Original Article

Outcome of Febrile Neutropenia in Children: A Tertiary Health Care Center Experience

Md Imrul Kaes[1], Afiqul Islam[2], Chowdhury Yakub Jamal[3], Mousumi Saha[4], Indira Chowdhury[5]

Abstract

Background: *Febrile neutropenia (FN) is a serious event in children with cancer; associated with various complications and mentionable adverse outcome.*

Objective: *To identify the outcome of febrile neutropenia in children with cancer.*

Materials and Methods: *This prospective observational study was conducted from October 2017 to November 2018 in the Department of Pediatric Hematology and Oncology, BSMMU. Children (age<18years) with malignancy who were admitted with febrile neutropenia or admitted patients who had developed febrile neutropenia onward were enrolled in this study. Finally, the outcome of each episode of FN was analyzed.*

Results: *Total of 61 patients with 68 febrile neutropenic episodes were studied. Male patients were 62.29% and female patients were 37.70% with a mean age of 7 years. Majority were ALL (50.8%) followed by AML (29.5%), NHL (11.4 %) and solid tumor (8.1%). Bacterial infection was confirmed by culture in 14.7% episodes, 11.7% episodes had positive blood culture. Most of the isolated organisms were gram-negative (90%). Cough (39.7%), bleeding (19%) and diarrhea (17.64%) were the common clinical manifestations in those febrile neutropenic episodes. The mean duration of neutropenia was 9 days, 55.88% of episodes had prolonged neutropenia (Absolute neutrophil count ≤100/mm 3). Profound neutropenia was recorded in 47 % episodes and significantly associated with adverse outcome. Age ≥10 years also significantly associated with adverse outcome. The treatment success rate was achieved in76.4 % of episodes. A composite adverse event was observed in 23.52% of episodes; with mortality in 11.76%.*

Conclusion: *Febrile neutropenia was a common complication in hematological malignancy. Although most of the episodes of febrile neutropenia had been treated successfully, mortality was significantly higher. Profound neutropenia and age ≥10 were significant risk factors for dreadful outcome.*

Key words: *Neutropenia, Febrile neutropenia, Childhood cancer, Infection.*

Date of received: *21.10.2022*

Date of acceptance: *20.02.2023*

DOI: https://doi.org/10.3329/kyamcj.v14i01.65304

KYAMC Journal. 2023; 14(01): 07-10.

Introduction

Neutropenia is an anticipated side effect of chemotherapy and its relationship with the severity and duration of infection has been well established.[1] Febrile episodes occur in about one third of neutropenic episodes in children treated with chemotherapy.[2] Febrile neutropenia renders children extremely vulnerable to life threatening infections; studies have demonstrated a high incidence of sepsis in paediatric cancer patients; rates up to 12.8%. [3] Febrile neutropenia is also responsible for significant morbidity as 20%-30% and about 10% of hospital mortality.[4] So, it is considered as an oncology related medical emergency.[5]

Standard therapy for FN has traditionally been hospital admission and prompt initiation of empirical antibacterial antibiotics; guidelines published by the Infectious Disease Society of America (IDSA) still recommended this as time trusted management for children.[6] Mortality associated with FN ranges from 2 to 6% in children and it was 10% a decade ago, the current rate indicates a much better improvement in management resulting in a favorable impact.[7]

Nevertheless, this mortality rate still remains substantial, warranting further improvement. Many studies from developed

1. Assistant Professor, Dept. of Paediatric Haematology & Oncology, Khwaja Yunus Ali Medical College & Hospital, Sirajgonj, Bangladesh.
2. Ex. Professor, Dept. of Paediatric Haematology & Oncology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh.
3. Professor, Dept. of Paediatric Haematology & Oncology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh.
4. Assistant registrar, Dept. of Paediatrics, Bangabandhu Sheikh Mujib Medical College Hospital, Faridpur, Bangladesh.
5. Assistant Professor, Dept. of Paediatric Haematology & Oncology, Chattogram Maa O Sishu Hospital Medical College, Chattogram, Bangladesh.

Corresponding author: Md Imrul Kaes, Assistant Professor, Dept. of Paediatric Haematology & Oncology, Khwaja Yunus Ali Medical College & Hospital, Sirajgonj, Bangladesh. Cell Phone: +8801719382542, Email: kaesimrul.pho@gmail.com

countries have reported the importance of prompt management and outcome of FN. However, reports from the resource limited low and middle-income country like Bangladesh are lacking. In this context this study was designed to identify the burden of febrile neutropenia and describe the demographic, clinical features, laboratory data and management outcomes of febrile neutropenia in pediatric cancer patients at tertiary health care center; Bangabandhu Sheikh Mujib Medical University (BSMMU) of Bangladesh.

Materials and Methods

This was a prospective observational study; conducted from October 2017 to November 2018 in the Department of Pediatric Hematology and Oncology, Bangabandhu Sheikh Mujib Medical University (BSMMU). Children age<18 years with malignancy (both hematological malignancy and solid tumor) who were admitted with febrile neutropenia or admitted patients who had developed febrile neutropenia onward were enrolled in this study; after getting clearance from IRB committee of the University. Children with fever/ neutropenia but without malignancy or known case refectory cytopenia like inherited bone marrow failure syndromes were excluded from the study.

After taking informed written consent, history was taken about clinical symptoms and recently used chemotherapy with their intensity. Thorough physical examination was done. Associated co morbidity like diarrhea, shock, DIC, severe bleeding manifestation were recorded. Complete blood count (CBC) was done by sysmax automated analyzer, on every alternate day. serum glutamic pyruvic transaminase, serum electrolyte and serum creatinine were done in every patient in the laboratory of Paediatric Hematology and Oncology. X-ray chest was done in those; who had respiratory complaints in the radiology and imaging department, BSMMU. Blood culture and sensitivity (Automated BACTEC 9240 machine), urine routine microscopic examination & culture and sensitivity were done in every patient. Blood was collected for complete blood count, metabolic workup and blood culture. In selected patients stool routine microscopic examination & culture and swab form skin wound, throat, ear was cultured. Patients were followed up regularly; to identify clinical course and management outcome of each febrile neutropenic episode.

All data was recorded systematically in preformed data collection form after getting informed written consent from parents of patients. The data was collected and edited manually. The entered data was checked, verified and analyzed manually. Statistical analysis test was performed by using SPSS, version 22. The data was presented in tabular or diagrammatical form. For categorical variables frequency percentage were done. And qualitative data were analyzed by Chi-square test, Fisher exact. and relative risk (RR) measurement. p-value <0.05 was considered as significant

Results

A total of 68 episodes of FN was observed during the study period involving 61 patients. Out of these 61 patients, 56 (91%) had hematological malignancy and 5(8%) had Solid tumor; distribution as follows 31 Acute lymphoblastic leukaemia (ALL), 18 acute myeloid leukaemia (AML), 7 Non-Hodgkin Lymphoma (NHL) and 5 had solid tumors (2 Hepatoblastoma, 1 Neuroblastoma, 1 Ewing sarcoma & 1 RMS) (Figure 2). Male-female ratio was (1.65 :1) (Figure 1). Majority of the patients 40 (65.57%) were below 10 years of age. (Table I)

Out of total 68 episodes 32 (47 %) of the episodes had profound neutropenia; profound neutropenia is marked as when absolute neutrophil count was ≤100/mm 3, whereas 38 (55.8%) episodes were associated with prolonged neutropenia (>7 days) (Table II). Mean duration of neutropenia was 9.1 days and range were 4-19 days.Considering clinical feature cough was most common association presented in 27 (39.7%) episodes. Followed by bleeding 19 (27.94%), diarrhea 12 (17.64%), urinary complaints 8 (11.76%), skin/soft tissue lesion 7 (10.29%), mucositis 3(4.4%), ear discharge 3(4.4%) and CNS manifestations 2(2.9%). Bacterial infection was confirmed by culture in 10 (14.7%) episodes. Blood culture was positive in 8 episodes, urine and wound swab was positive in one each episode. Where most the isolated organism wire gram negative (90%).

Considering treatment outcome: Patients of 35 (51.4%) episodes had discharge and 17(25%) episodes continue treatment after recovery from FN episodes consider as success. Combined adverse event was observed in 16 episodes in total 68 episodes and isolated adverse event observed in 19 episodes; as 8(11.76%) death, 6(8.8%) shock, 3(4.4%) discharge against medical advice and 2(2.9%) episodes needed ICU support were consider as adverse outcome.

In the majority cases (44.1%) antibiotics were started within 6-12 hours. But that time to antibiotic was not associated with adverse outcome of this study. Type of cancer, prolonged neutropenia and bacteremia also were not proven as an associated factor for the adverse outcome of febrile neutropenic episode (Table IV). In contrast, Age ≥10 (10 out of 25 vs. < 10 y 6 out of 43; p value 0.0146) (Table V) and profound neutropenia (14 out of 32 vs non profound neutropenic 2 out of 36; p value 0.0039) were strongly associated with adverse outcome (Table III).

Table I: Age distribution of the 61 study subjects (n=61)

Age (in years)	Frequency (n)	Percentage (%)
<10 years	40	65.57
≥ 10 years	21	34.42
Total	61	100.00
Mean±SD	7.13± 3.399	
Range (Min -Max)	0.5 – 14.0 years	

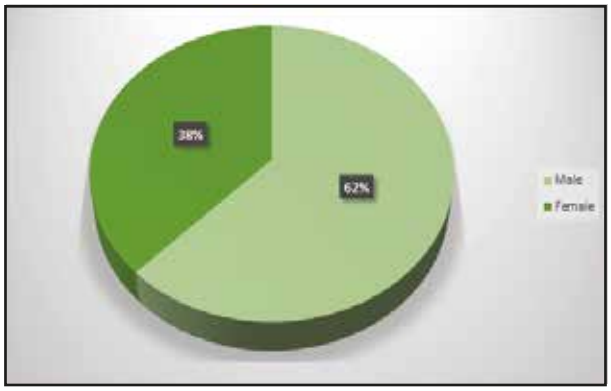

Figure 1: Pie diagram showing sex distribution. Male patients were 28 (62.29%) and female patients were 23 (37.71%). Male: Female was 1.65:1.

Table II: Level of neutropenia of 68 episodes (n=68)

Neutrophil count/ mm	N	Percentages
<1000 - 500	10	14.7%
<500 - 200	18	26.47%
<200	40	58.88%
Total	68	100.00%

58.88% had very severe neutropenia 58.8%, followed by sever 26.47% and moderate neutropenia in 14.7% of episodes.

Table III: Association of composite adverse outcome with profound neutropenia in 68 episodes (n=68)

Profound neutropenia	Adverse outcome present	Adverse outcome absent	RR 95% CI	P value
Present (32)	14	18	7.87 (1.93 - 32)	0.0039 ^{s}
Absent (36)	2	34		

32 profound neutropenic episodes 14 were associated with adverse outcome vs out of 36 non-profound neutropenic episodes 2 had adverse outcome. P value was significant.

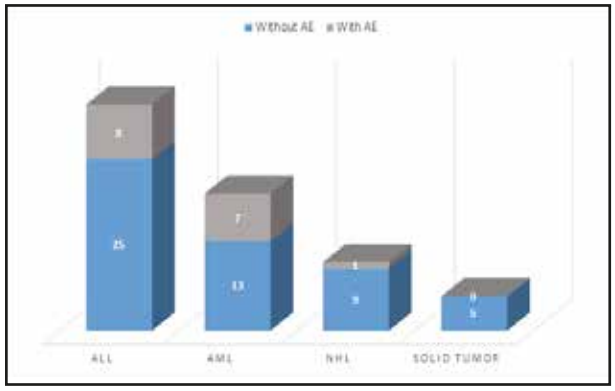

Figure 2: Stacked column diagram showing distribution of total 16 composite adverse outcome in different types of cancer in total 68 episodes.

Table-IV: Association between hematological cancer and solid tumor with composite adverse outcome in total 68 episodes. (n=68)

Cancer type	Adverse event	Without adverse event	P
Hematological cancer (63)	**16**	**47**	**0.33**
Solid tumor (5)	**0**	**5**	

Fisher exact test was done. 16 episodes of 63 hematological malignancies were associated with adverse outcomes. P value was not significant.

Table V: Relation of different age groups with composite adverse outcomes in 68 episodes. (n =68)

Age group	Adverse event	Without adverse event	X^2	P
<10 (43)	6	37		
≥10(25)	10	15	5.9606	0.0146
Total (68)	16	52		

X^2 test was done. P value significant. Age ≥10 was associated with adverse outcome of this study.

Discussion

Neutropenia and infection are common and anticipated side effects of chemotherapy. Febrile neutropenia is responsible for significant hospital morbidity (20%-30%) and (10%) mortality .[8] Previous studies reported that the clinical profile of febrile neutropenia in children from LMICs (low/middle- income country) also differs significantly from that in the more affluent nation .[9] The current study was also done in tertiary health care canter of a resource-limited country; Bangladesh with an aim to identify clinical features, outcome and risk factors associated with adverse outcome of febrile neutropenia. In this current study, adverse event outcome was found more in older age groups. It may be due to older children got more intensive chemotherapy. Age more than 10 years is also considered as a high-risk factor adverse outcome of febrile neutropenia in different guidelines.[10]

One study had shown that increased risk of adverse outcome becomes apparent as the degree of neutropenia increased.[2] In this current study; 32 episodes had profound neutropenia. Profound neutropenia was also identified as a significant risk factor for adverse outcome in this study. Fourteen episodes had adverse events associated with profound neutropenia. Bloodstream infection was the most common site of infection in febrile neutropenic patients mentioned by several studies.[11] In this current study, majority (11.7%) organisms were isolated from blood. Time to antibiotics is also considered as an important predictor of outcome in FN; in different studies. It is also considered as a tool of quality of supportive care measures. Delay in starting antibiotics is an independent risk factor for poor outcome.[12] In this study in majority cases (44.1%) antibiotics were started within 6-12 hours. Time to initiation of antibiotics was also assessed for adverse outcome, but the result was not significant. A study of tertiary health care center of Pakistan, found that out of 872 episodes of febrile neutropenia; where 1.4% expired.[13] In the current study among the adverse events; mortality was higher 11.76% and 2.9% of patients required PICU admission, 8.8% needed aggressive fluid resuscitation. This poor outcome in LMIC is may be due to lack of supportive care; limited facilities of isolation and intensive management for most of the critically ill patients.

That study was concluded with giving an impression about the load of febrile neutropenia, associated clinical & laboratory features with management outcomes of in pediatric cancer patients at tertiary health care center setting. There is scope for further detailed & large-scale study on that serious issue; findings of current study may guide those future studies.

Conclusion

Febrile neutropenia was a common complication in hematological malignancy. Although most of the episodes of febrile neutropenia had been treated successfully, mortality was significantly higher. Profound neutropenia and age ≥10 were significant risk factors for dreadful outcome.

Acknowledgment

We express my gratefulness to our teachers & colleagues of the department of Paediatric Haematology & Oncology of Bangabandhu Sheikh Mujib Medical University.

References

1. Klastersky, J,Science and pragmatism in treating and preventing neutropenic infection. The Journal of antimicrobial chemotherapy 1998; 41(suppl_4): 13-24.

2. Castagnola, E, Fontana V, Caviglia I, Caruso S, Faraci M, Fioredda, F, et al. A prospective study on the epidemiology of febrile episodes during chemotherapy-induced neutropenia in children with cancer or after hemopoietic stem cell transplantation. Clinical infectious diseases 2007; 45(10):1296-1304

3. Ellis M. Febrile neutropenia. Ann N Y Acad Sci. 2008; 1138(1): 329-350.

4. Klastersky J, De Naurois J, Rolston K, Rapoport B, Maschmeyer G, Aapro M, et al. Management of febrile neutropenia: ESMO clinical practice guidelines. Annals of Oncology 2016; 27(suppl 5): 111-118.

5. Wisplinghoff, H, Seifert H, Wenzel RP, Edmond MB. Current trends in the epidemiology of nosocomial bloodstream infections in patients with hematological malignancies and solid neoplasms in hospitals in the United States. Clinical Infectious Diseases 2003; 36(9):1103-1110.

6. Freifeld, AG, Bow EJ, Sepkowitz, KA, Boeckh, MJ, Ito JI, Mullen CA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. Clinical infectious diseases 2011; 52(4): e56-e93.

7. Basu, SK, Fernandez ID, Fisher SG, Asselin BL, Lyman GH. Length of stay and mortality associated with febrile neutropenia among children with cancer. Journal of clinical oncology 2005: 23(31):7958-7966.

8. Klastersky J, De Naurois, J, Rolston K, Rapoport B, Maschmeyer G, Aapro M, et. Management of febrile neutropenia: ESMO clinical practice guidelines. Annals of Oncology 2016, 27(suppl_5): 111-118.

9. Badr M, Hassan T, Sakr H, Karam N, Rahman DA, Shahbah D, et al. Chemotherapy induced neutropenia among paediatric cancer patients in Egypt: risk and consequences. Mol Clin Oncol. 2016; 5(3): 300-306.

10. Ammann RA, Hirt A, Lüthy AR, Aebi C. Identification of children presenting with fever in chemotherapy-induced neutropenia at low risk for severe bacterial infection. Medb Pediatr Oncol 2003; 41(5): 436-443.

11. Ahmadzadeh A, Varnasseri M, Jalili MH, Maniavi F, Valizadeh A, Mahmoodian M, et al. Infection pattern of neutropenic patients in post-chemotherapy phase of acute leukemia treatment. Hematology reports. 2013; 5(4): e15.

12. Fletcher M, Hodgkiss H, Zhang S, Browning R, Hadden C, Hoffman T, et al. Prompt administration of antibiotics is associated with improved outcomes in febrile neutropenia in children with cancer. Pediatric blood & cancer 2013; 60(8) :1299-1306.

13. Alam, MM, Fadoo Z. Febrile neutropenia in pediatric cancer patients: Experience from a tertiary health care facility of Pakistan. Pediatric Infectious Disease 2014: 6(3) :89-93.