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Clinical Profile of Febrile Neutropenia in Children with Acute Leukemia

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Abstract
Introduction: *Febrile neutropenia is the most common cause of morbidity and mortality in leukemic patients. These children mostly require parenteral antibiotics because an absolute neutrophil count <500 cells/mm3 conferred a high risk of bacteremia though their correlation with positive blood cultures were rarely proven. This study was undertaken with the sole aim of finding the clinical profile of febrile neutropenia in children with leukemia in our hospital and the various factors influencing its occurrence and its prognosis.*
Materials and Methods: *This hospital based descriptive study was conducted at IMCH Calicut between Jan2014-Dec2015 and included all leukemic children presenting with one or more febrile neutropenic episodes (fever >38.3 C or 101.5F & ANC <500).*
Results: *Total of 38 children with 53 febrile neutropenic episodes were encountered. Children above 5 years of age (n=8/18; CI 41.1%; p=0.004) and those with severe anemia (Hb<7g/dl) had statistically significant (n=8/19; CI 29.6%; p=0.012) correlation with mortality.*
Conclusion: *This study established correlation between the age, type of malignancy, severity of anemia and organisms grown in febrile neutropenic children and their risk of mortality.*
Keywords: *Neutropenia, Absolute Neutrophil Count, Leukemia.*

Introduction

Acute leukemia is the most common of all childhood malignancies accounting for about 30% of its total incidence. Approximately 1 in 2000 children will develop it before the age of 15 years. The cure rate of acute leukemia is 80-90% in developed countries[1].

Febrile neutropenia is the most common cause of morbidity in leukemic patients. Fever is the principal sign of infection in neutropenic patients and frequently may be the only evidence of infection[2]. The major causes of febrile neutropenia in leukemia are chemotherapy, systemic infections, immunosuppression and immunodeficiency associated with cancer[3]. A systemic review of literature showed that age, nutritional status, chemotherapy dose and intensity, low base line blood counts are all risk factors for greater mortality and morbidity[4,5].

Fever is defined as a single oral measurement of 38.3^0C or 2 measurements of 38^0C separated by atleast one hour[6]. Mild neutropenia is defined as

absolute neutrophilic count (% PMN neutrophils + % band forms) <1500, moderate neutropenia ANC 500-1000, severe neutropenia <500[7].

Traditionally children with malignant disease who present with fever and neutropenia are hospitalised for parenteral antibiotics. The foundation for such a practice is based on the study by Bodey in 1966 indicating that an ANC <500 cells/mm^3 conferred a high risk of bacteremia[1].

Very few studies have been conducted in India based on febrile neutropenia[8]. No such study was conducted in Kerala to evaluate the outcome. The available studies had several limitations including retrospective analysis of small study populations lacking independent validation or missing values and differences in predictive factors considered.

This study was undertaken with the sole aim of finding the clinical profile of febrile neutropenia in children with leukemia in our hospital and the various factors influencing its occurrence and its prognosis.

Aims of the Study

1. To study the clinical profile of febrile neutropenia in children with leukemia.
2. To study the co-morbidities in severe febrile neutropenia in children with leukemia.
3. To study the common organisms associated with infections in febrile neutropenic children and the pattern of antibiotics to which it responds.

Materials and Methods

Study Design: Hospital based descriptive study

Population: All children with febrile neutropenia admitted to Institute of Maternal and Child Health leukemia ward with fever >38.3^0 C or 101.5F & ANC <500 cells/mm^3.

Settings: Leukemia ward in Institute of Maternal and Child Health, Medical College, Calicut

Study Period: One year (January 2014 to December 2015).

Inclusion Criteria: All children with leukemia {ALL or AML} with febrile neutropenia {fever >38.5^0 c & ANC<500 cells/mm^3} admitted to Institute of Maternal and Child Health, leukemia ward from Jan 2017 to Dec 2017.

Exclusion Criteria: Patients who received prior bone marrow transplantation.

Methodology: To include children presenting with febrile neutropenia from January 2015 to December 2016 presenting to IMCH, Calicut who satisfy the inclusion criteria after excluding those who come under exclusion criteria.

Method of Study: All children with leukemia (AML/ALL) admitted to paediatric wards with true fever (A single axillary measurement of 38.3^{0}C or 2 measurements of 38^{0}C separated by atleast one hour) and severe neutropenia (ANC <500 cells/mm^3) are included in the study.

The patients are followed up throughout the hospital stay till discharge and the outcome is noted in terms of return of counts to normal, resolution of fever, discharge of the patient or death.

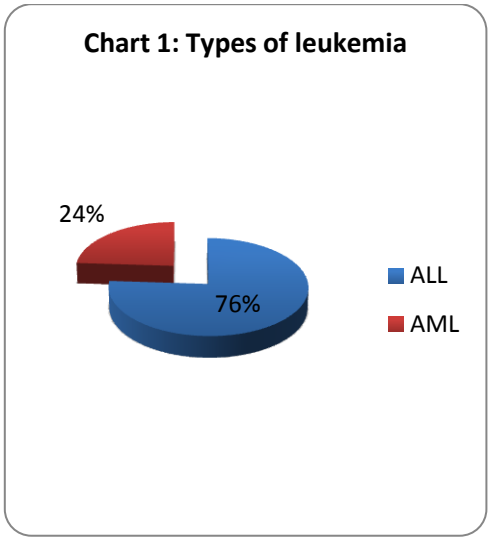
A pre-written proforma is filled in based on clinical examination and questionnaire which includes age, sex, type of leukemia, date of diagnosis of leukemia, fever, ANC, number of neutropenic episodes, stage of leukemia, details of chemotherapy, systemic involvement, I V site infection, PEM, microbiologic flora, antibiotic sensitivity and the outcome.

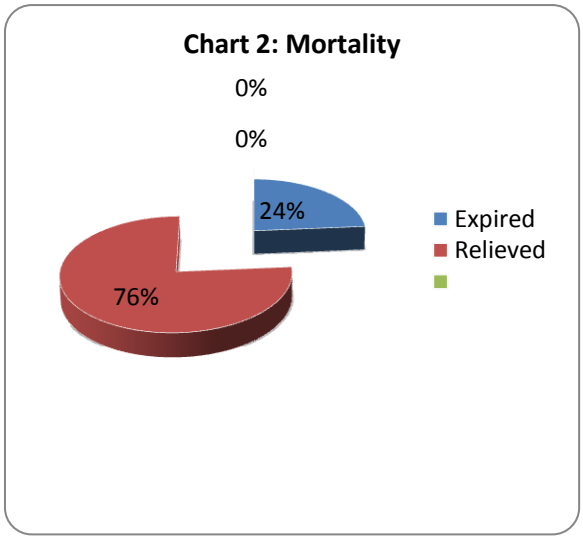
Since a single patient can have multiple episodes during the study period, both the number of patients and the number of events are taken into account. The outcome of variables like age, sex, mortality are measured based on number of subjects whereas type and phase of leukemia, culture positivity, organism grown, antibiotic sensitivity, previous episodes are based on number of episodes.

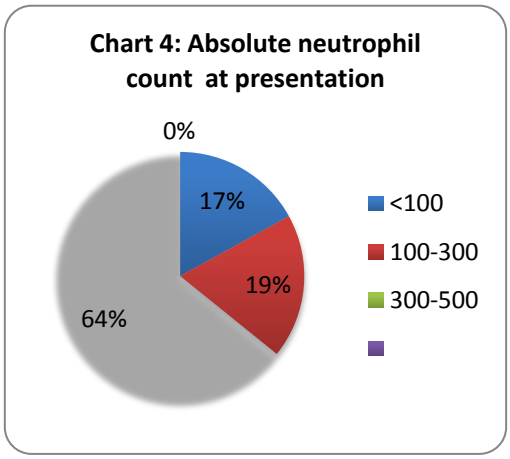
Blood cultures are taken prior to antibiotic therapy and broad spectrum antibiotics are administered according to the current protocol. Blood culture results are noted to study the common organisms associated with infections in febrile neutropenic

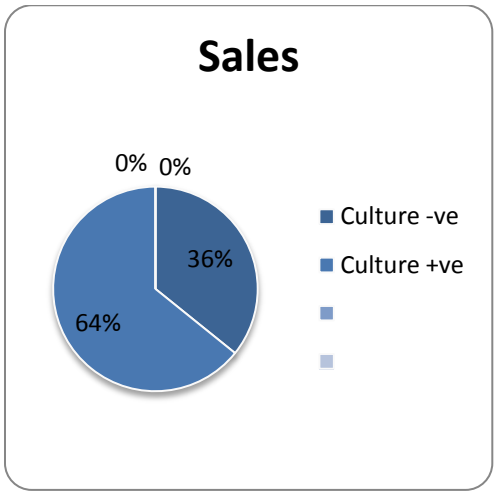
patients and the antibiotic sensitivity patterns of organisms. The patients are followed up throughout the hospital stay till discharge and irrespective of the treatment protocol and measures taken to overcome neutropenia the outcome as described above is noted. By statistical analysis the comorbidities in severe febrile neutropenia in leukemic patients are studied in our hospital settings.

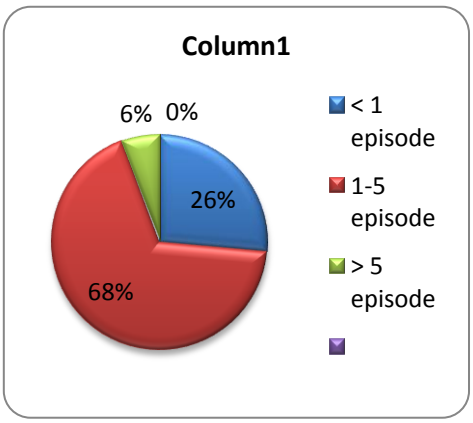
Observations

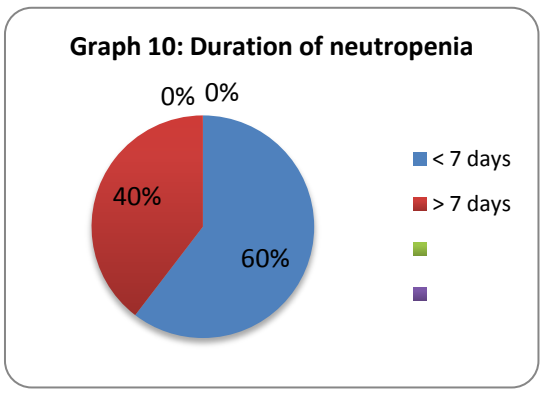












Results

Table 1: Age & mortality

p = 0.004 **n = 38.**

Age	Expired	Relieved	Total
<5 yrs	1[5%]	19[95%]	20[100%]
>5 yrs	8[41.1%]	10[58.9%]	18[100%]
Total	9[23.7%]	29[76.3%]	38[100%]

Table 2: Severe anaemia [Hb<7g/dl] and mortality

Hemoglobin	Expired	Relieved	Total
<7g/dl	1 [3.8%]	25[96.2%]	26[100%]
>7g/dl	8[29.6%]	19 [70.4%]	27 [100%]
Total	9 [17.0%]	44[83.0%]	53[100%]

P value 0.012

The death rate was found to be more [29.6%] in children who presented with severe anaemia and this was found to be statistically significant.

Table 3: Thrombocytopenia <50,000 and mortality

Platelet count	Expired	Relieved	Total
PLT<50,000	2[8.3%]	22[91.7%]	24[100%]
PLT>50,000	7[24.1%]	22[75.9%]	29[100%]
Total	9[17%]	44[83%]	53[100%]

P value = 0.127

The death rate was found to be more [24.1%] in children who presented with thrombocytopenia, even though clinically significant this was not found to be statistically significant.

Table 4: Correlation between culture positivity and outcome

Culture	Expired	Relieved	Total
Negative	5 (14.7%)	29 (85.3%)	34 (100.0%)
Positive	4 (21.1%)	15 (78.9%)	19 (100.0%)
Total	9 (17.0%	44 (83.0%)	53 (100.0%)

P value 0.555

Among culture positives 21.1% expired as compared to 14.7% deaths in culture negatives. This was clinically significant even though statistically insignificant.

Table 5: Number of previous neutropenic episodes and mortality

No of previous neutropenic episodes	Expired	Relieved	Total
Nil	2 (14.3%)	12(85.7%)	14(100.0%)
1 -5	5(13.8%)	31(86.2%)	36(100.0%)
>5	2(100.0%)	0 (0%)	10(100.0%)
Total	9 (17%)	44 (83%)	53 (100%)

p value = 0.07

The more the previous neutropenic episodes the more was the mortality rate. However this was found to be statistically insignificant but clinically significant [p=0.07].

Table 6: Correlation between leukemia and mortality

Type of leukemia	Expired	Relieved	Total
ALL	4(10.5%)	34 (89.5%)	38(100.0%)
ALL relapse	2(100.0%)	0 (0%)	2 (100.0%)
AML	2 (16.6%)	10 (83.4%)	12 (100.0%)
AML relapse	1(100.0%)	0 (0%)	1 (100.0%)
Total	9 (16.9%)	44 (83.1%)	53(100%)

p value 0.022

Most of the deaths occurred in children with ALL (66% of deaths). There were 2 cases of relapse in children with ALL and 1 case of relapse in patients with AML. 100% mortality was observed in children who had febrile neutropenia in the relapse phase and this was statistically significant.

Table 7: Phase of treatment of leukemia and mortality

Phase of treatment [ALL]	Expired	Relieved	Total
CNS relapse	2[100%]	0[0%]	2[100%]
Consolidation	0[0%]	1[100%]	1[100%]
Induction phase 1	2[13.3%%]	13[86.7%]	15[100%]
Induction phase 2	1[12.5%]	8[87.5%]	9[100%]
Interim maintenance	0[0%]	3[100%]	3[100%]
Maintenance	1[25%]	3[75%]	4[100%]
Protocol M	0[0%]	1[100%]	1[100%]
Reinduction phase 1	0[0%]	2[100%]	2[100%]
Reinduction phase 2	0[0%]	3[100%]	3[100%]

Phase of treatment [AML]			
Induction	1[12.5%]	7[87.5%]	8[100%]
Maintenance	0[0%]	2[100%]	2[100%]
Consolidation	1[50%]	1[50%]	2[100%]
Relapse	1[100%]	0[0%]	1[100%]
Total	9[17%]	44[83%]	53[100%]

There were children in various stages of leukemia such as induction phase 1, induction phase 2, consolidation phase, maintenance phase, reinduction phase and relapse phase. Majority of the children were in ALL induction phase 1. There were totally 9 deaths with ALL contributing 66% of cases. However, 100% mortality was recorded among children in relapse (ALL – 2 ; AML).

Table 8: Duration of neutropenia and mortality

Duration of neutropenia	Expired	Relieved	Total
Neutropenia< 7 days	3 (9.4%)	29 (90.6%)	32 (100.0%)
Neutropenia>7 days	6 (28.6%)	15 (71.4%)	21 (100.0%)
Total	9 (17.0%)	44 (83.0%)	53 (100.0%)

p value 0.069

21 of the neutropenic episodes lasted for > 7 days and was associated with 6 cases of mortality as against 3 cases of mortality among the 32 neutropenic episodes that lasted for less than 7 days. However this observation also turned out to be statistically insignificant.

Table 9: Type of organism and mortality

Type of organism	Expired	Relieved	TOTAL
NIL	5 (14.7%)	29 (85.3%)	34 (100.0%)
CONS	2 (25.0%)	6 (75.0%)	8 (100.0%)
GNB	0 (0%)	1 (100.0%)	1 (100.0%)
E.Coli	0 (0%)	1 (100.0%)	1 (100.0%)
MRSA	1 (25%)	3 (75%)	4 (100.0%)
Acinetobacter	0 (0%)	1 (100.0%)	1 (100.0%)
Micrococci	0 (0%)	1 (100.0%)	1 (100.0%)
Pseudomonas	1 (100.0%)	0 (0%)	1 (100.0%)
Staph aureus	0 (0%)	1 (100.0%)	1 (100.0%)
Streptococci	0 (0%)	1 (100.0%)	1 (100.0%)
Total	9 (17.0%)	44 (83.0%)	53 (100.0%)

p value 0.73

Even though the most common organism grown was CONS, maximum mortality was seen with MRSA and pseudomonas infections.

34 neutropenic episodes among the 53(64%) were sterile. Among the culture positive cases majority grew CONS. Among them 2 cases of mortality were recorded.

1 case of MRSA expired and another case of mortality was associated with the growth of gram negative bacilli. 5 deaths had a sterile culture result.

Most of the children were found to have grade 1 PEM (21) out of whom 4 died. Among the 14 episodes associated with grade 2 PEM there were 3 casualties. Though they were statistically insignificant it was noted that presence of PEM had an effect on the mortality benefit.

Discussion

Febrile neutropenia is one of the most common cause of mortality and morbidity in children with leukemia. This study on febrile neutropenia included the population with acute leukemias excluding those who received prior bone marrow transplantation. The present study included 38 patients with 53 febrile neutropenic episodes documented over a period of 1 year between Jan 2017 – December 2017. A retrospective study conducted by Timothy et al[16] in Trinidad & Tobago involved 36 subjects with 71 episodes of febrile neutropenia documented between 2001 – 2008.

Table 11: Study Comparison (1)

Parameters	**Present study**	**Timothy et al[16]**
Study period.	Jan 2017 – Dec 2017.	May 2001 – Apr 2008.
No. of subjects.	38.	36.
No. of neutropenic episodes.	53.	71.
Frequenc of previous febrile neutropenic episodes	1-5.	1-5.
ALL cases	76.3%	43.7%
Culture positivity	35.8%	8.5%
Mortality rates	23.7%	8.5%

The present study and the study conducted by Timothy et al on comparison showed almost equal number of subjects with more than one febrile neutropenic episodes among subjects

There was no subject of age <1 yr. There was almost an equal distribution between those less than 5yrs (52.6%) & more than 5yrs (47.4%) admitted with febrile neutropenia.Only 2 children were of age >10 yrs. However there was a higher mortality among children > 5yrs of age (44.44%) as against those < 5yrs of age (0.05%). The incidence of febrile neutropenia was more among females [55%] as compared to males [45%].

76% of the cases were ALL and AML contributed to around a quarter of the cases. Out of the 38 children admitted due to febrile neutropenia 9 expired which contributed to 23.7 % mortality. Among the 53 neutropenic episodes almost 73.5% had ALL. Among the 53 episodes 39.6% had grade one PEM. The initial ANC in 64.2% cases were - 300-400 & the lowest ANC in 41.5% was 0. Maximum mortality was observed in children who had febrile neutropenia in the relapse phase and this was statistically significant.

In a study conducted by santolaya et al[14] it was found that 60% of febrile neutropenic episodes were caused by bacterial infections with or without bacteremia. In another study conducted by Hughes W T, Armstrong D, Bodey G P et al[20] showed that clinically documented infections occurred in 20%–30% of febrile episodes; common sites of tissue-based infection include the intestinal tract, lung, and skin and bacteremia occurred in 10%–25% of all patients, with most episodes occurring in the setting of prolonged or profound neutropenia (ANC, 100 neutrophils/mm3).

Table 12 – Study Comparison (2)

Parameters	Present study	Santolaya et al
Study period	Jan 2017 – Dec 2017	May 2009 – Aug 2010
No. of febrile neutropenic episodes	53.	177.
Blood culture positivity	35.8%	16.8%
Most common organism grown	CONS & MRSA	E.coli & S.aureus.

In this present study, 39.6% had neutropenia lasting for more than 7 days. In 67.9% episodes of

febrile neutropenia, previous episodes were one to five. The more the previous neutropenic episodes the more was the mortality rate. However this was found to be statistically insignificant but clinically significant. Out of the documented 53 episodes of neutropenia among the 38 subjects 3 of those had more than 5 preceding neutropenic episodes. 36 of those episodes were preceded by around 1-4 previous neutropenic episodes and 14 of them had no previous episodes. Among the 2 out of 3 with more than 5 neutropenic episodes succumbed to the disease. 5 among the 36 episodes with between 1-5 neutropenic episodes expired.

However only 2 among those with no previous neutropenic episode died. However this correlation was statistically insignificant (p=0.07).38 subjects 15 were readmitted for similar episodes during the study period. In our study 62.7% had cough as the presenting symptom and the most common form of systemic infection was LRTI accounting for 34.2%. Hypotension and DIC were the most common complications noted.

Pain et al concluded that early in the development of cytotoxic chemotherapy, during the 1960s and 1970s, gram negative pathogens predominated. Then, during the 1980s and 1990s, gram-positive organisms became more common because of increased use of indwelling plastic venous catheters, which can allow for colonization by and entry of gram-positive skin flora as documented in the Hughes, Bodey et al[20] study. Currently, coagulase-negative staphylococci are the most common blood isolates in most centers (Kanamaru et al[21]) .

But in this study, culture positivity was found in 35.8% & in positive cultures CONS was grown in 53%.Other studies also had similar results with maximum cultures being sterile. A study by Alison G. Freifeld, Eric J. Bow, Kent A. Sepkowitz et al[18-19], said majority of patients who develop fever during neutropenia have no identifiable site of infection and no positive culture results. Increased mortality was observed in children who had culture positivity. This was clinically significant even though statistically insignificant .Culture was positive in nearly one-third of cases (19) with a mortality noted in 4 episodes as against 5 among the 34 culture negative cases.

Even though the most common organism grown was CONS, maximum mortality was seen with MRSA and pseudomonas infections. 34 neutropenic episodes among the 53(64%) were sterile. Among the culture positive cases majority grew CONS. Among them 2 cases of mortality were recorded. 1 case of MRSA expired and another case of mortality was associated with the growth of gram negative bacilli. 5 deaths had a sterile culture result.

Most of the children had febrile neutropenia while they were on cytosine arabinoside and daunorubicin. The majority of patients who develop fever during neutropenia have no identifiable site of infection and no positive culture results. Nonetheless, the Panel recommends that every patient with fever and neutropenia receive empirical antibiotic therapy urgently (ie, within 2 h) after presentation, because infection may progress rapidly in these patients. this was shown in the Hughes et al study. Our patients received Ceftazidime/ Netilmycin as the first line antibiotic in 79.3% cases.

The incidence of severe anaemia with Hb <7 g/dl during presentation was 50.9%.54.7% of children had a platelet count of less than 50,000. The death rate was found to be more in children who presented with severe anaemia and this was found to be statistically significant. There were 26 neutropenic episodes with haemoglobin >7gm/dl, among whom there was only one casualty. However among the remaining 27 episodes there were 8 casualties confirming a strong correlation between the low Hb values and mortality which was found to be statistically significant (p=<0.05).

The death rate was found to be more in children who presented with thrombocytopenia, however this was not found to be statistically significant. 29 neutropenic episodes were associated with a platelet count of <50000. Among these episodes

there were 7 instances of casualties. 24 episodes had platelet count above 50000 with only 2 casualties. The very same finding was seen in another study by Ozer H, Armitage JO, Bennett CL et al and Rolston KV[4,5]. A systemic review of literature showed that age, nutritional status, chemotherapy dose and intensity, low base line blood counts are all risk factors for greater mortality and morbidity.

21 of the neutropenic episodes lasted for > 7 days and was associated with 6 cases of mortality as against 3 cases of mortality among the 32 neutropenic episodes that lasted for less than 7 days. However this observation also turned out to be statistically insignificant. Nearly 41% of children (22) had a lowest ANC of zero and another 34% contributed for an ANC of around 100. 25% had ANC's above 200 throughout the episode. Most of the children were found to have grade 1 PEM (21) out of whom 4 died. Among the 14 episodes associated with grade 2 PEM there were 3 casualties. Though they were statistically insignificant it was noted that presence of PEM had an effect on the mortality benefit.

Conclusions

- From this study we analyzed the various parameters associated with febrile neutropenia in children.
- There was however a higher mortality among children more than 5 yrs of age admitted with febrile neutropenia.
- Although most of them were suffering from ALL in the induction phase, mortality rates were higher among patients with ALL in relapse.
- Respiratory complaints were the common manifestations in leukemic children presenting with febrile neutropenia, though in more than 60% the blood cultures were sterile.
- However among the positive cultures CONS was the most commonly grown organism, with MRSA, GNB, micrococci and pseudomonas contributing for the rest.
- Children with severe anaemia had an increased mortality rate
- Children who developed febrile neutropenia in the relapse phase had a higher mortality
- The association of certain parameters studied like low platelet count, presence of protein energy malnutrition, duration of neutropenic episodes, number of previous neutropenic episodes and culture positivity were statistically insignificant even though clinically significant. Probable reasons for the above could be a small sample size, only patients with severe febrile neutropenia were included, viral and fungal cultures were not done.
- These limitations need to be overcome and the study requires a larger sample size for achieving better statistically significant correlation.

Limitations

1. The study population was small.
2. Fungal and viral cultures not done.
3. Only severe febrile neutropenic patients were included in this study.

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