COST-EFFECTIVENESS OF TREATING FEBRILE NEUTROPENIA IN CHILDREN WITH CANCER IN RESOURCE-LIMITED SETTINGS

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ABSTRACT

Background: Febrile neutropenia in children on intensive chemotherapy is very frequent requiring urgent evaluation and management, imposing a significant strain on the already available limited resources in low-middle-income countries (LMIC) **Objective**: To evaluate the need of cost-effectiveness in managing in-hospital FN and explore the mechanisms to implement in public sector LMIC to pave the way for cost-minimization **Methodology**: Prospective extraction of patient level costs from hospital records to evaluate the costing of injectable antimicrobial and inotropes provided by the hospital management free of cost as part of the comprehensive childhood cancer care. **Results**: A total of 250 FN episodes were analyzed, all of them managed in the inpatient unit, complete cost data were extracted for these FN episodes. The analysis revealed that despite subsidized purchase of antimicrobials and supportive care materials FN has a huge burden on the public sector hospital resources whereas length of hospital stays, blood products, laboratory tests and staff consultations were excluded. Majority of these patients were of acute leukemia, having the last session of chemotherapy in a week time in 87% and majority on intensive chemotherapy and suffered from respiratory tract infections and mucositis. More than half had severe derangements of Laboratory parameters and gram-negative septicemia among positive cultures. The mean estimated cost per FN episode was around 15,000 PKR. **Conclusion**: Febrile neutropenia exerts a huge burden on childhood cancer care services emphasizing the need to explore the cost-effectiveness in FN management by different mechanisms including parents' health literacy to promote early seeking behavior, emergency management, shared care therapy and social support and standardized de-escalation of therapy to minimize the costs.

INTRODUCTION

Febrile neutropenia (FN) is an emergency in childhood cancer care and one of the most frequent complications of chemotherapy. urgent evaluation and treatment of FN are integral components to

prevent fatal complications including death. These episodes occur more frequently during and following chemotherapy for acute hematological malignancies like acute leukemia and lymphoma rather than solid tumors. Evaluation of FN and its risk grouping is essential to manage it according to risk stratification. Timely management includes early administration of antimicrobials and good supportive care in the in-patient unit based on clinical and laboratory parameters [1].

Severe infection usually is defined by bacteremia, a positive culture, invasive fungal infection, or localized infection with high risk of spread. Multiple prospective studies are needed to validate variables linked with severe infection and to help them differentiate from low-risk infections [2] which can be treated on an out-patient basis, preferable by families and healthcare providers (BAVLE) with evidence-based safety instead of routine inpatient treatment of FN [3]. Good practice statement of recent FN guidelines for clinically unstable FN child, urgent empiric antibacterial therapy is advised to improve survival of these children with invasive infection along with supportive care to stabilize the patient though others advise to wait to review neutrophil counts to avoid unnecessary antibiotics administration linked with resistance, costs, and drug toxicity [4].

There is paucity of research in resource limited settings to gauge the burden of chemotherapy linked febrile neutropenia and infections urging treatment to reduce morbidity and mortality of children with cancer, but simultaneously cost-effective measures to reduce strain on the available resources using multicomponent approach of health literacy, shared care system, standardized de-escalation to oral therapy in outpatients after documenting this complex issue precisely.

MATERIALS AND METHODS:

Study Design: Prospective observational cohort study

Settings: Paediatric Haematology/ oncology unit, Children's Hospital Lahore Pakistan

Duration: The study was done from 1st October 2018 to 31st December 2018

Sampling Technique: The sampling was done by probability method and data was collected from the patient files who were admitted in the inpatient unit with the diagnosis of febrile neutropenia during this study period.

Sample Size: 250 children having febrile neutropenia and admitted in the unit.

Inclusion Criteria: Children aged 1-18 years old on active chemotherapy sessions for haematological or solid malignancies either inpatients or the Chemobay diagnosed with febrile neutropenia and admitted in the inpatients unit and started treatment for FN.

Exclusion Criteria:

1- Children with fever with benign haematological disorders

2- Children with fever with relapsed malignances
3- Children with cancer on Palliative care
4- Children undergoing hematopoietic stem-cell transplantation

Data Collection Procedure

Data were retrieved from the files of these patients and Performas were filled after they got admitted and completed when they discharged or expired from the event. The data collected for the demographic characteristics, clinical and laboratory parameters, time to antibiotics, number and days of antimicrobial, Granulocyte Colony-stimulating Factor (G-CSF) and inotropes, costing of treatment therapies and length of hospital stay (LOS). The data was collected after the IRB approval. Data analysis was done by SPSS 23.

RESULTS

The study analyzed 250 FN episodes**.** The study included children with cancer with a mean age of 6.27+/-3.5 years with 59% boys. They lived far from Children's Hospital Lahore (CHL) with 78% living at > one hour journey and the majority, 58% were suffering from Acute lymphoblastic leukemia. They treated the child at home with either paracetamol (78%) or oral antibiotics prior seeking treatment at the primary treatment center (PTC). They claimed reasons for delaying urgent treatment for febrile Neutropenia (FN) as financial issues (23%), unavailability of transport or escort (34%), lack of knowledge of urgency of treatment (30%) or negligence (13%). These children received chemotherapy sessions in < 72 hours in 53%, within a week in 34% and later than a week in 13%. (Table 1)

Majority of these children suffered from respiratory infections (48%), followed by gastrointestinal (25%), fever alone21% and mucositis in 81%. (Figure 1) These children were symptomatic for almost a day in 52%, for 1-5 days in 43% and >5 days in 5% at home before arrival at CHL. The platelets were < 50,000 in 57% and 50-100,000 in 26% and their Hemoglobin < 8 Gm in 50% and 810 Gm in 39%. WBC was <1000 in 61%, 1-3000 in 39% with the mean WBC 1.46 and median 1.00 and absolute neutrophil count (ANC) of <100 in 60% and 1-300 in 40% cases. The data pertaining to time to antibiotics (TTA) showed that only 14% received their first antibiotics in < 60 minutes, 58% in 1-3 hours, and 28% in > 3 hours of arrival in hospital. Only 115 stayed inpatients for less than 48 hours and 80% of these patients were

discharged home, 17% expired and 3% abandoned treatment. Injection tazobactam- piperacillin and amikacin was used as a first line antibiotics and GCSF was given 75/250 (30%) cases mainly in solid malignancies. The p-value for use of GCSF and type of malignancy, cost and ANC was 0.000 and for hospital stay was also statistically significant 0.048 but not for outcome (0.147)

The cost calculated for these FN patients were <10,000 PKR in 129/250 (52%), 10-50,000 PKR in 110/250 (44%) and >50,000 PKR in 4%. These costs included subsidized rates of injectable antibiotics, inotropes and antifungal medicines and it did not include bed charges, staff and other hospital charges at the time of admission and discharge. The cost of treatment when compared with hospital stay of > 48 hours showed p-value of 0.000 and 0.012 when compared with absolute neutrophil count ANC of <100 in 148/250.(Figure 2)

Table 1: Demographic profile of children with Febrile Neutropenia (n=250)

Characteristics	Domain	Category		N (%) or value
Demographic Profile	Age (years)			Mean=6.27 Median=6.00
	Gender	Male Female		147 (59%) 103 (41%)
Diagnosis	ALL Sarcoma			145 (58%) 41 (16%)
	Lymphoma			25 (10%)
	Neuroblastoma & Wilms Tumor			25 (16%)
	Others			14 (6%)
Distance from Home	< 1 Hour			55 (22%)
	1-3 Hours			86 (34%)
	>3 hours			109 (44%)
Reasons for Dealy in seeking treatment	Financial issues			57 (23%)
	Escort/Transport issue			84 (34%)
	Negligence			32 (13%)
	Lack of knowledge/Communication/Counselling			77 (30%)
Awareness among caregivers regarding febrile neutropenia management			Adequate Inadequate	108 (43%) 142 (57%)
Treatment at Home prior to seek treatment	Paracetamol at home			195 (78%)
	Oral Antibiotics at home			55 (22%)
Last Chemotherapy given	<3 days			133 (53%)
	3-7 days			86 (34%)
	>7 days			31 (13%)

Figure 1: Types of Infections

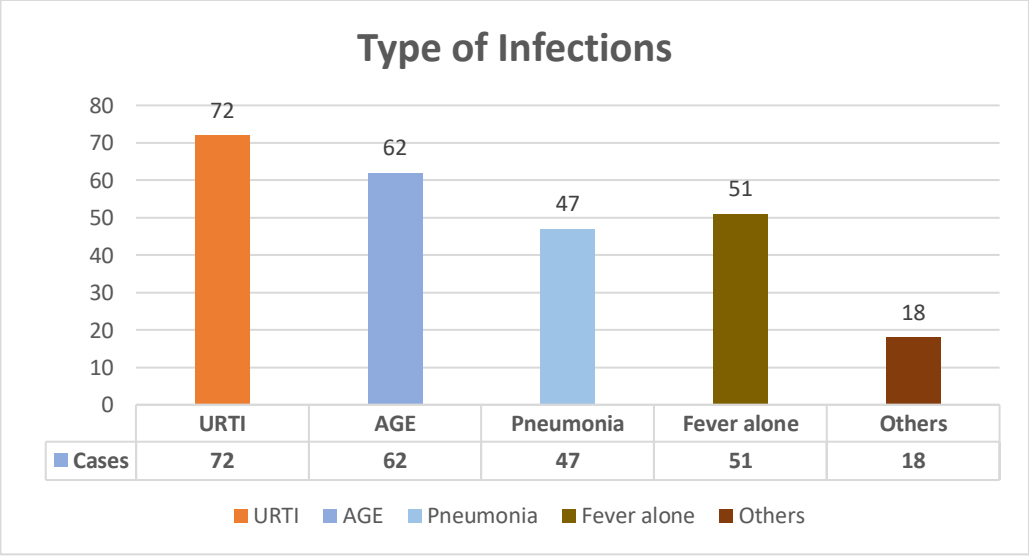
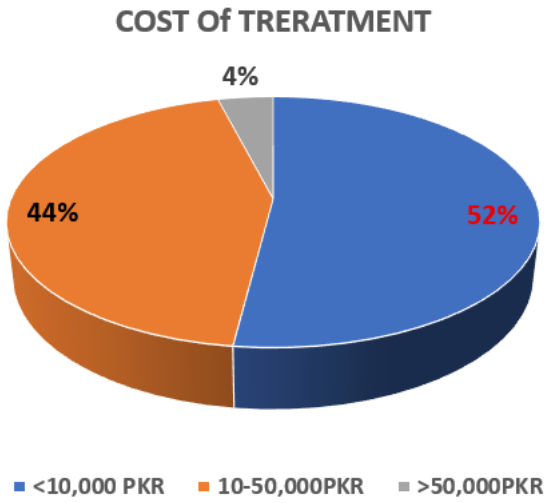


Table 2: Laboratory Parameters

Parameter		N	%
Hemoglobin	< 8Gm%	124	50%
	8-10 Gm%	97	39%
	>10 Gm%	29	11%
WBC Mean=1.4 Median=1.00	<1000	151	61%
	1-3000	99	39%
ANC	<100	149	60%
	1-300	101	40%
Platelets	<50,000	141	57%
	50-100,000	66	26%
	>100,000	43	17%

Figure 2: Cost of Treatment for Febrile Neutropenia Patients



DISCUSSION

For the 250 FN episodes documented in this study, the mean age was 6.27 years and majority diagnosed with leukemia. Whereas another study done in a high-income country (HIC), mean age was 5.8 years and 48% females and 52% were acute leukemia patients and rest solid tumors and relapsed malignancies. 56% of cases had fever alone without any focus and mortality of 0.9% documented while in our study, 41% were females,58% acute leukemia cases, relapsed cases were excluded, fever without any focus in 51/250 (24%) cases and 17% expired (42/250) [5].

In a study where high risk cases were assigned with acute lymphoblastic leukemia ALL patients on intensive chemotherapy than maintenance, WBC <300 cells/mm^3 , platelets <50 G/L, Hemoglobin > 9 Gm/dl, radiologically confirmed pneumonia, ANC < 500 cells/mm^3 While in our study mean WBC was

1.4, ANC <100 in 60%, Haemoglobain > 8gm/dl in 50%, Platelets were < 50 G/L in 57%, radiologically confirmed pneumonia in 19% cases were documented [6]. When low-risk febrile neutropenia patients were treated on an outpatient basis, it turned out to be cost-effective (51% reduced cost) than routine inpatient management with easy follow-up and was preferred by many families and healthcare providers shown on surveys done [7].

Far distances make families unable to reach timely to manage FN in LMIC. Long distance from primary treatment center (PTC) results in delay reaching the PTC not only for febrile neutropenia patients but also for newly diagnosed childhood cancer cases like Retinoblastoma resulting in compromised outcome in LMIC (p-value=0.02) [8]. Among multiple reasons of delay were socioeconomic barriers in 57% cases. Another study done at Children's Hospital Lahore showed 65% cases living at >200KM distance from CHL and lack of private transport to help travel in emergency to the PTC, average monthly income of <150USD in 80% and need to borrow money to facilitate their visits and loans in 58% [9].

The limited financial capacity and long-distance travels to the treatment centers of families make an impact on all aspects of care of children with cancer, these financial challenges resulting in distress, affect parental decision-making and ability to understand instructions given by the healthcare providers [10].

This study showed that subsidized purchase of injectable antibiotics, antifungals and inotropes costed <50,000 PKR in most of the cohort treated in the CHL while a study done in Australia showed expenditure while spending A$20,396 for in-hospital and mean healthcare of home-based FN treatment per patient costed in low-risk patients was Australian dollars (A$)7765, so exploring more patients are treated at home to increase the savings [11].

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In this study, the cost analysis didn't include hospital and staff consultation visits. The study done in Mexico, analyzed two groups of children with febrile neutropenia being managed inpatients and outpatients and the cost analysis data showed an average savings of $1,087 per FN episode if managed on an outpatient basis, with a 92% reduced total cost per episode when compared to inpatient treatment. As total duration of hospital stays, and daily consultations were the major high-cost cause in the inpatient pool of FN children. Therefore, this study suggests adopting a step-down approach to promote outpatient FN management to facilitate huge cost savings without harming patients in public sector [12].

This study also showed statistically significant relationship between the cost and length of stay in hospital (LOS) of 0.000.Another study done in Australia depicted the costs were much higher for high-risk FN

patients (over 17000 Australian $) when compared with low-risk FN cases (around $ 10,000) with hospital length of stay (LOS) only modifiable factor linked with cumulative care costs suggesting low-risk FN management preferably in outpatient settings [13].

In our study, 52% of participants were sick at home for less than 24 hours and 43% (108/250) for up to 5 days; 58% had acute leukemia. Research indicates that prolonged neutropenia and leukemia, high fever (> 38.5 ^{0} C) and elevated C-reactive proteins predict severe infection at admission. These identified variables must be validated prospectively to differentiate them from low-risk children [14 15] Time to antibiotics TTA of less than an hour was achieved in 13% in our study, although many studies have shown that organized and multicomponent quality improvement initiatives can enhance patient care with injectable antibiotic administration within an hour. [16, 17] In this study chemo was given in 72 hours in 53% and within a week in 34% cases where prophylaxis G-CSF could have helped in prophylaxis of FN as no facility of community-based GCSF administration available in LMIC. A study done showed a cost benefit analysis supporting prophylactic use of G-CSF more widely in patients treated with chemotherapy [18].

This study described that Febrile Neutropenia has been a huge strain on childhood cancer care in public sector hospitals in low-middle-income countries LMIC like Pakistan. There is an immense need to improve health literacy of the parents, nurses and doctors for standard care protocols of febrile neutropenia along with exploring sustainable families socio-economic support and shared care oncology services to share the load of primary childhood cancer treatment centers [19].

Febrile neutropenia patients account for 25% of total admissions with majority coming late after symptomatic at home. The awareness of families regarding adequate management of febrile neutropenia ranged from 19% (full) to 72% (some) and 9% (none) and this lack of knowledge accompanied by financial constraints in 46% of caregivers [20]. These families may benefit from increased financial and psychosocial support during anti-cancer treatment as Febrile neutropenia FN has a huge effect on the quality of life of children with cancer during intensive chemotherapy sessions and their parents [21].

Our families Knowledge was only 43% about FN management. Parents having children with cancer require guidance to receive full information with materials which can be well understood to tackle the different aspects of the disease including side effects. There are many resources for parental education and information which can help them cope and self-manage their children while away from the hospital and not connected with any shared care unit nearby [22. 23]. The shared care centers linked with PTC can help in managing these FN patients near their homes away from cancer centers not only doing labs but also antibiotic administration as a cost-effective measure in this regard [24].

There are many countries considering home-based FN pathways initiatives in children with cancer and showing promising results like minimizing bed-days in the inpatients, reducing cost and enhancing parental satisfaction but requires additional human resources like trained nurses and strict safety guidelines to follow [11].

CONCLUSION: Chemotherapy-associated febrile neutropenia imposes a substantial burden on paediatric oncology services. This underscores the importance of evaluating cost-effective strategies for managing febrile neutropenia, including enhancing parental health literacy to encourage timely medical consultation, optimizing emergency care protocols, implementing shared care pathways, providing social support, and standardizing therapy de-escalation processes to reduce overall costs.

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