN) patients with documented fungal infections were not included in the study.

Data fields included the patient's age, gender, diagnosis, culture, time to positive blood culture, isolate types and characteristics, appropriate antibiotics cover, clinical source of bacteremia, intensive care admissions, and outcomes. An initial assessment was made in the emergency room upon the arrival of the patient as history and physical examination. Blood cultures (central/peripheral) and full blood count were sent to the emergency room. Other tests were sent according to the localizing symptoms. The onset of infection was counted from the date of the first blood culture sent on arrival in the emergency room.

A total of 391 febrile neutropenia (FN) episodes were documented among 86 patients that required hospital admission from January 2017 to December 2017. During these 391 FN episodes, 153 isolates were cultured, including 114 skin contaminants and 39 isolates treated with antibiotics. These 114 skin contaminants included coagulase-negative organisms (CoNs). Only those CoNs were considered treatable, which were positive for at least one more subsequent culture or if culture was drawn from the central venous line.

Fever was defined as an oral temperature measurement of >38.3 °C on a single occasion or a temperature of >38 °C that persists over 1 hour. A neutrophil count (ANC) of 500 cells/mm^3 or less, or an ANC expected to decrease to <500 cells/mm^3 during the next 48 hours, was considered neutropenia, while ANC <200 was defined as very severe neutropenia.[7] Patients with FN who were on intensive chemotherapy protocols were considered high risk and admitted per departmental guidelines. They included acute lymphoblastic leukaemia (ALL), including Relapses, non-Hodgkins lymphoma(NHL), patients receiving high dose chemo followed by Stem cell rescue and allogenic bone marrow transplant, Solid tumours on intense compressed chemo cycles, patients with a duration of neutropenia >10 days or profound neutropenia (<100/mm^3) and patients with additional health problems (such as respiratory, neurologic problems, hypotension, hypoxia, GI symptoms).

All febrile neutropenic patients were started on Piperacillin/Tazobactam within one hour of presentation to the emergency department as per hospital policy. Piperacillin/Tazobactam is first line antibiotic for FN patients at our hospital, and it is chosen based on local sensitivity patterns. For patients with hemodynamic instability at presentation, the choice of antibiotic is Meropenem/Imipenem along with Vancomycin. Multidrug-resistant (MDR) organisms were defined as those resistant to 2 or more antibiotics.[7] Following modifications with resistant organisms were made in case of: 1)Hemodynamic instability, and/or, 2) If the patient has a positive blood culture with suspected resistant organisms: a) MRSA, early initiation of Vancomycin, Teicoplanin or Linezolid, b) VRE, early use of Linezolid, c) ESBLs, early use of a Carbapenem, d) *Klebsiella pneumoniae* carbapenemase (KPC), *Acinetobacter* early use of Polymyxin/Colistin.

The empiric antibiotic was considered appropriate if it was active against the isolated organisms in vitro. The source of bacteremia was determined by isolating organisms from specimens other than blood (urine, sputum, tracheal aspirate, wound, central catheter) or based on the clinical evaluation of the treating physician.

Statistical Package for Social Sciences (SPSS) version 23.0 was used for the data analysis. Data analysis included descriptive statistics. The chi-square test was used to evaluate an association between categorical variables. The p-value ≤0.05 was considered statistically significant.

RESULTS

Three hundred and ninety-one episodes of febrile neutropenia (FN) documented among 86 patients required hospital admission from January 2017 to December 2017. The mean age of our patient population was 4.7±2.7 years . There were 39(45.3%) boys and 47(54.7%) girls. Most patients came from Punjab and Khyber Pakhtunkhwa (77, 89.5%). The rest of the patients came from other areas of Pakistan and Afghanistan. The primary diagnosis was acute

lymphoblastic leukaemia in 44 patients (51.2 %), followed by Non-Hodgkin's Lymphoma and Ewing's Sarcoma in 10 patients (11.6%). Twenty-five percent of kids had other cancer diagnoses (Table-I). Blood cultures were sent in each FN episode at the presentation. 65% of patients had risk factors like mucositis, central venous lines, or surgical wounds (Table-I).

Table-I: Patient Characteristics (86 Patients Included in the Study who Needed Admission for Febrile Neutropenia During 391 Episodes).

Parameters	Categories	Frequency(%)
Gender	Boys	39(45.3)
	Girls	47(54.7)
Demographics	Punjab	39(45.3)
	KPK	38(44.2)
	Baluchistan	1(1.2)
	Afghanistan	7(8.1)
	Kashmir	1(1.2)
Primary Diagnosis	Non-Hodgkin Lymphoma	10(11.6)
	Acute Lymphoblastic Leukemia	44(51.2)
	Wilm's Tumor	4(4.7)
	Osteosarcoma	1(1.2)
	Ewing's sarcoma	10(11.6)
	Germ cell tumor	1(1.2)
	Neuroblastoma	7(8.1)
	Others	9(10.5)
Risk factors	Central catheter	7(8.1)
	Central catheter and mucositis	4(4.7)
	Mucositis	45(52.3)
	None	30(34.9)

Enterococcus Fecium, Escherichia coli+ Streptococcus, Enterococcus faecium+ Acrococcus viridians, Klebsiella+ Pseudomonas, Stenotrophomonas maltophilia+ Escherichia Coli each. All these polymicrobial growths were multi-drug-resistant except *Aeromonas+Acinetobacter*. *Aeromonas* and *Acinetobacter* in this culture were both sensitive to piperacillin/tazobactam. Other MDR organisms included five isolates of *Escherichia coli* and one each with MRSA and *Streptococcus pneumoniae* (Table-II).

Clinical source of infection, based on history and examination in patients with positive blood cultures, was GI tract in 24(61.5%) patients, ENT and skin wounds in 4 patients each (10.3% each), chest and CVL in 3 patients each (7.7% each), and urinary tract infection in 1 patient (2.5%). While in 11(28.2%) patients with positive blood cultures, organisms were cultured from specimens other than blood (Table-III). Thirty-four (87%) patients with positive blood cultures could receive appropriate antibiotics. Patients who could not get appropriate antibiotics were those who died before culture sensitivity was reported. Mean days to positive culture were 3.6±0.2 days (range 2-6 days). Two (5.1%) cultures were positive in 48 hours, 18 (46.2%) after 72 hours, 11(28.2%) after 4 days, 6 (15.4%) after 5 days and 2(5.1%) after 6 days (Figure-1). Most isolated organisms were used as an empiric antibiotic at our centre and were sensitive to Piperacillin/Tazobactam (35.9 %, n=14). Ten (25.6%)

Table-II: Organisms Isolated in 39 Blood Cultures with number of MDR Organisms in each Type and their Outcome

Organism Type	Isolate Frequency	Multidrug Resistant (MDR) Organisms	ICU Admission	Deaths
Escherichia coli	16	6	3	2
Polymicrobial cultures	6	5	4	3
Pseudomonas aeruginosa	4	-	1	1
Streptococcus pneumoniae	3	-	1	1
Salmonella typhi	2	-	-	-
Klebsiella pneumoniae	2	-	1	1
Hemophilus influenzae	1	-	1	1
MRSA*	1	1	-	-
MSSA**	1	-	-	-
Bordetella	1	-	-	-
Vibrio parahaemolyticus	1	-	-	-
Aeromonas salmonicida	1	-	-	-
Total n (%)	39(100%)	12(30.8%)	12(30.8%)	9(23 %)

**MRSA (Methicillin resistant Staphylococcus aureus), **MSSA (Methicillin sensitive Staphylococcus Aureus)*

Thirty-one (79%) organisms were Gram-negative. One polymicrobial culture grew both Gram-positive and negative organism. Multi-drug resistance was present in 12(30.8%) organisms. Poly-microbial isolates were 6(15.4%). Polymicrobial organisms included *Aeromonas+ Acinetobacter*, *Escherichia coli+* isolates were sensitive to Meropenem rather than Piperacillin/Tazobactam, while six (15.4%) isolates were only sensitive to Colistin and Amikacin.

Twelve patients (30.7%) had ICU admission, and 9(23.0%) of them died**.** Five (42.0%) out of 12 patients with MDR organisms died (p=0.066). All these five

patients with MDR organisms could not receive appropriate antibiotics as the sensitivities were reported after the death of these patients. Of 39 cultured isolates, *Escherichia coli* was the most frequent organism in 16(41.0%) isolates, and it was followed by *Pseudomonas* aeruginosa (n=4, 10.3%) and *Streptococcus pneumoniae* (n=3, 7.7%) patients each (Figure-2).

Table-III: Clinical Source of Bacteremia as per Treating Physician's Initial Assessment (n=39)

Clinical Source of Infection	Frequency(%)
Gastrointestinal tract	24 (61.5)
Lower respiratory tract infections	3 (7.7)
Upper respiratory tract infections	4 (10.3)
Urinary tract infections	1 (2.5)
Surgical Wound	4 (10.3)
Central venous lines	3 (7.7)

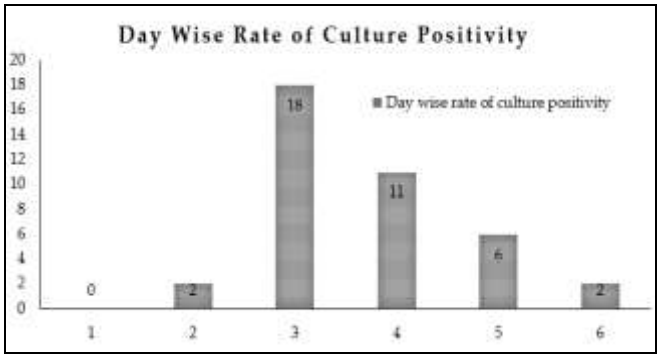

Figure-1: Days to Positive Blood Cultures

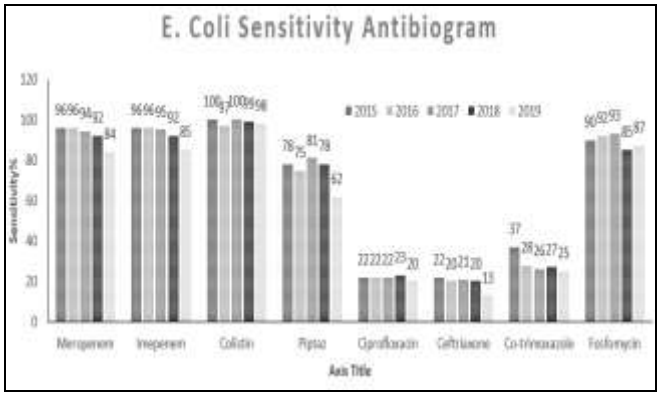

Figure-2: Escherichia Coli Sensitivity Antibiogram for Admitted Patients

DISCUSSION

Febrile neutropenia (FN) is a frequently encountered complication of cancer treatment, especially in hematologic malignancies. Most FN episodes are confined to the period of initial diagnosis and intensive treatment. Fever is often the only sign of infection in children with cancer because of their suppressed inflammatory responses. As FN is considered a medical emergency, prompt identification of organisms and timely antibiotics administration can prolong the survival of pediatric cancer patients and improve their quality of life.[8,9]

In our study, we found that most affected patients had background diagnosis of hematologic malignancies compared to patients with solid tumours. The primary diagnosis was acute lymphoblastic leukaemia in 44 patients (51.2 %), followed by Non-Hodgkin's Lymphoma in 11.6% of patients. FN affecting haematological malignancies more often can be attributed to the fact that there are primary bone marrow involvement and more intensive chemotherapy regimens being used, leading to prolonged and profound neutropenia in these children.[10]

Gram-negative bacteremia was found to be more prevalent in our population as compared to gram-positive bugs. Seventy-nine percent (79%) of bugs were gram-negative in our study. A study conducted by Patil *et al*. revealed the frequency of occurrence of Gram-negative bacteria to be about 47.43% (n=37), slightly lower than that of Gram-positive bacteria with 52.57% (n=41).7 In another study by Härtel *et al*. gram-positive organisms were again more common.[10] This can be because coagulase-negative organisms (CoNs), considered environmental contaminants and not treated, were excluded in our study, leading to gram-negative bacteremia being a more common finding in this study.

Multi-drug resistance is an emerging threat for cancer patients predisposed to infections due to poor immune function. In a study conducted at our centre in 2010, they evaluated 1603 episodes of bacteremia.[3] Of them, 227(35.6%) cultures grew E. coli, with 98(43.2%) E. coli isolates being multidrug-resistant. Multiple risk factors were associated with multidrug-resistant Escherichia coli bacteremia, which included the pediatric age group, presence of a central venous line, and prior use of Piperacillin/Tazobactam within 90 days of documented infection. They found the 30-day mortality rate as 35.2% (80/227). Significant risk factors associated with mortality were ICU admission and profound neutropenia.[4] In contrast to this study, we found that 28.2 % of isolates were MDR organisms, but it was not found to be a significantly associated risk factor for mortality in our pediatric population (p=0.066).

Kelly *et al*. conducted a study where they found 29 bacteremia episodes in 459 (6.3%) febrile visits by

167 patients. Bacteremia was found in 4.4% of patients with porta-caths and 16.2% with peripherally inserted catheters. The relative risk of bacteremia was 3.7 (95% CI: 1.8-7.4) times more in patients with external catheters than those with internal catheters (p<0.001).8 A clinically documented source for fever was noted in 21% of patients (p=0.004). In our study documented source of infection on clinical examination was found in almost all patients with positive cultures, and only 7.7 % of patients had central venous catheters as a risk factor for bacteremia. This difference in results can be due to the limited number of patients with central lines in our low, and middle-income setup.

Although blood culture has been the historic gold standard for identifying organisms, it may take days to identify isolate and days for drug sensitivity testing. Eighty-seven percent of patients (n=34) with positive cultures could receive appropriate antibiotics. All patients who could not get an appropriate antibiotic died before culture sensitivity was reported. This emphasizes the need for rapid identification of blood-stream organisms for a timely transition to targeted antibiotic therapy for effective patient care. The more promptly appropriate antimicrobials are prescribed and administered, the lower the mortality rates for patients with septicemia.[11] Significant improvements have been seen in the last few years to reduce the time to identify pathogens isolated from positive blood cultures. Rapid identification of micro-organisms directly from positive blood cultures (BC) combined with an antimicrobial stewardship program (ASP) has shown improved outcomes in febrile neutropenic episodes.[12,13] One study by Daniels *et al*. studied the impact of matrix-assisted laser desorption/ ionization time-of-flight mass spectrometry (MALDI-TOF) compared to conventional identification via blood cultures on antibiotic management and out-comes.[14] Pediatric intensive care unit admission rate after septicemia was less frequent in the MALDI-TOF group (23.1 versus 37.2%, p0.02).[15,16] Rapid identifica-tion using MALDI-TOF provided fast and reliable microbiological results [17] that can improve outcomes in an established ASP.[18] Another newer method to rapidly identify pathogens in low and middle-income countries is next-generation sequencing(NGS) which is rapid and cost-effective. These newer methods will help decrease mortality and morbidity in pediatric oncology patients.[19,20]

CONCLUSION

Bacteremia occurred in 9.97% of the FN episodes requiring inpatient admission in our study. MDR pathogens were associated with high rates of mortality and morbidity. The sensitivity of isolated micro-organisms to Piperacillin-Tazobactam justifies its empiric use in FN pediatric oncology patients in our setting. Rapid identification of organisms using modern, cost-effective methods directly from positive BCs can provide rapid and reliable microbiological results. Rapid identification of organisms combined with an established antibiotic stewardship programme may improve treatment outcomes and decrease hospital costs in Low and middle-income countries.

Conflict of Interest: None.

Author's Contribution

Following authors have made substantial contributions to the manuscript as under:

ZS: Study design, data acquisition, data interpretation, critical review, approval of the final version to be published.

RW & SJK: Conception drafting the manuscript, interpretation of data, approval of the final version to be published.

RQ & KM: Data analysis, drafting the manuscript, data interpretation, approval of the final version to be published.

NS: Data interpretation, critical review, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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