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CLINICO-ETIOLOGICAL PROFILE OF INFECTIONS IN PAEDIATRICS PATIENTS OF HAEMATOLOGICAL MALIGNANCIES FROM A TERTIARY CARE HOSPITAL IN CENTRAL INDIA

Dr Monika Mishra*	PG Resident *Corresponding Author
Dr Preeti Malpani	Professor and HOD
Dr Prachi Chaudhary	Associate Professor
Dr Dharmanshu Chaube	Assistant Professor

ABSTRACT Hematological malignancies comprise a major health problem in society due to its high mortality and morbidity. Immunocompromised state due to disease itself and the cytotoxicity of the drugs used during chemotherapy, makes patients more susceptible to infections and its complications. Infections further increases the morbidity of these patients and influences the outcome of chemotherapeutic response. Advances in antimicrobial prophylaxis and chemotherapy have decreased the disease severity and improved the survival rate. Thus, prevention and treatment of infections are vital in the management of acute leukemia. There is lack of data on clinical and etiological profile of infections in leukemia patients.

KEYWORDS : Leukemia, Chemotherapy, Neutropenia, Bloodstream infections, Blood culture

INTRODUCTION

Hematological malignancies comprise a major health problem in society due to its high mortality and morbidity. Immunocompromised state due to disease itself and the cytotoxicity of the drugs used during chemotherapy, makes patients more susceptible to infections and its complications. Infections in leukemia patients not only increases the morbidity of these patients but also influences the outcome of chemotherapeutic response. The primary disease, long-term repetitive chemotherapy, accompanied by infection in the lungs, digestive tract, oral cavity, anus, etc., all led to decreased immune functions [1]. Advances in antimicrobial prophylaxis and chemotherapy have decreased the disease severity and improved the survival rate. Thus, prevention and treatment of infections are vital in the management of acute leukemia.

The major cooperative group trials also showed that the most important cause of treatment-related mortality (TRM) is infections. In UK ALL 2003 trial, sepsis was the most common cause of TRM and risk of infection-related mortality was higher during induction [2]. Information on the clinical and microbiological profile of infections is very important to reduce the morbidity and mortality and also to formulate an optimal antibiotic policy.

In a resource limited settings as ours, specific knowledge about infections and their causative agents will improve the supportive care and eventually the disease outcomes. Unfortunately, there is a real paucity of epidemiologic data on paediatric cancers in Central India. In advent of same we designed and conceived the present study in a tertiary care centre aiming to study and define the clinical and etiological profile of infections in patients of haematological malignancies among paediatric age group and also to correlate clinicoetiological profile of infections with stage of chemotherapy.

MATERIALS AND METHODS

This cross-sectional observational study was conducted at a tertiary care hospital in Indore, Madhya Pradesh. The study was conducted from August 2021 to July 2022 after clearance from the Institutional Ethics Committee.

Inclusion Criteria

All children (under 18 years) newly diagnosed or known cases of haematological malignancies presenting with signs and symptoms of infection were included.

The patients of ALL were stratified (based on iCiCle risk criteria) into standard-risk (SR), intermediate-risk (IR) and high-risk (HR) groups according to age, white blood cell count, immunophenotype, cytogenetic and molecular aberrations, prednisolone response, morphological remission at the end of induction therapy, minimal residual disease (MRD) at the end of induction therapy and the beginning of consolidation therapy.

When presenting with signs and symptoms of infection, a detailed clinical history was taken and a thorough physical examination was done to find the focus of infection. A clinical case report form was filled at this stage to record all the relevant details including type of leukemia and phase of chemotherapy.

Case Definitions

Microbiologically Diagnosed Infections- clinically significant pathogen was identified from a normally sterile specimen, or from an affected site, by culture or biopsy.
Clinically Diagnosed Infections- fever was accompanied by appropriate clinical findings, for example, pulmonary infiltration or inflammation of the skin or soft tissue.
Fever of Unknown Origin- no clinical, radiological or microbiological evidence of infection.

Complete blood count with absolute neutrophil count, blood cultures, chest x-rays and urine analysis were done in all patients recruited for the study. Cultures were taken from the PICC (Peripherally Inserted Central Catheter) line and peripheral blood at the onset of fever, escalation of antimicrobials and/or deterioration of general condition of patients attributed to infection. Cultures were also taken from other sites (eg, urine, stool, ear discharge) whenever clinically indicated. Also other clinically relevant investigations and imaging were done e.g, Urine routine, stool routine, serum galactomannan, CT chest and Paranasal sinuses etc.

Statistical Analysis

The data from each patient was compiled on Microsoft Excel Sheet as descriptive statistical analysis was done. Chi-square test was applied and p-value was calculated wherever applicable.

RESULTS

Total 100 cases with hematological malignancies were enrolled in the study, of which maximum patients were falling in age group 5-10 years (47%) with mean age 5.67 year. Of the total patients, maximum were of B-cell ALL (76%), followed by AML (13%), T-Cell ALL (6%), JMML (4%) and CML (1%). Nearly half of patients were belonging to High risk group (54%).

The most common clinical symptom observed was fever (95%) and the leading cause for hospitalization was respiratory tract infections (44%). Pneumonia (39%) was the most common infection in patients of hematological malignancies followed by septicemia (14%). Maximum cases of infections are clinically documented (CDI-57%) followed by microbiologically documented ones (MDI- 43%).

Table 1: Diagnosis During Infection Episode

Diagnosis	Count	Percentage
Pneumonia	39	39.00%
Septicemia	14	14.00%
Acute Gastroenteritis	12	12.00%
Urinary Tract Infection	12	12.00%
Cystitis	2	2.00%
Abscess	7	7.00%
Upper Respiratory Tract Infection	3	3.00%
Otitis Media	2	2.00%
Sinusitis	2	2.00%
Tonsillitis	1	1.00%
Mucormycosis	1	1.00%
Kerato-conjunctivitis	1	1.00%
Malaria	1	1.00%
Chicken pox	1	1.00%
Molluscan contagiosum	1	1.00%
Herpes labialis	1	1.00%

Of the total recruited cases, maximum had TLC <4000/cmm (67%) and ANC <500/cmm (44%). Neutropenia was more severe during initial phases of chemotherapy. Causative organisms have been isolated in 51% cases – 32% bacteria, 10% fungus, 6% parasites and 3% viral. Overall positive Bacterial cultures were obtained from 19 cases (19%).The most commonly isolated pathogens were Staphylococcus aureus (6%) and pseudomonas (6%) , Klebsiella (2%), E.coli (2%), CONS (2%) and Proteus (1%). There were more number of Gram negative isolates as compared to Gram positive ones.

Table 2: Culture Results Of Various Sites

Cultures		Count	Percentage
Blood Culture (100)	Sterile	81	81.00%
	Staph aureus	6	6.00%
	Pseudomonas	6	6.00%
	CONS	2	2.00%
	Klebsiella	2	2.00%
	E.coli	2	2.00%
	Proteus	1	1.00%
Urine Culture (11)	E.coli	6	54.5%
	Pseudomonas	1	9.1%
	Proteus	1	9.1%
	Sterile	3	27.3%
Pus Culture (5)	Sterile	3	60%
	Staph aureus	2	40%
Central Line Tip Culture (1)	CONS	1	100%

Observed death rate was 7%. The association between Outcome of infection episode and Phases of chemotherapy was found to be statistically significant (P-0.014). The patients who succumbed were all in initial phases of chemotherapy (Induction and Interim-maintenance). The leading cause of death was found to be bloodstream Infections (71.4%) and respiratory tract infections (28.6%).

DISCUSSION

Our study was a cross-sectional observational study aimed at assessing the incidence of infections in children with leukemias and to assess the clinical profile, laboratory parameters, microbiological profile, and the outcome of infections.

Majority of patients were of B-cell ALL (76%) which is consistent with prevalence of various types of leukemia in general population [3]. As per our study, among B-cell ALL patients, there were higher frequency of infection episodes in high-risk patients as compared to intermediate and standard-risk ones. This result was following the same pattern as that of study conducted by Rajeswari, et al. in Trivendrum, Kerala [4]. where infection rate was 58.9% in High- risk group and 45.8% in standard-risk ones. However, Li SD et al, observed in their study that there were no differences among the three risk groups, that is,15.4% in HR versus 19.6% in IR versus 19.9% in SR [5]. This large variation in infectious complications might be explained by factors including the severity and duration of neutropenia, the nature and intensity of antineoplastic therapy, the use of empiric antibiotic therapy and other host-related factors.

In our study, we encountered a wide spectrum of infections, of which majority were involving Respiratory tract (44%) followed by Bloodstream (15%) and Urinary tract (14%). Similar findings were reported by Rajeswari et al., [4][1] and Jain H et al., [6] where Respiratory system was the commonest system involved (25%). The study conducted by B Roy et al., Infections in Acute Leukemia in Indian Children showed that the skin and soft tissue was the commonest site of infection, accounting for 26.83% of all infection, closely followed by respiratory tract ones (21.95%) [7].

The most frequent infections in our study were CDI (57%) followed by MDI (43%). Similar results were quoted by - Lee MS et al [8] with 47% CDI and 19% MDI. With regard to ANC levels, most of the infections (44%) occured when the granulocytopenia was severe (<500/cmm) as suggested by various studies reported worldwide [5,7,8]. Because patients with leukemia have abnormal white blood cells, the quality and quantity of neutrophil chemotaxis and phagocytosis are decreased after chemotherapy and bone marrow suppression.

Among all identified causative organisms (51% of cases), majority were bacterial (32%) followed by fungal (10%). Also, O'Connor D et al.,[2] during their study observed similar results- 68% bacterial infections, 20% fungal, and 12% viral. Offending microbes were cultured from blood (19%), urine (8%), pus (2%) and central line tip culture (1%). As revealed by other studies, Gram negative organisms are involved in majority of infections and staphylococcus has been playing an increasingly important role, we have observed 57.8% of culture proven bacterial infections with predominant Gram-negative ones [4,5,6,8,9].

The most common specific bacteria detected were Pseudomonas (31.6%) and Staph aureus (31.6%). It is therefore imperative that antibiotics used in the treatment and prophylaxis of infections in paediatric ALL have adequate efficacy against pseudomonal species and other Gram negative bacteria. Fungal organisms were responsible for only a small portion of the total infections in this study (10%). The most frequent fungal infection was pneumonia. Aspergillus was the most frequent fungal pathogen detected (7 cases). Viral infections were diagnosed infrequently in this study. There was single episode of Herpes, Molluscan contagiosum and Chicken pox each.

Our analysis demonstrated 7% mortality rate and all of them occurred during initial phases of chemotherapy (42.9%

during induction and 57.1% during interim maintenance) and neutropenic patients, which is comparable to results of other studies [2,4]. Thus, increased awareness of the potential for septic complications is required when caring for patients during these high-risk periods. Out of all deaths 71.4% were attributed to bloodstream infections (MDI and CDI) and 28.6% to respiratory infections. 42.8% cases were of microbiologically identified (2 bacterial and 1 fungal) infections while in remaining 57.2%, the organisms could not be isolated and they were considered bloodstream infections as per clinical findings.

Febrile neutropenia and documented infections, especially severe bacterial and invasive fungal infections, interfere with the uninterrupted administration of chemotherapy; therefore, reducing these events could further improve outcomes of leukemia treatment.

Limitations

This study was conducted on a small number of patients. There were very few culture proven infections so, the sensitivity pattern and its correlation with other factors could not be studied well.

CONCLUSIONS

The present study describes the clinical and etiological profile of infection episodes in leukemia children admitted to the haematoncology unit of largest tertiary care public health institute of Madhya Pradesh. We conclude that emergence of infections are more common among high-risk groups, with neutropenia and during initial phases of chemotherapy. Prompt initiation of broad-spectrum antibiotics with efforts to isolate causative organisms is required to understand the emerging patterns of antibiotic resistance and to formulate the antibiotic policy.

Larger studies conducted over longer duration are recommended in future to generate data on clinical profile of infections and antibiotic susceptibility of causative organisms.

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