

# Frequency and Culture Sensitivity of Febrile Neutropenic Episodes in Paediatric Patients of Acute Lymphoblastic Leukemia on Chemotherapy

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## Abstract

**Background:** To determine frequency of febrile neutropenia episodes (FN) in patients of acute lymphoblastic leukaemia (ALL) on chemotherapy and to study different type of organisms isolated in them along with their sensitivity to different antibiotics.

**Methods:** In this descriptive study children of either gender diagnosis of ALL and on any one of the initial four phase of chemotherapy including induction, consolidation, interim maintenance and delayed intensification were followed prospectively from start till end of that particular phase. The chemotherapy protocol used in the centre is BFM protocol. Patients who developed fever ( $\geq 38^{\circ}\text{C}$ ) during this time and turned out to be neutropenic ( $\text{ANC} \leq 500/\text{mm}^3$ ) underwent blood culture (on Bectec). Antimicrobial susceptibility profile was done by Kirby Bauer disc diffusion method on Muller Hinton agar, according to CLSI 2006 guidelines.

**Results:** Mean age of children was  $5.5(\pm 3.0)$  years. Of 94 ALL patients enrolled in the current study, 46% were younger than 5 years and 73% were males. Out of 94 37 (39%) developed fever and neutropenia. The mean (SD) temperature of all the children was  $38.9 (\pm 0.3)^{\circ}\text{C}$ . The mean (SD) absolute neutrophil count (ANC) was  $264.0 (\pm 149.2)/\text{mm}^3$ . Out of 37 children who developed febrile neutropenia, 25% had positive blood cultures. The most common isolate was *Klebsiella* (44.4%), followed by *Pseudomonas aeruginosa* (33.3%) and *Staphylococcus aureus* (22.2%). *Klebsiella* was sensitive to most of the antibiotics tested except cephalosporins. Sensitivity of *Pseudomonas* was 100% to ceftazidime and cefotaxime while *Staph. aureus* was 100% sensitive to ceftazidime, imipenem and ciprofloxacin.

**Conclusion:** Nearly two-fifths of the children with ALL developed febrile neutropenia. A quarter of them showed positive blood cultures. The most common pathogen found in our study was *Klebsiella*, followed by *Pseudomonas* and *Staphylococcus aureus*. Most of the antibiotics tested for the *Klebsiella* were shown to be effective except cephalosporins. For *Pseudomonas*, Cefazidime and Cefotaxime were 100% sensitive, while for *Staphylococcus* Cefazidime, Imipenem and Ciprofloxacin showed 100% sensitivity.

**Key words:** Febrile neutropenia, Acute Lymphoblastic Leukaemia, Chemotherapy.

## Introduction

Virtually all chemotherapy regimens can produce myelosuppression and neutropenia (absolute neutrophil count  $< 500/\text{mm}^3$ ).<sup>1,2</sup> It poses a risk of life threatening infection in cancer patients. Prevalence of FN in ALL patients is 42%, representing significant disease burden thus need for monitoring patients receiving chemotherapy for fever and neutropenia cannot be overemphasized.<sup>3</sup> In a case, where fever (temperature  $\geq 38^{\circ}\text{C}$ )<sup>1</sup> and neutropenia occurs during treatment course, immediate assessment and treatment is required.<sup>1</sup>

Time to antibiotic administration (TTA) is found independently associated with mortality within 28 days and each increase of 1 hour in TTA raised risk of mortality within 28 days by 18%.<sup>4</sup> It is important to determine etiology of FN to give prompt pathogen specific regimen in order to reduce mortality and morbidity. As bacterial etiology of FN is changing with time and with the emergence of newer antibiotics as well as it is different in different geographical areas, the clinician must have knowledge of the prevalence of causative bacteria and their antibiotic sensitivity in these patients so that appropriate empirical therapy

can be given. This study assessed the frequency of FN in ALL patients receiving chemotherapy as well as the type and isolation rate of causative bacterial agents and their sensitivity pattern in our region thus will be helpful in improving treatment modalities.

### Patients and Methods

This descriptive study was carried out from September, 2011 to February, 2012 at oncology department of Children Hospital PIMS. All children of either gender admitted in ward with diagnosis of ALL and were on any one of the initial four phase of chemotherapy including induction, consolidation, interim maintenance and delayed intensification were followed prospectively from start till end of that particular phase. The chemotherapy protocol used in the centre is BFM protocol. Patients who developed fever ( $\geq 38^{\circ}\text{C}$ ) during this time, their blood samples were sent to lab for cell counts and those who turned out to be neutropenic ( $\text{ANC} \leq 500/\text{mm}^3$ ) their blood sample was collected for bacterial culture study in Bactec blood culture bottles and were proceeded through automated blood culturing system (Bactec 9050, BD, USA). Antimicrobial susceptibility profile was done by Kirby Bauer disc diffusion method on Muller Hinton agar using antibiotic discs of commonly used antimicrobial agents according to CLSI 2006 guidelines<sup>5</sup>. Culture and sensitivity results were recorded.

### Results

Majority (73%) were males. The age ranged between 1-12 years. Amongst children with febrile neutropenia, out of 37 children, 15 (40.5%) children were less than 5 years of age, 21 (56.8%) were aged between 5 and 9 years while 1 (2.7%) child was aged 10 years. Whereas, of 57 children without febrile neutropenia, 28 (49.1%) were aged less than 5 years, 21 (36.8%) and 8 (14%) were 5 to 9 and 10 and more years of age respectively. The difference in the distribution of age categories between children who had febrile neutropenia and those who did not have it was not statistically significant ( $p=0.068$ ). The mean (SD) absolute neutrophil count (ANC) was  $264.0 (\pm 149.2)/\text{mm}^3$  with median and mode of  $253.0/\text{mm}^3$  and  $200.0/\text{mm}^3$  respectively. The range of absolute neutrophil count was between 0 and  $500/\text{mm}^3$  (Table 1). Out of 94 children 37 (39%) were diagnosed to have febrile neutropenia. No statistically significant difference was seen between those who developed and who did not develop febrile neutropenia regarding the phases of chemotherapy ( $p=0.060$ ) (Table 2). Out of 37 children who developed febrile neutropenia, 9 (25%) had

positive blood cultures. Of 37 children with febrile neutropenia, 4 (44.4%) cultures showed growth of Klebsiella, 3 (33.3%) showed growth of Pseudomonas and 2 (22.2%) cultures showed growth of Staphylococcus aureus (Table 3).

**Table 1 - Distribution of absolute neutrophil count by phases of chemotherapy (n=94)**

Variable	Absolute neutrophil count		
	Mean (SD)	Median	Range (min - max)
Remission induction	273.1 ( $\pm 137.9$ )	266.0	(106 - 475)
Consolidation	266.6 ( $\pm 180.6$ )	200.0	(31 - 480)
Interim maintenance	220.0 ( $\pm 151.7$ )	300.0	(45 - 315)
Delayed intensification	291.8 ( $\pm 121.4$ )	246.0	(0 - 500)

**Table 2: Comparison of distribution of phase of chemotherapy between those who had and those who did not have febrile neutropenia (n=94)**

Phase of chemotherapy	No. of FN cases	Patients who did not develop FN	Total Patients	% of FN
Remission induction	13	19	32	41%
Consolidation	11	13	24	46%
Interim maintenance	3	17	20	15%
Delayed intensification	10	9	19	53%

**Table 3 - Antibiotic sensitivity and resistant pattern (in percentage) of various pathogens in blood positive children**

Antibiotics	Klebsiella		Pseudomonas		Staphylococcus	
	Sensitivity	Resistant	Sensitivity	Resistant	Sensitivity	Resistant
Amikacin	100.0%	0.0%	0.0%	100.0%	0.0%	100.0%
Ceftriaxone	25.0%	75.0%	0.0%	100.0%	0.0%	100.0%
Ceftazidime	50%	50%	100.0%	0.0%	0.0%	100.0%
Cefuroxime	0.0%	100.0%	0.0%	100.0%	100.0%	0.0%
Cefotaxime	0.0%	100.0%	100.0%	0.0%	0.0%	100.0%
Imipenem	100.0%	0.0%	66.6%	33.3%	100.0%	0.0%
Levofloxacin	100.0%	0.0%	0.0%	100.0%	0.0%	100.0%
Augmentin	100.0%	0.0%	0.0%	100.0%	0.0%	100.0%
Ciprofloxacin	100.0%	0.0%	0.0%	100.0%	100.0%	0.0%
Piperacillin	100.0%	0.0%	0.0%	100.0%	0.0%	100.0%
Tobramycin	100.0%	0.0%	0.0%	100.0%	0.0%	100.0%

## Discussion

Febrile neutropenia is a common problem in children being treated for oncological diseases. Epidemiological studies have demonstrated a high incidence of sepsis in paediatric patients receiving chemotherapy, shown to be approximately 12.8% in children age 1-9 years and 17.4% in children aged 10-19 years, making febrile neutropenia a worrying and serious complication.<sup>6</sup> Comparison of present study results, with those published by other centers in the world, has shown many similar, and a few different findings.<sup>7,8,9</sup> In a study conducted in New Dehli India on febrile neutropenia in ALL patients blood cultures were positive in 31% cases. Among them 67% were due to gram negative organisms and 33% due to gram positive organisms showing predominance of gram negative like our study. E-coli was the commonest isolate (45.7%) in gram negative and Staphylococcus aureus was commonest (39%) in gram positive organisms.<sup>7</sup> A German study having 14.6% organism isolation rate showed contrasting results to ours with gram positive organisms being predominant (61%) and 36% gram negative.<sup>10</sup> A prospective cohort study from Italy demonstrated a higher prevalence of gram negative bacteria as compared to gram positive and mortality was also significantly higher from gram negative bacterial infections (16.9% vs 5.6%).<sup>11</sup> Another study from Pakistan in which gram negative cultures were studied, pseudomonas was the most common (38%) and the resistance pattern of pseudomonas and enterobacteraceae against cefepime, meropenem, ciprofloxacin, ceftriaxone, tobramycin, cefoperazone and imipenem were 60%, 13%, 80%, 67%, 40%, 90%, 10% and 80%, 20%, 88%, 72%, 20%, 90% and 4% respectively.<sup>12</sup> Among all the phases of chemotherapy highest rate of febrile neutropenia occurred in induction phase in our study (35%) as this phase is most intensive. Similar pattern is reported in above mentioned Indian study conducted in Dehli where 45.25% infections occurred in induction phase.<sup>7</sup>

There were major changes in type and range of pathogens causing infection in neutropenic patients during last decades. Gram-negative organisms were more prevalent in the first decade following introduction of chemotherapy for leukemia. During 1980s and early 1990s gram positive pathogens increased. With beginning of new century, gram-negative bacilli have re-emerged and there is rapid increase in antimicrobial resistance as well.<sup>13</sup>

As bacterial etiology of febrile neutropenia is changing with time and it is different in different geographical areas, the clinician must have knowledge of the

prevalence of causative bacteria and their antibiotic sensitivity in these patients so that appropriate empirical treatment can be given. This study assessed the type and isolation rate of causative bacterial agents and their sensitivity pattern in our hospital and thus will be helpful in improving treatment modalities.

From the current study, we should stress the importance of frequent reviewing of the type, frequency, severity and outcome of infectious complications, in such critically ill patients over the years in order to detect changing epidemiologic patterns. One of the criteria established in the management of febrile neutropenia is the absolute neutrophil count at presentation. ANC counts  $< 0.2 \times 10^9/L$  are found to be associated with a higher risk of infection and bacterial sepsis.<sup>14</sup> Similar association was observed in the present study.

## Conclusions

1. Nearly two-fifths of the children with ALL enrolled in the current study developed febrile neutropenia. Among children who had developed febrile neutropenia, a quarter of them showed positive blood cultures. The most common pathogen found in our study was Klebsiella, followed by Pseudomonas and Staphylococcus aureus.
2. Most of the antibiotics tested for the Klebsiella were shown to be effective except cephalosporins. For Pseudomonas, Cefazidime and Cefotaxime were 100% sensitive, while for Staphylococcus Cefazidime, Imipenem and Ciprofloxacin showed 100% sensitivity.

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