Original article

# Burden of febrile neutropenia in paediatric oncology: Experience from Children's Hospital Lahore Pakistan

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## ABSTRACT

Background: Infection is the major cause of morbidity and mortality in children with cancer. Chemotherapy induced febrile neutropenia-associated mortality is much higher in low-middle-income countries than in high-income countries, emphasizing the need of prevention, early identification and timely management of infection related complications in these children. Objective of this prospective study was to analyze the burden of chemotherapy induced febrile neutropenia and to assess the leading risk factors.

Patients and methods: Prospective cohort study was done in 100 patients with febrile neutropenia (fever of 38.3°C and ANC <500) admitted in the Haematology/Oncology Department of Children's Hospital Lahore (CHL) from July to August 2016. All the children on curative chemotherapy were included in this study and children with relapse and on palliation were excluded from this study. Risk factors including knowledge of parents and caregivers about febrile neutropenia, travel time from home to hospital and duration of symptoms at home before seeking treatment and reasons for delayed response in these children's febrile illness, were analyzed for duration of hospital stay considered as a burden on the Haematology/Oncology Department. Data regarding their age, sex, and clinical features, baseline CBC, course of therapy, hospital stay and understanding of caregivers regarding febrile neutropenia was analyzed. The first line therapy was IV Piperacillin-Tazobactam and IV Amikacin. SPSS-16 software was used to analyze the data and a p-value of $\leq$0.05 was considered as statistically significant.

Results: Total 100 patients with age ranging from <1 to 15 years were included. Male to female ratio was 1.7:1, 72% of the cases had Acute Lymphoblastic Leukaemia and 28% with solid tumors. About, 28% had last chemotherapy received in 72 hours, 30% in last week and rest in more than a week time 36% had upper respiratory tract infections, 18% gastrointestinal infections, 20% mucositis, 10% no focus found and rest 16% had other manifestations. Only 2 % presented in less than one hour of start of symptoms, 27% <24 hours, 61% in <5 days and 10% >5 days duration of symptoms. 45% had Hb <8 gm/dL, 33% had platelets <50,000 mm$^3$, and 54% had WBC <1000 and 63% had ANC <100. 29% presented with the first episode while 51% had 3 or more febrile neutropenia episodes. 28% cases stayed 1 hour distance from CHL while 72% had to travel >1-5 hours to reach the primary treatment center. 66% received paracetamol at home, 17 had oral antibiotics while 17% had no treatment before reaching hospital. Only 19% caregivers had adequate awareness regarding adequate management of febrile neutropenia, 72% had some understanding while 9% had no knowledge about febrile neutropenia. 46% had financial issues, 41% were unaware while, 13% showed negligence in seeking treatment. Only 2 patients stayed for a day, 46% stayed for 5 days and 48% for more than 5 days.

Conclusion: Febrile neutropenia episodes accounted for 25% of monthly admissions of the Haematology/Oncology Department of Children's Hospital Lahore. Majority of these caregivers had inadequate basic knowledge of standard management of febrile neutropenia aggravated by increased travel time from their homes to the hospital.

Keywords:

Chemotherapy, Febrile Neutropenia, Low-Middle-Income country, Health Education

## INTRODUCTION

Febrile neutropenia (FN) is a potentially fatal complication and is treated as an emergency globally. Traditionally the treatment of FN warrants immediate hospitalization, intravenous antibiotic administration and close supervision as a standard of care.[1] Children having cancer die due to infections 1.5 fold more than the common paediatric population as these patients with neutropenia are more susceptible to have severe bacterial infections and their complications.[2] Bone marrow suppression is the major toxicity for most chemotherapy regimens in childhood cancer. Therefore, fever and neutropenia are a common complication of cancer therapy. Management of FN requires considerable efforts of Paediatric Haematology/Oncology health care personnel and resources.[3]

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In children being treated for Acute Lymphoblastic Leukaemia, the rates of infection-associated mortality are around 10-fold higher in low- and middle-income countries than in high-income countries. Acute leukemia's are a group of aggressive malignancy associated with a high risk of infectious complications during chemotherapy as they are highly prone to develop infections due to factors associated with the disease itself (bone marrow replaced by blast cells resulting in neutropenia and impaired granulocyte function), treatment regimens causing neutropenia, and individual risk factors in each patient making them more prone to develop viral, bacterial or fungal infections.[4] The children with cancer having fever of 38.3°C and an absolute neutrophilic count (ANC) less than 500/mm$^3$ have traditionally been managed as inpatients with broad-spectrum antibiotics until fever and neutropenia improves. This conventional method has reduced mortality linked with severe bacterial infections. On the other hand infections are the major cause of treatment-related mortality in resource-limited settings.[5] In low-middle-income countries, there are various logistical hurdles in the management of FN in the form of limited availability of hospital beds and trained health professionals, inadequate hospital emergency services, high costs due to prolonged hospital stay and intravenous antibiotics along with disrupted dynamics of patient and family life. Febrile neutropenia is a major cause of high morbidity and mortality in children receiving chemotherapy with baseline malnutrition in most of these centers as malnourished children develop more severe FN with the same chemotherapy protocols than children with good nutrition.[6] Though numerous studies have been published regarding FN, risk stratification, and standards of care of FN management, only very few studies have been reported in public sector hospitals in low-middle-income countries to evaluate the burden of chemotherapy-induced adverse events like febrile neutropenia. This study aims to evaluate the burden and various risk factors for inadequate management of febrile neutropenia in paediatric cancer in resource limited settings in a tertiary care public sector hospital of Lahore.

## PATIENTS AND METHODS

The Oncology Department of The Children's Hospital Lahore is a 60-bedded unit providing free treatment to over 1000 new childhood cancer cases each year and over 200 admissions per month of malignancies requiring urgent curative and supportive care with bed occupancy rate around 200%. The FN cohort accounted for 25% of new admissions per month in the unit with crowded inpatients and around two patients on one bed ratio making infection prevention and control practices more difficult. This prospective cohort study enrolled 100 children (age 1 to 15 years), diagnosed with malignancies (Acute Lymphoblastic Leukaemia and solid tumor malignancies), who were receiving myelosuppressive chemotherapy, developed FN between July 2016 to August 2016, and were hospitalized in the unit. In addition to clinical and demographic data, the caregivers of these children were interviewed using a questionnaire regarding their knowledge about febrile neutropenia, its management at home and reasons for delayed response in addition to long travel time from home to hospital to seek urgently needed treatment. The data was analyzed using SPSS16. A p-value of less than 0.05 was considered as statistically significant.

## RESULTS

A total of 100 patients were included in the study. Among them, 63 (63%) were males and 37 (37%) were females with age range from <1-15 years. Among total, 46% was less than 5 years old and 54% were 5-15 years old. Majority including 72 (72%) of these cancer patients were being treated for Acute Lymphoblastic Leukaemia and remaining 28 (28%) for various solid organ malignancies like neuroblastoma, Wilms tumor, sarcoma and lymphomas. 58 (58%) of these children have had their chemotherapy (ranging from 24 hours to ten days and mean of 72 hours) in one-week time before developing FN.

These children had upper respiratory tract infections in 36%, acute watery diarrhea in 18%, mucositis in 20%, pneumonia in 4% and fever alone in 10% cases without any obvious source of infection. Only 28% of these children were staying close to the Primary Treatment Center of <1-hour travel, 33% at 3 hours travel and 39% more than 3 hours travel time from CHL. In 29% of these children, it was their first episode of febrile neutropenia and 20% had 1-3 episodes while, 51% cases have had more than 3 episodes. Among these patients, 66% took Paracetamol doses and 17% had oral antibiotics before reporting to hospital for further management.

These children were symptomatic at home for febrile neutropenia from <24 hours in 29%, 1-5 days in 61% and for more than 5 days in 10% cases before they were brought to hospital for definitive treatment. The children were reported with significant delay (p-value

Table 1. Laboratory values and duration of hospital stay

| Laboratory parameters | *n* (%) |
|---|---|
| ***White Blood Cells (WBC)*** | |
| <1000 | 54 (54%) |
| 1000-3000 | 39 (39%) |
| >3000 | 07 (7%) |
| ***Absolute Neutrophil Count (ANC)*** | |
| <100 | 63 (63%) |
| 100-500 | 29 (29%) |
| 500-1000 | 08 (8%) |
| ***Platelets counts*** | |
| <100,000 | 54 (54%) |
| >100,000 | 46 (46%) |
| ***Haemoglobin*** | |
| <8 gm/dL | 45 (45%) |
| >8 gm//dL | 55 (55%) |
| ***Duration of hospital stay*** | |
| <48 hours | 6 (6%) |
| 2-5 days | 46 (46%) |
| >5 days | 48 (48%) |

<0.001) in case of caregivers with lower awareness and health education. Similarly, distance of homes from the treatment facility also contributed significantly (p-value = 0.013) in the delayed reporting of the patients. About, 72% of the caregivers had inadequate awareness and health education regarding FN and 40% had either no money or no one to escort these patients to the hospital. About, 75% of these children stayed >48 hours in the Oncology Department which is already overcrowded with 200% bed occupancy rate. The children with lower WBC and lower ANC had prolonged hospital stay.

Table 1 shows majority of these children had WBC <1000, ANC <100 and 54% had their platelets <100,000 and 45% with hemoglobin <8 gm/dL as they seek medical treatment late. The children having low values of Total White Blood Cell count and Absolute Neutrophil count at admission (after being remained sick at home before brought in to the hospital) had longer duration of hospital stay depicting the burden of FN on the public sector department in resource limited settings.

## DISCUSSION

This study demonstrated the burden of febrile neutropenia in a public sector hospital with monthly 25% admissions with prolonged hospital stay and extent of lack of adequate health education and counseling of the caregivers about bringing the child on chemotherapy with fever to medical emergency for evaluation and urgent treatment with only 19% having adequate knowledge of FN and rest had no or mild to moderate understanding and thus bringing their children after being symptomatic for FN at home for >24 hours in around 70% of cases. The results this study are in line with a study from Indonesia that these parents of children with cancer have limited knowledge due to very less time given by health professionals to educate these families and therefore they expressed the need of more comprehensive information regarding the child's illness and this problem was the one the most common among unmet needs of these families.[7] Another study from Indonesia showed that the parents desired to have more time and information from doctors in more than 90% cases. Although poor socioeconomic status and their own low education played an important role in their reduced understanding of whatever information was given to them by the health professionals.[8] A study from Pakistan showed that there were late admissions for FN due to financial reasons or lack of health education after being symptomatic for almost two days after they had chemotherapy during the last ten days and were critical on arrival made their management difficult.[9] Due to inadequate education instead of seeking treatment in hospital these children were treated with oral paracetamol (66%) and oral antibiotics in 17% as also shown in a previous study that oral antibiotics are used inappropriately by these children without proper evaluation and close follow up.[3] In present study 48% children with FN stayed more than 5 days in hospital putting a huge economic burden on the families and health resources. Pakistan being a Low-Middle-Income country and a non-welfare state with minimal health insurance system inpatient FN management incurs enormous strain on health-care resources.[9] A study done in Australia showed that total length of hospital stay is the major contributor to cost of FN treatment, with an average cost per day of around AUD 2000 with more prolonged stay in high risk FN children with a median 6.5 days of hospitalization.[10] In a previous study done in this center by Ahmad and coworkers sowed the mean estimated cost for Pharmaceutical category alone among all the health care expenditures for one FN patient was 15000PKR and total of 3.8 million PKR over the span of three months study time with >95% FN children staying for >48 hours.[11]

In this study the families of affected children had to travel long distances to the Children's Hospital Lahore with 72% staying more than one-hour drive and 40% had financial constraints in bringing the children for FN management resulting in prolonged morbidity and hospital stay. Friedrich and co-authors concluded that socioeconomic factors such as poverty, parent's education status and long distance travelling from home

to primary treatment center are major challenges in LMIC in completing their cancer therapy.[12] In present study, majority of patients had ANC <100 $mm^3$ at presentation (61%) and more than half had Platelets <100,000 $mm^3$. As shown by a study done by Alam and colleagues in 2014 in Aga Khan Hospital Karachi that the children with severe neutropenia and thrombocytopenia had prolonged FN >5 days and these two risk factors were among others labeled as high risk.[13]

Acute Lymphoblastic leukemia patients had more frequent FN episodes than solid tumors, among 80% of two episodes cohort and 72% of >2 episodes of FN and therefore more financial burden as compared to solid malignancies as also reported in a previous study from USA that the health-care costs of chemotherapy-related adverse events for patients with haematological malignancies were 2-3 times more than for solid tumor patients.[14] In this study 70% of these children had significant source of infection and remaining only either mucositis or fever alone and 71% were having more than one episode of FN and they were symptomatic at home for more than one day in 71% or their hospital stay was longer than five days due to persistence of symptoms. A study from India in 2014 also documented the independent risk factors for poor outcome being presence of significant source of infection and fever lasting for more than 5 days and previous history of infection.[15]

## CONCUSION

Febrile neutropenia episodes accounted for 25% of monthly admissions of the Haematology/Oncology department of Children's hospital Lahore. Majority of these caregivers had inadequate basic knowledge of standard management of febrile neutropenia exacerbated by increased travel time from their homes to the hospital and logistics resulting in prolonged hospital stay of these children who could have been managed better and faster on out patients basis if brought in earlier, decreasing the burden on the inpatients department. Health education of parents and caregivers is of utmost importance to prevent and manage FN effectively. Need of capacity building in pediatric oncology in LMIC, focusing on the shared care concept establishing satellite clinics in various districts to help manage FN patients along with sustainable social support, is essential for provision of standard childhood cancer care.

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