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Original Article

Pattern of Bacterial Infections in Paediatric Patients with Chemotherapy-Induced Neutropenia

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ABSTRACT

Objectives: To determine the frequency of bacterial infections and their sensitivity to various antibiotics in paediatric cancer patients having chemotherapy-induced neutropenia.

Study Design: Cross-sectional study

Place and Duration of Study: Paediatric Oncology ward, Combined Military Hospital, Rawalpindi Pakistan, from Jul 2018 to Jan 2019.

Methodology: A total of 205 children aged one year to 12 years undergoing chemotherapy and having neutropenic fever were included. Complete history, full physical examination and related blood, microbiological and radiological investigations were undertaken. Antibiotics were given as per protocol.

Results: In our study, the bacterial infections in paediatric cancer patients with chemotherapy-induced neutropenia was found in 45(21.95%) patients. Of these, gram-positive organisms were found in 25(55.5%) patients and gram-negative in 20(44.4%).

Conclusion: The frequency of bacterial infections in paediatric patients with chemotherapy-induced febrile neutropenia is quite high, with a high percentage of gram-positive bacteria.

Keywords: Bacterial infections, Chemotherapy-induced neutropenia, Gram-positive bacteria.

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INTRODUCTION

Febrile neutropenia (FN) in paediatric cancer patients is quite common and a direct consequence of chemotherapy.[1] Fever in patients with neutropenia may rapidly progress to life-threatening infection within a few hours. Therefore, prompt recognition, assessment and treatment of neutropenic patients with broad-spectrum antibiotics is mandatory.[1,2]

Chemotherapy-induced febrile neutropenia (CIFN) is considered life-threatening with haemato-logical malignancies(reported as above 80%) and with solid tumours(around 50%).[3] The management of CIFN patients is still considered a challenge.[4] Usually, no causal infection is identified, while 10-20% are secondary to bacteraemia.1 The incidence of Gram-negative bacteraemia has recently increased in febrile neutropenic patients.[5] Continuous surveillance of the pattern of bloodstream infection is necessary in febrile neutropenia (FN) patients to optimise the choice of antibiotics.[6] Selecting the right antimicrobials is possible only if we know the local microbial spectrum and their sensitivity pattern.[7] In a previous study at the paediatric oncology department in the year 2000, Staphylococcus aureus was the most frequent gram-positive isolate, and E coli was the most common gram-negative isolate. Treatment with the standard combination of Amikacin and Ceftazidime showed an overall response rate of 61.3%. The mortality due to infections in this series was 22%.[8,9]

Considering the evolving pattern of bacterial pathogens and their sensitivity to antibiotics, we embarked on this study to determine the type of bacterial infections, the pathogenic bacteria and their sensitivity to various antibiotics in paediatric patients with CIFN. The basis of this study was to identify the latest infectious organisms being isolated from blood cultures and their sensitivities to various antibiotics. The results will help us in improving the management of paediatric cancer patients with chemotherapy-induced febrile neutropenia.

METHODOLOGY

The cross-sectional study was carried out at the Paediatric Oncology Department, Combined Military Hospital, Rawalpindi, from July 2018 and January 2019 after approval from the Institutional Review Board. The sample size was determined by the WHO sample size calculator.[10]

Inclusion Criteria: Paediatric cancer patients of either gender, aged 1 to 12 years, undergoing chemotherapy and having neutropenic fever, were included in the study.

Exclusion Criteria: Patients who developed fever within one day after chemotherapy, fever occurring during or within 6 hours of transfusion of blood, blood

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products and other intravenous fluids, patients who had already taken broad-spectrum antibiotics in the recent past, and patients with other causes of neutropenia like aplastic anaemia were excluded.

The study recruited 205 patients suffering from febrile neutropenia while undergoing chemotherapy. The patients' selection was based on documented fever (100.6 F or more) and neutropenia on complete blood count. A complete history, detailed physical examination, and pertinent haematological, microbiological, and radiological investigations were obtained from all patients. At least two sets of blood cultures were obtained from each patient. All neutropenic patients were given intravenous antibiotics when they developed a fever as per protocol. Antibiotics were given within one hour of fever after collecting samples for cultures.

Statistical Package for Social Sciences (SPSS) version 24.0 was used for the data analysis. Quantitative variables were expressed as Mean±SD and qualitative variables were expressed as frequency and percentages. Chi-square test was applied to explore the inferential statistics. The *p*-value lower than or up to 0.05 was considered as significant.

RESULTS

The study recruited 205 patients during the study period. The mean age was 6.02±2.25 years. Out of the 205 patients, 143(69.76%) were male, and 62(30.24%) were females. Majority of the patients had a diagnosis of acute lymphoblastic leukaemia (82 patients, 40%), whereas 63(30.73%) patients had acute myeloblastic leukaemia. Other tumours included lymphoma (45 patients, 21.95%) and retinoblastoma (15 patients, 7.32%). Antibiotic susceptibility patterns are shown in Table-I.

Table-I: Antibiotic Susceptibility Pattern (n=45)

Antibiotics	Sensitive	Resistant
Amikacin	39(86.67%)	06(13.33%)
Ampicillin	14(31.11%)	31(68.89%)
Amoxacillin-clavulanate(20/10ug)	38(84.44%)	07(15.56%)
Azithromycin	39(86.67%)	06(13.33%)
Cefixime	39(86.67%)	06(13.33%)
Cefoperazone	33(73.33%)	12(26.67%)
Ceftriaxone	38(84.44%)	07(15.56%)
Ciprofloxacin	40(88.89%)	05(11.11%)
Clarithromycin	33(73.33%)	12(26.67%)
Collistin	40(88.89%)	05(11.11%)
Linezolid	41(91.11%)	04(8.89%)
Meropenem	45(100.0%)	00(0.0%)
Penicillin	14(31.11%)	31(68.89%)
Pipercallin-tazobactam	41(91.11%)	04(8.89%)
Polymyxin B	40(88.89%)	05(11.11%)
Teicoplanin	33(73.33%)	12(26.67%)
Trimethoprim sulfamethoxazole	40(88.89%)	05(11.11%)
Vancomycin	45(100.0%)	00(0.0%)

It showed that Vancomycin and Meropenem were found to be 100% sensitive, followed by Linezolid (91.11% sensitive) & Piperacillin-Tazobactam (91.11% sensitive).

In our study, the frequency of bacterial infections in paediatric patients with CIFN was found in 45(21.95%) patients, as shown in Table-II. Of these, gram-positive bacteria were found in 25(55.55%) and gram-negative bacteria in 20(44.44%) patients. It was clear that the majority of positive bacterial infections were seen in acute myeloblastic leukaemia. The stratification of bacterial infection for the type of bacteria is shown in Table-III. Staphylococcus Aureus was the most common gram-positive organism, with 11 positive cultures and 44% of gram-positive strains.

Table-II: Bacterial Infection with respect to Diagnosis (n=45)

Diagnosis	Bacterial Infection		*p*-value
	Yes	No	
Acute Lymphoblastic Leukemia	15(18.29%)	67(81.7%)	0.097
Acute Myeloblastic Leukemia	20(31.7%)	43(68.25%)	
Lymphoma	09(20%)	36(80%)	
Retinoblastoma	01(6.6%)	14(93.3%)	

Table-III: Bacterial Infection with respect to Type of Bacteria

Gram Positive Organisms	No of Positive Cultures	% of Gram Positive	% of Total
Staph Aureus	11	44	24.4
Coagulase negative Staph	04	16	8.8
Group D Streptococcus	03	12	6.6
Streptococcus pneumoniae	04	16	8.8
Streptococcus pyogenes	03	12	6.6
Gram Negative organisms	No of Positive Cultures	% of Gram Negative	% of Total
Pseudomonas aeruginosa	04	20	8.8
Klebsiella pneumoniae	05	25	11.1
Serratiamarcescens	03	15	6.6
Acinetobacter baumannii	02	10	4.4
BurkholderiaCepacia	01	5	2.2
Escherichia coli	02	10	4.4
Enterobacter	03	15	6.6

DISCUSSION

Chemotherapy-induced neutropenia continues to be a major risk factor for life-threatening infection in paediatric cancer patients. The risk of infection in these patients is directly proportional to the severity and duration of neutropenia.[9,10] In our study, bacterial infections during febrile episodes in paediatric patients with chemotherapy-induced neutropenia were found in 45(21.95%) patients. Of these, gram-positive bacteria were found in 25 (55.5%) and gram-negative bacteria in 20(44.4%) patients. In a previous study conducted at the same paediatric oncology department, 29 bacteria

were cultured in 62 febrile episodes. 15(51.7%) were gram-positive, and 14(48.3%) were gram-negative isolates.

The microbiological pattern of infection, particularly in febrile neutropenic patients, has changed significantly in the last decade. This change has led to a shifting epidemiology from gram-negative to gram-positive microorganisms. This was also evident in our study. Recent other studies have identified that the most common bacteria in these patients were coagulase-negative Staphylococci, alpha-haemolytic Streptococci, and Staphylococcus Aureus.[11,12] The knowledge of prevailing microorganisms in each region is important to start the appropriate empirical antibiotic therapy immediately.[13] A study from Spain reported a continuous rise in Gram-positive bacteraemia, although the incidence of gram-negative bacteraemia remained unchanged. The most commonly isolated bacteria in this study were Staphylococci and S. viridans.[14]

In another multicentre study on febrile neutropenic patients in the USA, documented gram-positive pathogens as a cause of 62% and 76% of bloodstream infections in 1995 and 2000, respectively, while only 22%and 14% of all bloodstream infections originated from gram-negative pathogens at the same time.[15] It is mandatory to start antibiotic therapy at the first suspicion of neutropenic infection in order to reduce the mortality and morbidity associated with this condition. The microbiological tests take at least 3 to 4 days to complete. Therefore, the local knowledge of the bacteria and their relative sensitivity to antibiotics is important in initiating appropriate treatment while waiting for the results.

A Cochrane database systematic review (2013) showed similar efficacy of Ceftazidime, Cefepime, Meropenem, Imipenem-Cilastatin and Piperacillin-Tazobactam. However, the latter was associated with lower mortality in a review of 44 trials.[16] Another meta-analysis showed that the addition of aminoglycosides did not improve the outcome, while it significantly increased renal failure rates.[17] Therefore, most of the guidelines recommend firmly a β-lactam monotherapy.[18,19] Only German experts suggest the inclusion of an aminoglycoside in the initial empirical therapy in case of severe sepsis or septic shock from a large retrospective study.[19] At present, glycopeptides are not recommended for first-line empirical therapy unless a high suspicion of gram-positive infection, hemodynamic instability, known MRSA colonisation or high prevalence of MRSA is present.[20]

Daptomycin and Linezolid can be used instead of Vancomycin in resistant cases of staphylococci and enterococci infections. With Daptomycin, a response rate of 85% has been reported in febrile neutropenic patients with gram-positive infections.[21]

CONCLUSION

The frequency of bacterial infections in paediatric patients with chemotherapy-induced neutropenia is very high, with a high percentage of gram-positive bacteria. A high index of suspicion, prevention, and early detection of bacterial infections should be done to manage them with better antibiotics to decrease mortality and morbidity.

Conflict of Interest: None.

Authors Contribution

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

SAC, & TG: Data acquisition, data analysis, drafting the manuscript, critical review, approval of the final version to be published.

SMB: Study design, data inter-pretation, drafting the manuscript, critical review, approval of the final version to be published.

SK, & TF: Concept, data acquisition, 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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