

ORIGINAL ARTICLE

CLINICAL COMPLICATIONS AND OUTCOME OF FEBRILE NEUTROPENIA IN CHILDREN AT A TERTIARY CARE HOSPITAL

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Background: Febrile neutropenia is well-known complication in patients on chemotherapy. Despite the improvement in managements, infections are still major cause of morbidity and mortality. This study was done to determine the various clinical complications in children with febrile neutropenia and outcome during the hospital stay in a resource limited setup. **Methods:** This study was conducted in Paediatrics Department, Ayub Teaching Hospital, Abbottabad from 2017 to 2019. Children with diagnosed case of acute lymphoblastic leukaemia (ALL) of age 2–15 years, getting chemotherapy, presented with fever and neutropenia were included. Clinical complications included thrombocytopenia, mucositis, profound neutropenia, ANC $<100/\text{mm}^3$ and lower respiratory tract infection. Outcome was taken as improvement (afebrile for 72 hours) or death. **Results:** Out of 136 patients, 84 (61.8%) were males and 52 (38.2%) were females. Mean age was 6.58 ± 3.49 years. Weight ranged from 5–58 Kg with mean weight 17.89 ± 8.54 . Improvement was in 107 (78.7%) patients while 29 (21.3%) died. Mucositis was in 67.6% patients and lower respiratory tract infection in 57.4% patients. Platelets count $<20,000/\text{mm}^3$ was present in 85 (62.5%) patients. **Conclusion:** Lower respiratory tract, mucositis and profound neutropenia are the major complications associated with high mortality in febrile neutropenia children.

Keywords: Fever, neutropenia, chemotherapy, acute lymphoblastic leukaemia, ALL

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INTRODUCTION

Fever and neutropenia are well-known complications along with infections in paediatric patients with malignancies including ALL getting chemotherapy and are about 29%.¹ In children with febrile neutropenia, presenting characteristics and outcome differ significantly from those found in adult oncology patients. Children should be admitted and started on intravenous antibiotics.² Despite the improvement in mortality due to infections who present with febrile neutropenia, infections are still major cause of morbidity and mortality in children presenting with malignancies receiving chemotherapy. The empirical use of antibiotics has greatly improved the outcome of fever in a neutropenic patients.³ The current standard of management of paediatric patients with febrile neutropenia is broad spectrum antibiotics and hospitalization.⁴ Patients with febrile neutropenia have different range of mortality and morbidity, depending up on available resources and hospital settings.

This study was done to determine the variety of clinical complications in children with febrile neutropenia and their outcome during hospital stay. There is very limited data about febrile neutropenia and associated complications in children in Pakistan. Pakistan is resource limited country; this study was done in a hospital with limited resources. Other centres with limited resources can also focus on treatment of

complications associated with febrile neutropenia and help in decreasing the morbidity and mortality.

PATIENTS AND METHODS

This was a retrospective descriptive study conducted in Paediatrics Department, Ayub Teaching Hospital, Abbottabad from May 2017 to September 2019, after getting approval from ethical review committee. The cases were taken from the record of the patients. Children diagnosed case of acute lymphoblastic leukaemia (ALL) of age 2 year to 15 years, who were getting chemotherapy at Institute of Nuclear Oncology and Radiotherapy (INOR) and presented with fever to Paediatric Department, Ayub Teaching Hospital, were included in the study. On complete blood count, the patients having neutropenia were included in study. All patients were high risk cases who were having age above 10 years or less than 2 years, initially presenting with total leucocyte count more than $50,000/\text{mm}^3$, T-cell immunopheno type, chromosomal abnormalities including MLL gene, hypodiploidy, Philadelphia chromosome, and slow response to initial treatment. Children with other malignancies were excluded.

Fever was taken as axillary temperature of 38 °C and above. Neutropenia was taken as absolute neutrophil count (ANC) $<1,500/\text{mm}^3$, with profound neutropenia taken as ANC $<100/\text{mm}^3$. Platelet count $<100,000/\text{mm}^3$ was taken as thrombocytopenia and platelet count $<20,000/\text{mm}^3$ were transfused platelets, as these patients were at risk of bleeding. Mucositis was

labelled on examination by inflammation of oral mucosa. Lower respiratory tract infection was diagnosed by history of fever, cough, shortness of breath and clinical examination having decrease air entry, bronchial breathing, or crackles and chest X-ray showing infiltrates or lobar pneumonia. Patients' age and weight was documented on proforma. When patient remained afebrile for 72 hours, it was taken as improvement. Improvement or death were taken as outcome.

Data was analyzed on SPSS-20. Outcome and complications including mucositis, lower respiratory tract infection, ANC <100/mm³ and platelets <20,000/mm³ were documented on proforma and data analysed as frequency. Chi-square test was applied and results were taken significant with $p < 0.05$.

RESULTS

There were total 136 patients, 84 (61.8%) males and 52 (38.2%) females. Patients' age ranged from 2 to 15 years with mean age 6.58±3.49 years. Weight of patients ranged from 5 to 58 Kg with mean weight 17.89±8.54 Kg. Out of 136 patients, 107 (78.7%) patients improved and 29 (21.3%) patients died. Mucositis was present in 92 (67.6%) while 44 (32.4%) were not having mucositis. Lower respiratory tract infection was present in 78 (57.4%) cases. Abnormal findings on chest X-ray were found in 86 (63.8%) patients. Platelets count <20,000/mm³ was present in 85 (62.5%) patients. ANC <100/mm³ was present in 101 (74.3%) patients. There was significant relationship between sex and outcome with $p = 0.034$ (Table-1).

Platelet count <20,000/mm³ had a significant correlation with outcome ($p = 0.001$) (Table-2). With ANC <100/mm³ there was significant correlation with the outcome (Table-3). Patients with lower respiratory tract infections had significant relationship with outcome, ($p < 0.001$) (Table-4). There was also significant correlation between outcome and mucositis along with ANC <100/mm³ with $p = 0.016$ and 0.005 respectively. In patients with ANC <100/mm³ there was presentation with lower respiratory tract ($p = 0.016$) (Table-5). The patients with platelet count <20,000/mm³ and ANC <100/mm³, and patients with extreme neutropenia were more prone to bleeding.

Table-1: Gender versus outcome [n (%)]

Gender	Improved	Death	Total	p
Male	71 (66.4)	13 (44.8)	84 (61.8)	0.034
Female	36 (33.6)	16 (55.2)	52 (38.2)	

Table-2: Platelets count versus outcome [n (%)]

Platelets count <20,000	Improved	Death	Total	p
Yes	59 (55.1)	26 (89.7)	85 (62.5)	0.001
No	48 (44.9)	3 (10.3)	51 (37.5)	

Table-3: Absolute Neutrophil Count <100 versus outcome [n (%)]

ANC <100	Improved	Death	Total	p
Yes	73 (68.2)	28 (96.6)	101 (74.3)	0.002
No	34 (31.8)	1 (3.4)	35 (25.7)	

Table-4: Lower Respiratory Tract Infection versus outcome [n (%)]

Lower respiratory tract infection	Improved	Death	Total	p
Yes	51 (47.7)	27 (93.1)	78 (57.4)	0.000
No	56 (52.3)	2 (6.9)	58 (42.6)	

Table-5: ANC <100/mm³ versus lower respiratory tract infection [n (%)]

ANC <100	Lower Respiratory Tract Infection		Total	p
	Yes	No		
Yes	64 (82.1)	37 (63.8)	101 (74.3)	0.016
No	14 (17.9)	21 (36.2)	35 (25.7)	

DISCUSSION

Morbidity and mortality in paediatric cancer patients depends highly on the infections and complication due to febrile neutropenia. The treatment strategy is determined by the aetiology of febrile neutropenia, time to establish the diagnosis and risk of related complications. Advancement in field of medicine has also altered the management of patients with ALL. Management for ALL has become more intensive. It is associated with more severe complications like oral mucositis; diarrhoea with damage to mucosal barrier and opportunistic infections of respiratory tract. Even oral flora causes infection.

The diagnosis of the complications in children on chemotherapy is significantly associated with ten-fold increase in risk of death. Despite availability of strong antibiotics and their use, sepsis is the most important prognostic marker of mortality. Pneumonia is associated with eight times more risk of death and fungal infections have five-fold increased risk. Many of these complications are associated with a long stay during the course of treatment and death.⁵

Study conducted by Narayanan MP *et al*⁶ showed that Coagulase-Negative Staphylococci and Methicillin Resistant Staphylococcus aureus along with Klebsiella and Acinetobacter species and Pseudomonas aeruginosa are the most common pathogens causing infection in children with febrile neutropenia. Another study showed fungal pathogens as cause of infection in children on chemotherapy. Akhtar *et al*⁷ included 94 ALL patients and about 39% developed febrile neutropenia. Out of these patient blood cultures were positive in 25% patients with Klebsiella being the most common microorganism, i.e., 44.4%, followed by Pseudomonas aeruginosa and Staphylococcus aureus being 33.3% and 22.2% respectively.

In one specialized centre of Ethiopia a study conducted by Assefa *et al*⁸ included children with malignancies, ALL to solid tumours getting chemotherapy and presented with febrile neutropenia. Of 60 patients 60% were male as our study male proportion is also 61.8%. In Assefa *et al* study mortality was 20% as compare to our study which has mortality of 21.3%. In their study the ANC <100/mm³ and thrombocytopenia along with sepsis was the major cause of mortality.

In one meta-analysis done by Phillips RS *et al*⁹ showed relationship between microbiologically defined infection and lower white cell counts. As in our study the patients with profound neutropenia were having more mortality with significant relationship between outcome and profound neutropenia ($p=0.002$). Anderson K, *et al*¹⁰ identified the two main factor as delay in initial assessment and start of treatment as hindrance in optimal management of children getting chemotherapy presenting with febrile neutropenia. Paolino J, *et al*¹¹ in their study made protocol and managed low risk cases of febrile neutropenia either as outpatient or those admitted with short stay admission with no mortality or intensive care unit admissions. But all of our patients were high risk cases including age above 10 years, initial presenting total leucocyte count more than 50,000/mm³, T-cell immunopheno type, and slow response to initial treatment. They were getting intensive chemotherapy and their presentation was with severe symptoms in need of admission.

Madney Y *et al*¹² in their study reported hepato-splenic fungal infection in paediatric patients with acute leukaemia on intensive chemotherapy. Majority of the patients got fungal infection during induction phase of chemotherapy and these infections had huge impact on outcome and delay in treatment. Meena JP *et al*¹³ included patients with febrile neutropenia having viral infections and found prevalence of viral infections as 76.5%. Rhinovirus and respiratory syncytial virus were the most prevalent types and associated with prolong stay and antibiotic use. We could not ascertain the cause of infection in our study due to lack of supporting investigations in our setup. Mahmud S *et al*¹⁴ included 50 paediatric patients with febrile neutropenia with Staphylococcus aureus and E. coli as the most common gram positive and gram negative micro-organism respectively. Infection related mortality was 22% as compare to our study having mortality of 21.3%. It is almost equal to our centre.

Naqvi SMA *et al*¹⁵ included 35 children with 64 consecutive episodes of febrile neutropenia with ALL being the most common malignancy and reported mortality of 12% in Aga Khan University Hospital, Karachi. As AKUH is one private centre with adequate resources, their mortality rate is almost half as compare to our study. Our study included children with high risk

ALL on chemotherapy. Rana ZA *et al*¹⁶ did study in Children Hospital Complex Multan and their study outcome mortality was 18% due to sepsis and febrile neutropenia. It is comparable to our findings.

Hussain F *et al*¹⁷ in Paediatrics Department of Lahore General Hospital included a total of 121 patients, 56 (46.28%) male and 65 (53.72%) females. In their study 12.40% children had pneumonia with febrile neutropenia as compare to our study where 57.4% patients were having lower respiratory tract infection. This is too high as compare to study by Hussain *et al*¹⁷.

There were limitations in our study as we did it retrospectively. Other hindrance is that due to lack of proper microbiological and culture/sensitivity services, the blood cultures were not sent and this study did not show the microorganism and their antimicrobial sensitivity pattern. Our centre does not have paediatric oncology department, so we might have not been able to get the actual number of patients with febrile neutropenia and associated complications. Well-equipped tertiary care centre studies are needed to define the complications and management strategies in specific paediatric haematology/oncology unit.

CONCLUSION

Lower respiratory tract, mucositis and thrombocytopenia along with profound neutropenia are the major complications of febrile neutropenia in children. There is high mortality in children with febrile neutropenia.

RECOMMENDATIONS

Larger studies are needed to define the complications and management strategies in specific paediatric haematology/oncology unit. It is need of the time to develop sub specialty units in the country for proper documentation and management of children with haematological malignancies.

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