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Factors Associated with Adverse Outcome in Pediatric Febrile Neutropenia: Results from a Tertiary Care Hospital

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Abstract

Background
Febrile neutropenia with childhood cancer alters the outcome significantly. To study the clinical and laboratory parameters, which predict the outcome among cancer patients with febrile neutropenia this study was undertaken.

Materials and Methods
The study included children less than 18 years with febrile neutropenia episodes. Clinical and hematological / laboratory parameters were recorded during each episode. Hemoglobin, total leucocyte count, platelet count, absolute neutrophil count, absolute monocyte count and serum C-reactive protein (CRP) levels at the onset of febrile neutropenia episode were analyzed as predictors of outcome of febrile neutropenia. The outcome was measured in terms of mortality, duration of fever and need for Intensive care unit (ICU) stay.

Results
The study consisted of 88 episodes in 40 children with a median (IQR) age of 5.9 (3.79, 10) years. In 67.5% of Children's Leukaemia was the underlying disease. Mean (±SD) hemoglobin concentration was 8.8 ± 1.71 g/dl. Profound neutropenia was seen in 32(36.5%) episodes. Most common infection was lower respiratory infection (30.7%). Absolute monocyte count < 100 cells/cu.mm was found to predict a duration of fever > 7 days (p=0.030).Thrombocytopenia (< 50,000) and CRP (>90 mg/L) were found to be significant predictors of mortality (p <0.001 and 0.017, respectively), and the need for prolonged ICU stay (p =0.027 and p=0.048, respectively).

Conclusion
Thrombocytopenia and elevated CRP are significant predictors of mortality and the need for prolonged ICU stay, whereas low hemoglobin level, leukopenia and low absolute neutrophil count (ANC) were not associated with of adverse outcome in febrile neutropenia episodes.

Key Words: Children, Febrile neutropenia, Predictors, Outcome.

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1- INTRODUCTION

Febrile neutropenia (FN) is a potentially fatal condition in patients with childhood malignancies receiving cytotoxic chemotherapy for the underlying malignancy (1). It also increases the morbidity in terms of prolonged hospital and intensive care unit (ICU) stay, increased need for ventilator and inotropic supports, prolonged and upgraded antibiotic therapy directly reflecting on the elevated cost of treatment in the resource poor countries. Children with neutropenia are prone to dangerous infections and in the era of emerging antibiotic resistance and multidrug resistant organisms it significantly poses a therapeutic challenge. Aggressive treatment with broad spectrum antibiotics in an inpatient setting till defervescence and recovery of neutrophil count is the cornerstone in the management of febrile neutropenia (2). Though mortality has declined drastically over the years with the use of Imipenem and **c**arbenicillin, indiscriminate use of antibiotics and lengthy hospitalisation increase the risk of multidrug resistance apart from causing additional emotional and economic burden on the parents (3, 4).

In addition to empirical antibiotic treatment, the management includes a detailed clinical examination, multiple blood cultures from different sites and body fluids, including cultures from all lumens of a central venous line if present, and other investigations. There is no single correct antibiotic choice rather, a decision should be based on the patient's history and clinical findings, focus of infections, local antibiotic resistance patterns, and toxicity/cost profiles of antibiotics. Recently, the disease-free survival rates have increased significantly in children with cancer with advances in cancer treatment such as increase in the use of colony stimulating factor, intensification of chemotherapy protocols and stem cell transplantation (5).

As not all children are at the same risk for serious complications, stratification based on risk factors has become a prime requirement. Several studies have prospectively validated their models for low risk criteria (2, 6). A prospective – multicentre study included 5 independent variables: serum C-Reactive Protein (CRP) level ≥ 90mg/L, hypotension, identification of relapse of leukaemia as cancer type, platelet count ≤ 50,000 cells/cu.mm, and recent receipt of chemotherapy to assess the risk for invasive bacterial infection and concluded that identification of these risk factors was helpful in stratification of children into high or low risk groups. Some investigators even emphasized the advantages of outpatient management and early discharge of low risk patients. Higher prevalence of protein energy malnutrition, with poor tolerance to chemotherapeutic drugs in resource-poor countries makes risk stratification of these febrile neutropenia patients to predict the outcome and mortality (7, 8).

This study was conducted to evaluate the role of haemoglobin level, total leucocyte count, platelet count, Absolute neutrophil count, Absolute monocyte count and serum CRP levels at the onset of febrile neutropenia episode on the outcome of febrile neutropenia.

2- MATERIALS AND METHODS

2-1. Study population and design

This prospective observational study was conducted in a Kasturba Medical College, Manipal- India, and a tertiary care centre. All children aged <18 years admitted from March 2015 to July 2016 with febrile neutropenia were included. The study was approved by the Institutional Ethics Committee. A child was included in the study at the onset of fever (temperature > 38°C), and neutropenia (Absolute Neutrophil Count [ANC] < 1000cells/cu.mm). Multiple

episodes of febrile neutropenia in the same child were analysed as separate episodes. Detailed history including demographic data (decimal age, gender), complaints, underlying disease (solid or non-solid tumours, stage of chemotherapy, interval since last chemotherapy), any past history of similar episodes, any prior antibiotic prophylaxis and use of Granulocyte – Colony Stimulating Factor (G-CSF) was obtained. Child was examined for potential foci of infection, organomegaly, any bleeding manifestations and findings were documented in a pre- validation pro-forma.

Laboratory investigations including haemoglobin level, leucocyte count, absolute neutrophil count, absolute monocyte count, platelet count, serum C-reactive protein (CRP) levels, were performed at the inclusion into the study. Haemoglobin levels, total leucocyte count and platelet counts were measured using an automated coulter counter (Beckman Coulter-COULTER ® LH 750 Haematology Analyser). To avoid discrepancy with coulter method, the counts were confirmed by a peripheral smear by a pathologist. Blood samples were collected for culture under strict aseptic precautions in BACTEC bottles and were sent for incubation and plated onto blood agar and McConkey media. In addition sputum, urine and stool examinations; imaging studies were performed when clinically indicated and findings were noted.

Child was followed up for any signs of worsening sensorium, need for ventilator and inotropic support, Mucocutaneous bleeding, renal insufficiency, hepatic dysfunction till the time for defervescence. Haemoglobin level, total leucocyte count, platelet count, Absolute neutrophil count, Absolute monocyte count and serum CRP levels at the onset of episode were analysed as the predictors of outcome of febrile neutropenia. The outcome was measured in terms of whether the child survived or succumbed, duration of fever and length for ICU stay.

2-2. Definitions

Fever was defined as an axillary temperature greater than $\geq 38^{\circ}C$ or $100.4^{\circ}F$ (5). Neutropenia was defined as absolute neutrophil count less than 1000cells/cu.mm (9). Profound neutropenia was defined as absolute neutrophil count <100cells/cu.mm (9). Platelet count less than 1,50,000/cu.mm was defined as thrombocytopenia.

2-3. Statistical analysis

Data analysis was done by using the Statistical Package for Social Sciences (SPSS) version15.0. Descriptive data was expressed as percentages, medians and interquartile ranges or as means and standard deviations. Statistical significance was calculated using students t- test for parametric data and Mann-Whitney U test for non-parametric data. Association between categorical variables was assessed using chi-square test or fisher exact test. A p- value of ≤ 0.05 was regarded as statistically significant.

3- RESULTS

3-1. Characteristics of febrile neutropenia episodes

During the 15-month prospective observational study, 44 children with febrile neutropenia who met the inclusion criteria were recruited into the study. Three children who were discharged against medical advice and one child who underwent bone marrow transplantation were excluded from the present study. Hence, a total number of 40 children with a total 88 consecutive episodes of febrile neutropenia were studied. This translates into an average of 2.2 febrile neutropenia episodes per child during the study period (**Figure.1**).

3-1-1. Demography

The median and Interquartile Range (IQR) age of study group was 5.9 years (3.79, 10.00). The youngest child was 6 months old and the eldest was 16.9 years at the time of diagnosis. The ratio of boys and girls was observed to be 1.66:1 (**Table.1**).

3-1-2. Underlying malignancy

Among 40 children included, haematological malignancies were the most common malignancies (77.5%), with acute lymphoblastic leukemia (ALL) contributing to 67.5% and the remaining being diagnosed with solid tumors. Among the haematological malignancies, ALL was the most common (87%) (**Figure.1**); the peak axillary temperature recorded during each episode was > 39°C in 55.7% (n=49) of the episodes. Central venous catheter was used during 3 episodes.

3-2. Spectrum of infections

Most common focus of infection in the study group was acute lower respiratory tract infection (30.7%) closely followed by acute gastroenteritis (28.4%). Skin and soft tissue infections were observed in four children in the study group were impetigo, pustulosis secondary to pseudomonas infection, herpes zoster and cutaneous aspergillosis. Vascular access related infections were seen in four episodes (4.6%), out of which one was central line associated blood stream infection. No focus for fever could be identified in 14.7 % of the episodes (n=13) included in the study.

3-3. Haematological and Biochemical Data

Febrile neutropenia episodes were not associated with severe anaemia**.** Haemoglobin level < 7 g/dl was seen in 12.5 % episodes (n=11), the mean haemoglobin concentration in the episodes studied was 8.8 ± 1.71 g/dl. The median (IQR), total lymphocyte count (TLC) was 1,250 cells/cu.mm (800 and 2,175 cells/cu.mm). Thrombocytopenia (< 1, 50,000 cells/cu.mm) was as an associated finding in most episodes of febrile neutropenia (73.9%) with 43.2% being mild to moderate and 30.7% severe. Profound neutropenia was seen in 32(36.5%) episodes. The median absolute neutrophil count was 174 cells/cu. mm. In 62.5% episodes the absolute monocyte count was less than < 100 cell/cu.mm. The median CRP in the episodes (n=77) was 38.3mg/L (10.75, 101) [CRP could not be measured in 11 episodes].

3-4. Microbiological Data

Blood cultures were sent in 69 episodes and organisms were isolated in ten cases, Coagulase Negative Staphylococcus aureus being the most common (n=3). Gram negative organisms like Escherichia coli, Klebseilla pneumoniae, Pseudomonas aeuroginosa, Acinetobactor and Edwardseilla were identified in 5 episodes. One child had Leuconostoc, a gram positive organism grown in the blood culture, who responded well with Cephalosporin. Among the ten episodes with culture positive sepsis, a focus was identifiable in only one episode. This was in a child with Klebsiella pneumonia sepsis in whom the same organism was cultured from sputum. Candida species were isolated from two throat swab cultures (n=4), and one ear swab culture (n=2). However, all these three children had a sterile blood culture. All the stool tests (n=6), wound swab (n=1), Cerebrospinal Fluid (CSF) (n=3), and urine cultures (n=2) done during the study period in the study group were sterile.

3-5. Management of febrile neutropenia episodes

Cephalosporins were used as first line drugs in 45.5 % of the episodes and in ten of such episodes grading up to higher antibiotics like Piperacillin, Teicoplanin and Vancomycin was required.

Teicoplanin and Piperacillin were started as first line antibiotics in four and five episodes respectively. Antifungals (Liposomal Amphotericin B and Fluconazole) were started in 21 episodes in the present study, in four episodes there was culture proven Candidal growth and in others they were started either empirically for persisting fever spikes or based on clinical diagnosis of oral / oesophageal / vaginal candidiasis. Out of 40 children included in the study, 38 were on prior Co-trimoxazole (TMP-SMP) prophylaxis for more than a week. The other two children were newly diagnosed to have malignancy and had prior antibiotic prophylaxis of < 1week. Granulocyte - colony stimulating factor (G-CSF) and blood products were used in 21.6% (n=19) and 40.9% (n=36) of the episodes.

3-6. Outcome of febrile neutropenia episodes

Recovery from febrile neutropenia was observed in 94.3% of the episodes. The mortality rate during the study period was 5.7% (five children). All five of them succumbed to the first episode of febrile neutropenia and were during induction phase. The median duration of fever in the episodes was 5 days. Persisting fever for more than 14 days was observed in four episodes. The median length of ICU stay was two days (**Table.1**).

3-7. Predictors of outcome of febrile neutropenia episodes

In the present study, variables like low haemoglobin (< 7g/dl), leukopenia (< 2000 cells/cu.mm), thrombocytopenia (<50,000cells/cu.mm), Absolute neutrophil count <100 cells/cu.mm, Absolute monocyte count < 100 cells/cu.mm, and CRP more than 90 mg/L, were studied as risk factors for the outcome of febrile neutropenia episode.

All children who succumbed had a platelet count less than 50,000 cells/cu.mm (p <0.001), and 80% of them had white blood cell (WBC) < 2000 cells/cu.mm, Absolute monocyte count (AMC) <100 cells/cu.mm and CRP > 90 mg/L, of which CRP was found to be statistically significant (p=0.017)

Haemoglobin, Total leucocyte count and Absolute neutrophil count were not associated with mortality or the duration of fever or the need for ICU stay (p > 0.05). Absolute monocyte count < 100 cells/cu.mm was found to predict a duration of fever > 7 days (p= 0.030). Thrombocytopenia and elevated CRP were found to be significant predictors of mortality (p <0.001 and p=0.017, respectively) and the need for ICU stay (p =0.027, and p=0.048, respectively) (**Table.2**).

Table-1: Outcome of febrile neutropenia episode

Outcome	Number of episodes (%)
Primary (n=88) Recovered Succumbed	 83(94.3) 5(5.7)
Time for defervescence (n=83)* < 7days 7-14days >14days	 59 20 4
Duration of fever*	Median 5(7,3) Range 1-25
Length of ICU stay in days (n=14)	Median 2(4,1)

* Five children who succumbed to the illness were excluded as they were febrile till the day of death.

Table 2: Predictors of outcome of febrile neutropenia

Haemoglobin (g/dl)	Primary outcome(n=88)		Duration of fever (n=83)*		ICU stay (n=88)	
	Recovered (n=83)	Succumbed (n=5)	< 7days	>7days	Yes	No
<7	10	1	8	2	1	10
>7	73	4	56	17	13	64
P- value	0.605 (NS)		0.816 (NS)		0.5 (NS)	
WBCcells/cu.mm						
< 2 000	61	4	44	17	10	55
> 2 000	22	1	20	2	4	19
P- value	1(NS)		0.083 (NS)		1(NS)	
Plt cells/cu.mm						
<50 000	22	5	15	7	8	19
>50 000	61	0	49	12	6	55
P- value	<0.001 **(S)**		0.245 (NS)		0.027 **(S)**	
ANCcells/cu.mm						
<100	29	3	20	9	7	25
>100	54	2	44	10	7	49
P- value	0.34 (NS)		0.27 (NS)		0.36 (NS)	
AMCcells/cu.mm						
<100	51	4	35	16	11	44
>100	32	1	29	3	3	30
P-value	0.36 (NS)		0.030 **(S)**		0.25 (NS)	
CRP mg/L(n=77)**			(n=72)*			
<90	55	1	45	10	7	49
>90	17	4	11	6	7	14
P- value	0.017 **(S)**		0.182 (NS)		0.048 **(S)**	

* Five children who succumbed to the illness were excluded as they were febrile till the day of death; ** CRP levels could not be done in 11 episodes; NS: Not Significant; S: Significant.

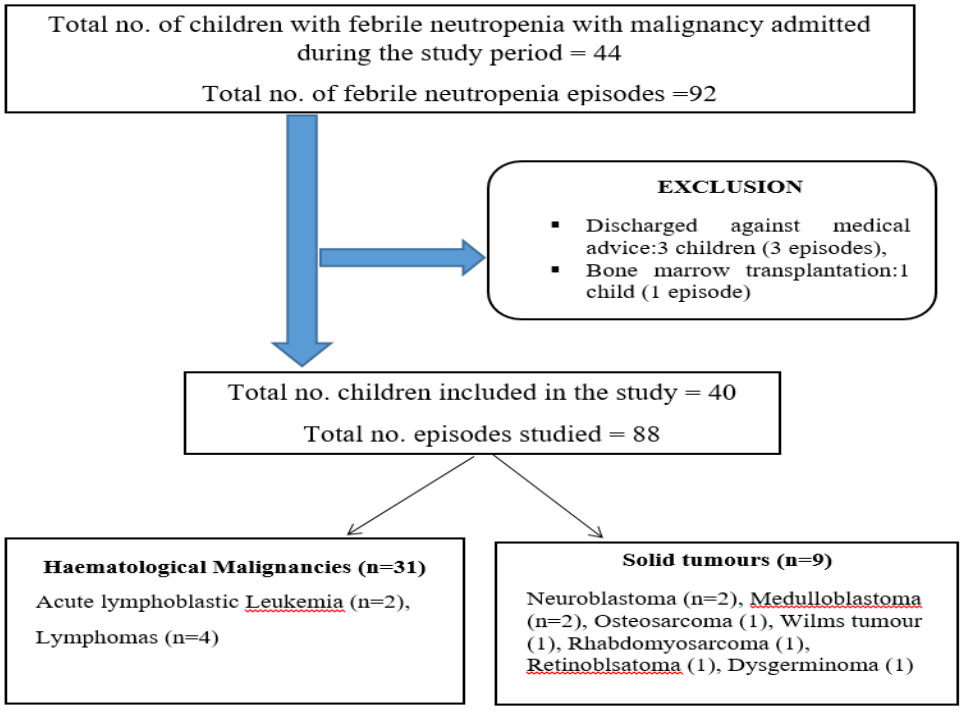

Fig.1: The profile of study population.

4- DISCUSSION

Febrile neutropenia is the major cause of prolonged hospitalisation among children with malignancies apart from hospitalisation for chemotherapy. Infections hinder the pause-less continuation of chemotherapy and also increase the risk of mortality. The standard therapy is hospitalisation and broad spectrum intravenous antibiotics. However, paediatric group is heterogeneous with suffering ranging from minor illness to extreme complications and sometimes even death. Early prediction of serious complications or mortality is of prime importance. Identification of low risk patients by a prediction tool helps in approaching this group with therapeutic strategies like oral medications, early discharge and even outpatient management (8, 10, 11). Likewise, early identification of high risk group helps planning more aggressive therapy (early admission, isolation and intravenous antibiotics with close monitoring for serious complications). Investigators like Talcott and Klastersky et al. carried out studies in adult cancer patients to validate risk assessment models which are in use for adults (6, 12).

Since the past 2 decades there were several publications made on prediction models for paediatric patients as well. Presence of risk factors like underlying disease characteristics (marrow involvement, advanced stage of cancer, relapse, and refractory tumours), profound or prolonged neutropenia, monocytopenia (<100/cu.mm), peak axillary temperature > 39°C, thrombocytopenia (<50,000/cu.mm) and co-morbidities (extensive bleeding, hypotension, hepatic dysfunction, renal insufficiency, altered mental status, and electrolyte imbalances), can predict serious complications, bacteraemia or mortality (9). Bothra et al. studied 155 episodes of febrile neutropenia and concluded that three predictors, namely history of more than two previous episodes of febrile neutropenia, abnormal chest radiograph and child on oral antibiotics at presentation for adverse outcomes. However they did not find any correlation in the parameters like haemoglobin levels, platelet counts and active noise control (ANC) in prediction of outcome. This is in contrast to the present study where low platelet count was significantly associated with the mortality (13). Prasad et al. also had a similar observation of absolute phagocyte count (i.e. AMC + ANC) to be associated with adverse outcome. However, they also found that presence of significant focus of infection; fever more than 35 degree C and lasting for more than 5 days and previous documented infection as independent risk factors for adverse outcome in multivariate analysis of 250 episodes in 183 children (14). Paganini et al. conducted a prospective, multicentre study to derive a scoring system to predict mortality in febrile neutropenia children with cancer. They concluded that a child comes under risk if one or more of the following risk factors were present at onset: advanced stage of malignancy, severe associated co-morbidities and bacteraemia.

In current study, all the five children who succumbed had bone marrow involvement and severe co-morbidities; two out of five had culture positive sepsis (9). Santolaya et al. prospectively evaluated 263 episodes in 170 children for five clinical and laboratory parameters namely: serum CRP ≥ 90mg/L, hypotension, identification of relapse of leukemia, platelets ≤ 50,000cells/cu.mm and recent receipt of chemotherapy for predicting the risk for invasive bacterial infection (15). While Klaassen et al., concluded that absolute monocyte count ≤ 100/cu.mm is associated with significant bacterial infection (3). In the present study, the febrile neutropenia episodes which resulted in mortality had platelet count of less than 50,000 / cmm and 80 % of them had total leucocyte

count of less than 2,000 / cmm. All of them had low absolute monocyte count of less than 100 / cmm and an elevated Serum CRP level of more than 90 mg/L which indicated the significantly higher risk of mortality. In such high risk patients, aggressive higher in- patient antibiotic and supportive therapy keeping in mind the hospital flora and early initiation of antifungal therapy may reduce the risk of mortality. Prospective studies by Santolaya et al. also identified these factors to be associated with higher mortality (15).

Absolute monocyte count of less than 100 / cmm in a febrile neutropenia episode was associated with a prolonged period of fever for more than 7 days ($p<0.05$). It may result in prolonged antibiotic and supportive therapy, prolonged hospital stay and more importantly break in chemotherapy which in turn may alter the outcome of the disease. Higher serum CRP of more than 90 mg/L and thrombocytopenia of less than 50,000 cmm were significantly associated with need for ICU stay.

4-1. Limitations of the study

1) Study was conducted in a single setting,
2) Sample size was limited, hence multiple logistic regression analysis was not possible,
3) The impact on the outcome of episode due to prior antibiotic therapy and medications used in chemotherapy before the admission were not analysed.

5- CONCLUSION

According to the results of this study thrombocytopenia and increased serum C-Reactive protein levels are significant predictors of mortality and of need for prolonged ICU stay, whereas low Haemoglobin level, leukopenia and low ANC were not associated with adverse outcome in febrile neutropenia episodes in children.

6- CONFLICT OF INTEREST: None.

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