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Evaluation of febrile neutropenia in diagnosed cases of acute lymphoblastic leukemia in children

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ABSTRACT

Background: Febrile neutropenia is a serious and most common complication of cancer therapy. A single oral temperature of greater than or equal to 101 F, or a temperature of greater than or equal to 100.4 F for at least an hour with ANC <500/μL, or less than 1000/μL with a predicted fall to less than 500/μL in the following 48 hours, are the criteria for its clarification.
Aims and Objectives is to study clinical profile of febrile neutropenia in ALL patients and to study the susceptibility patterns of pathogens and bacterial spectrum in culture positive febrile neutropenic patients in ALL.
Study design: It was a retrospective study.
Materials and Methods: Patients undergoing treatment and meeting the criteria for Febrile Neutropenia were included in study.
Results: The study was a retrospective that lasted a year. Children with febrile neutropenia undergoing chemotherapy were included in the research. The study emphasize the common infectious agents, their antibiotic sensitivity pattern. ANC being the most important parameter it was found that 15 patients (37.5%) had ANC <500/ microL and 25 patients (62.5%) had ANC between 500-1000 /microL which had fallen to <500/microL in next 24 hours.
Conclusion: Long-term neutropenia was linked to an increased risk of FN, and infections with a preponderance of Gram-negative bacteria were found in about 32.5% of patients.

1. Introduction

A hematological emergency, febrile neutropenia is brought on by the treatment of hematological malignancies.[1] Neutropenia is described as an Absolute Neutrophil Count (ANC) <500/μL or less than 1000/μL with an A hematological emergency, febrile neutropenia is brought on by the treatment of hematological malignancies. Anticipated decreases to less than 500/μL in the next 48 hour period. Neutropenic fever is a single oral temperature of 38.3ºC (101ºF) or a temperature of greater than 38.0ºC (100.4ºF) undergo for more than one hour in a patient with neutropenia.[2] Chemotherapy treatment has increased the survival rate for patients with hematological illnesses, but it also increases the risk of sepsis and bacteremia, which are major causes of morbidity and death.[3]

Over the last 4 decades, there has been a considerable fluctuation in the epidemiological spectrum of pathogens isolated from febrile neutropenic patients. Until the mid-eighties, Gram-negative Chemotherapy treatment has increased the survival rate for patients with hematological illnesses, but it also increases the risk of sepsis and bacteremia, which are major causes of morbidity and death. Bacteria were the most frequently isolated

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organisms. The most common Gram-positive bacterium was Staphylococcus aureus. Since then, the majority of infections in FN have been caused by Gram-positive bacteria (such as viridans streptococci and coagulase-negative staphylococci, CONS). *Enterococcus* was responsible for colonization in majority of the neutropenic patients and raise the problem of resistance to antibiotics, mainly glycopeptides.[4] Patients having malignancies and other immunocompromised conditions are more likely to be infected with opportunistic Gram-negative bacteria.[5]

Since the microbial etiology is not known at the initiation of treatment, choice of empiric therapy depends on the locally prevalent pathogens and their sensitivities, the risk group, the potential sites of infection and the cost of various regimens. At present, there are no national guidelines for treatment in these patients on cancer therapy in India. Therefore, we believed it was important to assess the pathogenic organisms, clinical profile, and pattern of antibiotic susceptibility in ALL individuals with FN. This study established the current spectrum of local flora and its susceptibility to the standard first line antibiotic regimen thereby, evaluating the efficacy of institution's current first line antibiotic regimen for febrile neutropenia in ALL patients. Studying the clinical profile of febrile neutropenic patients with ALL as well as the bacterial spectrum and pathogen susceptibility patterns in culture-positive febrile neutropenic patients with ALL are the goals and objectives.

2. Material and Methods

2.1. Study design

Retrospective research was done.

2.2. Study population

The study was carried out in the pediatric haemato-oncology ward of the pediatrics department at Government Medical College, Jammu, from November 1, 2020, to October 31, 2021. The trial involved children with febrile neutropenia who were receiving treatment for ALL. The study included patients with acute lymphoblastic leukemia who met the criteria for febrile neutropenia while receiving treatment in a pediatric oncology ward.

2.3. Inclusion criteria

Patients with Acute Lymphoblastic Leukemia undergoing treatment in SMGS HOSPITAL meeting the criteria for febrile neutropenia.

2.4. Exclusion criteria

Patients in which fever occurred within six hours or during the transfusion of blood or blood products were excluded.

2.5. Sampling procedure

For Blood culture studies, 2- 3 mL of blood sample in infants aged 1 month to 2 years, 4- 5 mL of blood for older children and 10-20 mL for adolescents was collected in the blood culture bottles under all aseptic precautions. Blood cultures was performed by conventional method. Blood culture bottles were overnight incubated at 37 degree Celsius, then Streaked on MacConkey agar, Blood agar and chocolate agar and then incubated for 24 hours. If growth was present, Gram staining was done to check Gram Positive or Negative Organisms and then Antibiotic sensitivity was checked. Culture plates were again incubated for 24 hours in 3 cycles before declaring it Negative for any organism. Cultures from different sites was obtained if needed, based on the clinical profile like swab culture, urine culture. For urine cultures, mid-stream urine sample was collected. For swab cultures, swab was passed deep into the base of the lesion to firmly sample the fresh border. Other investigations included complete blood count, chest x-ray. Details of patients who fulfilled inclusion criteria, history, physical examination and other details were recorded on a standard Proforma. Following Laboratory investigations like Complete blood count, Urine routine, Differential Counts and calculation of Absolute Neutrophil count, Blood culture, urine culture, swabs for culture, PBF for malarial parasite was done based on clinical profile.

3. Results

In this study 40% of the patients were in the age group of less than 5 years, 25 % between 5- 9 years, 25% between 10 and 14 years, 10% were in age group of >15 years respectively. Mean age is 7.5 years. Out of 40 patients in our study, 22 (55%) patients were male and 18 (45%) were females. 36 (90%) patients were of B-cell ALL while 4 (10%) patients were T-cell ALL (Table 1). Eighteen (45%) patients were in <5 years of age whereas 12 (30% were in age group of 5-9 years and 10 (25%) patients were in more than 10 years age group. While observing clinical profile of 40 patients in our study, it was observed that 13 (32.5%) patients of FN had tachycardia, 6 (15%) patients had Rashes, 6 (15%) Patients had tachypnea in which 2 patient had bilateral crepts and 1 patient had bilateral wheeze, 2 (5%) patients had hypotension, 2 (5%) patients had dehydration and 1 (2.5%) patient had oliguria while remaining 10 (25%) patients had no clinical signs. Duration of fever in study patients was mostly >5 days while in some patients it was <5 days. Thirty seven patients out of 40 had fever >5 days and only 3 patients had fever for 2 or 3 days. Leukocytes count was mostly <4000 cells/ cubic milimeters and 8 (20%) patients had leukocytes count <2000 cells/ cubic milimeters and 32 (80%) patients had leukocytes count between 2000-4000 cells/ cubic milimeters. ANC being the most important parameter it was found that 15

patients (37.5%) had ANC <500/ micro L and 25 patients (62.5%) had ANC between 500-1000 /microL which had fallen to <500/microL in next 24 hours (Table 2). Most of the patients were anemic and 6 patients (15%) had HB <7gm % and 34 patients (85%) had HB between 7-10gm%. Patients <7gm% received blood transfusions. Platelet count <1.5 lakh cells/ μL is thrombocytopenia and hence 3 categories were made to observe distribution of patients with thrombocytopenia in which platelet count between 1.0-1.5 lakh / μL was found in 5 patients (12.5%) and between 0.5-1 lakh / μL found in 22 patients (55%) and <0.5 lakh /μL was found in 13 patients (32%). Patients with Platelet Count <50000 /μL with bleeding manifestations were given platelet transfusions. Peripheral blood film was observed in the patients, 8 patients (20%) had microcytic hypochromic picture, 25 patients (62.5%) had normocytic blood picture, 3 patients (7.5%) had mild hypochromia and 4 patients (10%) had moderate hypochromia. No Malarial parasite was seen in PBF. The main focus of infection was blood and urine and on blood and urine culture, it was found that out of 40 patients, 3 (7.5%) patients had positive urine culture and 10 (25%) patients had positive blood culture (Table 3). Organisms isolated among study patients were *E.coli* (3 patients), MRSA (3 patients), *Enterococcus* (2 patients), Acinetobacter (2 patients), *Klebsiella* (2 patients), and Pseudomonas (1 patient). Organisms isolated from urine culture was only *E.coli* (100%) i.e. all 3 patients of urosepsis had growth of *E.coli* only, while organisms isolated from blood culture were MRSA (30%), *Enterococcus* (20%), Acinetobacter (20%), *Klebsiella* (20%) and pseudomonas(10%) (Table 4). Microorganisms isolated from blood and urine cultures were classified in gram negative organism and gram positive organisms. There were 5 culture (38.5%) positive for gram positive organisms and 8 culture (61.5%) positive for gram negative organisms. It indicates that gram negative organisms infection was more prevalent. Among Gram positive organisms, MRSA was isolated from 3 patients (60%) and *Enterococcus* was isolated from 2 patients (40%). It indicates that MRSA was the main causative agent among gram positive organisms. Among gram negative organisms, most common causative agent among these organism was *E.coli* isolated from 3 patients (37.5%) followed by Acinetobacter isolated from 2 patients (25%), klebsiella isolated from 2 patients (25%) which is followed by pseudomonas isolated from 1 patient (12.5%). The most sensitive drugs for isolated organisms were piperacillin-tazobactam and amikacin, which were followed by cefuroxime, gentamicin, cefepime, meropenem, nitrofurantoin, netilmicin, teicoplanin, vancomycin, cefoperazone, cefotaxime, and clindamycin. Therefore, patients with febrile neutropenia may benefit from the empirical administration of amikacin and piperacillin-tazobactam. Septicemia (22.5%) was the most common focus of infection followed by urosepsis and pneumonia (each 7.5%), septicemia with enteritis (2.5%), Enteritis (2.5%), Thrombophlebitis (2.5%), abscess (2.5%) and 52.5% of patients have unknown focus of infection.

Table 1: Oncological diagnosis of study patients

Oncological diagnosis	Number	Percentage
B cell all	36	90.0
T cell all	4	10.0
Total	40	100

Table 2: Absolute neutrophil count (ANC) among study patients

ANC /microL	Number	Percentage
< 500	15	37.5
500-1000	25	62.5
Total	40	100

Table 3: Culture positivity

Culture		Number	Percentage
Urine Culture	Positive	3	7.5
	Negative	37	92.5
Blood culture	Positive	10	25.0
	Negative	30	75.0

Table 4: Organism isolated from urine and blood culture

Culture	Organism isolated	Number	Percentage
Urine	*E.coli*	3	100
Blood	MRSA	3	30
	Enterococus	2	20
	Acinetobacter	2	20
	Klebsilla	2	20
	Pseudomonas	1	10

4. Discussion

The study was done to assess the clinical and microbiological profile, antibiotic sensitivity in patients with FN undergoing treatment for ALL. Majority of infections in the study were found in blood (22.5%), urine (7.5%), lungs (7.5%), GIT (2.5%) and soft tissue (5%) which was in concordance with other studies.[6–8] Fifty two percent patients were without primary site of infection. 7.5% of patients were positive for urine cultures and 10% of patients were positive for blood cultures. Culture positive FN episodes had been identified in 15–38% of patients in other studies also.[9–13] This study shows that gram-negative microbes predominate in febrile neutropenic ALL patients. These results were consistent with those of earlier studies that show *E. Coli* is the most commonly isolated Gram-negative bacterium.[14–16] Similar finding have been reported from India, Brazil and Turkey.[1,9,17,18]

From patients who were neutropenic, 67% of Gram-negative and 29.8% of Gram-positive infections were identified. According to this study, the majority of microorganisms in febrile, neutropenic ALL patients are gram-negative. These findings supported previous research demonstrating that *E. Coli* is the most often isolated Gram-negative bacterium. coagulase negative staphylococci and *E. coli* were the most often found Gram positive and Gram negative bacteria in an Iranian research with ALL.

While Gram negative bacterial infections were more common in western countries between 1970 and 1980, subsequent reports indicated a shift toward Gram positive Cocci infections. This is mostly caused by the widespread use of indwelling CVCs and fluoroquinolone prophylaxis, which inhibits the growth of aerobic Gram-negative bacteria in the gastrointestinal tract but not the growth of microaerophilic Gram-positive cocci.[19]

The choice of empirical antibiotic therapy for febrile neutropenia in ALL patients was aided by these findings. Additionally, piperacillin/tazobactam and amikacin were the first-line antibiotic therapy. Due to their double Gram negative cover and suitable sensitivity pattern, these medications are currently the preferred option. Additionally, this combination was given the go-ahead in the literature and was able to cover 80% of Escherichia coli strains on average.[20] The most prevalent Gram-positive isolates were *Enterococcus* and MRSA, both of which were vancomycin-sensitive. Our study's mortality rate was 5%, although previous research had found that it ranged from 5% to 39%.[8,18,20]

IN ALL there is high risk of developing FN. In high-risk FN, empirical therapy using piperacillin-tazobactam and amikacin as a first line produces satisfactory outcomes. Therapy should be customized to the most effective antibiotics based on the results of the bacterial culture. 5% of patients die while receiving treatment for febrile neutropenia in the hospital, according to this report.

5. Conclusion

The goal of the study is to identify frequent infectious pathogens and the patterns of antibiotic sensitivity associated with them. It demonstrates that an elevated risk of FN is linked to prolonged neutropenia. Infections confirmed by culture were present in about 32.5% of patients. In high-risk cases, empirical therapy using piperacillin-tazobactam and amikacin produces satisfactory clinical outcomes. Hence, even in this medical emergency, aimless use of higher antibiotics must be restricted, and therapy should be customized to the most appropriate antibiotic for the particular culture.

6. Source of Funding

None.

7. Conflicts of Interest

There are no conflicts of interest.

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