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Study of febrile neutropenia in aplastic anemia and hemato-oncological condition at tertiary care centre

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Abstract: Background: Febrile neutropenia (FN) is a common and potentially life-threatening complication of childhood cancer therapy. Patients with neutropenia are at a higher risk of acquiring infections compared to individuals with normal immune function. In severe cases, absolute neutrophil count (ANC) can be less than 500 per microliter. The aim of this study was to understand the clinical and etiological profile of febrile neutropenia in hemato-oncological and aplastic anemia patients in a tertiary care center in India and to determine the outcome of patients after starting empirical antibiotic therapy. Additionally, we aimed to formulate specific antibiotic therapy based on etiological data from our study.
Methodology: The study was conducted in the pediatric hemato-oncology department of a tertiary care center in India from March 2015 to September 2016. The study included 76 children aged between 1 month and 18 years diagnosed with febrile neutropenia in aplastic anemia and hemato-oncological patients. All febrile neutropenia patients received ceftriaxone and amikacin empirically according to the hospital protocol. Vancomycin was administered additionally to patients who had persistent fever, and fluconazole was initiated empirically in patients in whom fever persisted despite antibiotics on day 4 or 5. In culture-negative and stable patients, intravenous antibiotics were continued for 3 days or until ANC recovered to >500/μl. Bacterial pathogens in all samples yielding culture positivity were identified, and their antibiogram was recorded.
Results: The study found that febrile neutropenia occurs almost equally in all age groups, with a mean age of 6.2 $\pm$ 4.1 years. Males were predominantly affected, and the mean temperature was 101.7 $\pm$ 0.7350F. The mean ANC count was 257 $\pm$ 226.4 neutrophils/mm, and the mean duration of hospital stay was 6.7 $\pm$ 5.7 days. The respiratory system was the most commonly affected, followed by problems associated with the gastrointestinal tract. In other antibiotic therapies used for our patients empirically or according to the culture sensitivity, we found that the drugs used in decreasing order of frequency were piperacillin-tazobactam (14.4%), vancomycin (11.8%), metronidazole (10.5%), fluconazole (7.9%), meropenem (6.5%), and imipenem (2.6%), while linezolid, ciprofloxacin, and colistin were used in one patient each. Culture reports were positive in a total of 11 (14.5%) patients. No significant difference was found in mean ANC count, but a significant difference was found in the duration of hospital stay between culture-positive and culture-negative patients, with a difference of almost 10 days. The mortality rate was 2.6%.
Conclusion: Males were more commonly affected than females, and most patients presented with symptoms of the respiratory system, followed by the gastrointestinal and urinary tract systems. Most episodes of febrile neutropenia occurred during the induction phase of treatment of acute leukemia, with acute lymphoblastic leukemia being the most common malignancy followed by acute myeloid leukemia. Empirical therapy with ceftriaxone and amikacin leads to a satisfactory clinical outcome in febrile neutropenia. A significant difference was found in the duration of hospital stay between culture-positive and culture-negative patients, with a difference of almost 10 days between the two. The mortality rate in our study was found to be 2.6%.

Keywords: Neutropenia; Febrile; Anaemia; Hemato-oncology; Cancer therapy.

1. Introduction

Febrile neutropenia (FN) is a serious complication of childhood cancer therapy, which can be life-threatening. This condition increases susceptibility to infection due to chemotherapy-induced severe neutropenia, impaired innate and acquired immune responses, and disruption of physical immune defense barriers. Children are especially vulnerable to infections due to the detrimental effect of cytoreductive therapy on their developing immune system [1,2].

Patients with fever in severe chemotherapy-induced neutropenia are at a high risk for severe bacterial infections with poor outcomes if antibiotic therapy is delayed [3]. The appearance of fever with neutropenia during the treatment of hemato-oncological malignancies and aplastic anemia patients is the first manifestation of a potentially life-threatening bacterial infection. Prompt hospitalization of such patients and initiation of empirical intravenous therapy with broad-spectrum antibiotics has become the standard of care [4].

Despite significant advances in prevention and treatment, FN remains a concerning complication of cancer chemotherapy and a major cause of morbidity, healthcare resource use, and compromised efficacy resulting from delays and dose reductions in chemotherapy. However, with the widespread use of effective empirical antibiotics, the overall mortality rate has declined to approximately 1-3% for infections caused by gram-negative bacteria [4].

The choice of a specific antibiotic or combination of antibiotics is based on the specific pattern and frequency of bacterial infection at the institution, as well as antibiotic susceptibility profiles, cost, toxicity, and standards used at the center. As a consequence, the mortality rate related to FN has dramatically improved from 30% in the 1970s to 1% in the late 1990s [5].

Neutropenia, which constitutes the first line of the body's defense against diseases, is a common occurrence in cancer patients. The decline in the number of neutrophils associated with fever is known as febrile neutropenia (FN) and is considered an oncology emergency, which can lead to serious adverse consequences such as serious infection complications and death [6,7].

This study aims to understand the clinical and etiological profile of FN in hemato-oncological and aplastic anemia patients in a tertiary care center in India. There has been a scarcity of data about the clinic-etiological profile of FN from an Indian setup. This study will also examine the outcome of patients after starting empirical antibiotic therapy and help formulate specific antibiotic therapy based on the etiological data from our study.

2. Materials and Methods

This prospective observational study was conducted at the paediatric hemato oncological department of a tertiary care centre in Mumbai, India. The study was approved by the institutional ethics committee and was carried out from March 2015 to September 2016. The study enrolled a total of 76 patients who were aged from 1 month to 18 years and had febrile neutropenia in aplastic anemia and haemato-oncological patient including relapse cases. Neonates and those with non-oncological causes such as dengue, malaria, etc. were excluded from the study. Informed written consent was obtained from all patients.

Febrile neutropenia was diagnosed based on a single oral/axillary temperature of =38.3^{o}C (101^{o}F) or 38.0^{o}C (100.4^{o}F) for more than 1 hour, along with an absolute neutrophil count (ANC) =500/μl or =1000/μl with predicted rapid decline during the next 48 hours [8–10]. All febrile patients were evaluated for relevant history, physical examination, complete hemogram, liver function test, renal function test, serum electrolytes, and chest X-ray. Microbiological cultures of blood from peripheral vein, central line (if present), and urine were conducted routinely for all febrile episodes. Sputum, stool, and/or pus cultures were done when clinically indicated. Blood culture (two sets of blood culture, 5 ml each, one from central line and the other from peripheral line) was repeated every 48 hours if fever persisted.

Organisms were identified according to standard bacteriological procedures. All febrile neutropenia patients received ceftriaxone and amikacin empirically according to our hospital protocol. Once microbiological culture report was available, antibiotics were modified accordingly. However, in culture-negative patients, the same antibiotics were continued. Vancomycin was administered additionally to the patients who had persistent fever, and fluconazole was initiated empirically in patients in whom fever persisted despite antibiotics on day 4 or 5, in sinusitis with suspected fungal infection, pleuritic chest pain, or chest X-ray suggested presence of a fungal ball. In culture-negative and stable patients, intravenous antibiotics were continued for 3 days or until ANC recovered to >500/μl.

Bacterial pathogens in all samples yielding culture positivity were identified, and their antibiogram was recorded. Diagnosis, clinical features, chest X-ray findings, type of chemotherapy, duration of neutropenia, use of growth factor, culture positivity, antibiotic use, and outcome of febrile neutropenia were recorded for all patients. These outcomes were evaluated in terms of mortality, hospital stay, and recovery.

3. Statistical analysis

The data analysis was performed using SPSS software version 15 and Sigma plot version 12. A p-value of less than 0.05 was considered statistically significant. Descriptive statistics such as mean, standard deviation, median, and interquartile range were used to present quantitative data. Unpaired T-test was used to compare two study groups, while one-way ANOVA test was used for more than two groups, based on the normality test results. Qualitative data was presented using frequency and percentage tables. The association among various study parameters was assessed using the Chi-square test, and Fisher's exact test was used for 2×2 tables.

4. Results

4.1. Age group distribution

Febrile neutropenia was found to be evenly distributed across all age groups, with 28.95% of cases occurring in children aged 1 month to 3 years, 28.95% in those aged 3 to 6 years, 23.68% in those aged 6 to 9 years, and 18.42% in those above 9 years of age. The mean age of the 76 patients included in the study was 6.2 years, with a median age of 5 years (Table 1).

Table 1. Age wise distribution

Age (Years)	Percent
Up to 3 Years	28.95%
3 to 6 Years	28.95%
6 to 9 Years	23.68%
>9 Years	18.42%
Total	100.00%

4.2. Gender distribution of cases

In this study, the majority of patients were male, with 63 (82.89%) males and only 13 (17.11%) females, resulting in a male to female ratio of 4.84:1 (Table 2).

Table 2. Sex wise distribution

SEX	Percent
Male	82.89%
Female	17.11%
Total	100.00%

4.3. Type of cancer /hematological condition

Our study revealed that pre-B cell acute lymphoblastic leukemia (ALL) was the most common underlying diagnosis associated with febrile neutropenia, observed in 44 (57.89%) patients, followed by acute myeloid leukemia (AML) in 12 (15.79%) patients. Aplastic anemia and Hodgkin's lymphoma were observed in 4 (5.26%) patients each, while 3 (3.95%) patients had T cell ALL. Additionally, 2 (2.63%) patients had Wilms' tumor and hemophagocytic lymphohistiocytosis (HLH) each, and 1 (1.32%) patient each had Fanconi's anemia, hepatoblastoma, neuroblastoma, PNET, and rhabdomyosarcoma (Table 3).

Table 3. Type of cancer

Type of cancer/hematological condition	Percent
Pre B All	57.89%
AML	15.79%
Hodgkins lymphoma	5.26%
Aplastic anemia	5.26%
T Cell ALL	3.95%
HLH	2.63%
Wilms tumor	2.63%
Fanconis anemia	1.32%
Hepatoblastoma	1.32%
Neuroblastoma	1.32%
PNET	1.32%
Rhabdomyosarcoma	1.32%

4.4. No. of episodes of febrile neutropenia

The results of our study showed that among the 76 patients, 30 (39.47%) had experienced their first episode of febrile neutropenia, while 27 (35.53%) had a second episode, 10 (13.16%) had a third episode, 6 (7.89%) had a fourth episode, 2 (2.63%) had a fifth episode, and only one patient had experienced a sixth episode. These findings are summarized in Table 4.

Table 4. No of episodes

No. of episodes	Percent
1 ST	39.47%
2 ND	35.53%
3 RD	13.16%
4 TH	7.89%
5 TH	2.63%
6TH	1.32%
Total	100.00%

4.5. Clinical Presentation

The majority of patients with febrile neutropenia in our study presented with respiratory symptoms, accounting for 52 (68.42%) patients. Gastrointestinal symptoms were the second most common, with 24 (31.58%) patients presenting with such symptoms, while only 4 (5.26%) patients presented with symptoms of the urinary tract. Interestingly, none of the patients in our study presented with neurological manifestations (Table 5).

Table 5. Symptoms

Symptoms	Percent
Respiratory system	68.42%
GI System	31.58%
Urinary system	5.26%
CNS system	0.00%
Total	100%

4.6. Distribution of study group as per, chemotherapy received

In the present study, a majority of the patients, 63 (82.9%), had received chemotherapy, while 13 (17.1%) patients had not received chemotherapy. (Refer to Table 6 for details.)

Table 6. Chemotherapy received

Chemotherapy received	Percent
Yes	82.89%
No	17.11%
Total	100.00%

4.7. Distribution of study group as per, phases of chemotherapy

Among the 69 patients who received chemotherapy, 34 (49.3%) developed febrile neutropenia during induction phase, 12 (17.4%) during consolidation phase, 15 (21.7%) during maintenance phase, and 2 (2.9%) during pre-phase. The timing of febrile neutropenia was not documented for 6 patients. In contrast, all 7 patients who did not receive chemotherapy developed febrile neutropenia during the induction phase, (Table 7).

Table 7. Phase

Phase	Percent
	9.21%
Prephase	2.63%
Induction	48.68%
Consolidation	17.11%
Maintainance	22.37%
Total	100.00%

4.8. Antibiotics

In this study, all patients with febrile neutropenia were started empirically on Ceftriaxone and amikacin as per protocol. However, additional antimicrobial agents were required in some cases. Out of 76 patients, 11 (14.4%) required inj. piperacillin-tazobactum, 9 (11.8%) received vancomycin, 8 (10.5%) were treated with Metronidazole, 6 (7.9%) received Fluconazole, and 5 (6.5%) required Meropenam. Imipenam was required in two (2.6%) patients, while linezolid, ciplox, and colistin were each required in one patient according to their individual sensitivity pattern (Table 8).

Table 8. Antibiotic

Antibiotic	Percent
Ceftriaxone	100.00%
Amikacin	100.00%
Piptaz	14.47%
Vancomycin	11.84%
Flucon	7.89%
Metronidazole	10.53%
Meropenam	6.58%
Linezolid	1.32%
Imipenam	2.63%
Ciplox	1.32%
Colistin	1.32%

4.9. Distribution as per platelet count

In our study, we observed that 14 (18.42%) patients had a platelet count less than 10,000, while 18 (23.7%) patients had a platelet count between 10,000 to 25,000. Similarly, 12 (15.8%) patients had a platelet count between 25,000 to 50,000, 18 (23.7%) patients had a platelet count between 50,000 to 100,000, and 14 (18.4%) patients had a platelet count above 100,000. The median platelet count was 400,000 with a mean of 67,723 among the 76 patients studied (Table 9).

Table 9. Platelet

Platelet	Percent
<10000	18.42%
10000 to 25000	23.68%
25001 to 50000	15.79%
50001 to 1 lac	23.68%
>1 lac	18.42%
Total	100.00%

Table 10. Study Parameter

Study Parameter	N	Mean	Std. Dev	Median	IQR	Minimum	Maximum
Age (Years)	76	6.22	4.15	5.00	6.00	0.25	16.00
FEVER (F)	76	101.76	0.735	101.70	0.95	100	104
ANC	76	257.09	226.439	193.00	375.50	0	750
Duration of neutropenia (Days)	76	5.49	3.838	3.00	4.00	3	18
Duration of hospital stay (days)	**76**	**6.70**	**5.750**	**3.00**	**7.00**	**3**	**25**

Table 11. Study Parameter

Study Parameter	N	Mean	Std. Dev	Median
Hemoglobin	76	8.50	1.47	8.60
Platelet	76	67,723.00	84,890.000	40,000.00

4.10. Distribution of study group as per chest x-ray

In this study, out of the 76 patients, only 3 (4%) patients had chest x-ray findings suggestive of pneumonia, while the remaining 73 (96%) patients had a normal chest x-ray (Table 12).

Table 12. C-Xray

C-Xray	Percent
Pneumonia	3.95%
Normal	96.05%
Total	100.00%

4.11. Distribution as per USG abdomen+KUB

In this study, of the 76 patients evaluated, 24 presented with gastrointestinal symptoms. Among these patients, 3 (4%) were found to have ultrasonographic evidence of hepatomegaly with enterocolitis, 1 (1.3%) had bilateral enlarged echogenic kidneys, and 1 (1.3%) had moderate hepatomegaly, as shown in Table 13.

Table 13. USG ABDO+KUB

USG ABDO+KUB	Percent
B/L Enlarged echogenic kidneys	1.32%
Hepatomegaly with neutropeniccolitis	3.95%
Moderate hepatomegaly	1.32%
Normal	25.00%
Not done	68.42%
Total	100.00%

4.12. Distribution as per blood culture

In our study, we conducted blood culture on all patients, and found that 7 (9.2%) patients had positive cultures. Of these, 3 (4%) patients had grown coagulase-negative staphylococci, 2 (2.7%) patients had grown Pseudomonas aeruginosa, 1 (1.3%) patient had grown E. coli, and 1 (1.3%) patient had grown Salmonella typhi. Please see Tables 14 and 15 for further details.

Table 14. Total blood culture

Blood culture	Percent
Positive	9.21%
Negative	90.79%
Total	100.00%

Table 15. Blood culture

Blood culture	Percent
Cons	3.95%
E.Coli	1.32%
Pseudomonas aeuriginosa	2.63%
Salmonella typhi	1.32%
No growth	90.79%
Total	100.00%

4.13. Distribution of study group as per urine culture

Among the 76 patients included in our study, 4 (5.3%) had positive urine culture results. Specifically, two patients had pseudomonas aeruginosa growth, one patient had E. coli growth, and one patient had enterococcus organism growth. Please refer to Tables 16 and 17 for further details.

Table 16. Total urine culture

Urine culture	Percent
Positive	5.26%
Negative	94.74%
Total	100.00%

Table 17. Urine culture

Urine culture	Percent
E. Coli	1.32%
Enterococcus	1.32%
Pseudomonas	2.63%
No growth	94.74%
Total	100.00%

4.14. Distribution of study group as per types of organism

In the present study, among the 76 patients, 11 patients showed positive culture results. Among these patients, gram-negative organisms were identified in 7 cases (63.7%) while gram-positive organisms were identified in 4 cases (36.3%) (Table 18).

Table 18. Type of Organisms

Organisms	Blood culture	Urine culture	Total	Percent
Gram Positive	3	1	4	36.30%
Gram Negative	4	3	7	63.70%
Total				100%

4.15. Comparison of fever among study groups

In our study, we conducted a comparison of fever in patients with culture-positive and culture-negative results. The results showed that the mean fever in patients with culture-positive results was 102.1, while the mean fever in patients with culture-negative results was 101.1. However, the difference between the two means was found to be statistically insignificant (Table 19).

Table 19. Comparison of fever

Culture	Mean	Std. Deviation	Unpaired T test	P Value
Positive	102.15	0.67	1.951	0.055
Negative	101.70	0.73	Difference is not significant	

4.16. Comparison of ANC among study groups

We conducted a comparison between patients with culture positive and negative results and their ANC levels in our study. The mean ANC in patients with culture positive results was 168.7, while it was 272 in patients with culture negative results. However, this difference was not found to be significant. (See Table 20 for details.)

Table 20. Comparison of NAC

Culture	Mean	Std. Deviation	Unpaired T test	P Value
Positive	168.73	173.25	-1.409	0.163
Negative	272.05	232.01	Difference is not significant	

4.17. Comparison of duration of hospital stay among study groups

In this study, we analyzed and compared the duration of hospital stay between patients with positive culture results and those with negative culture results. The mean duration of hospital stay for culture-positive patients was 15.09 days, while for culture-negative patients, it was 5.28 days. The difference between the two groups was found to be statistically significant, indicating that culture-positive patients had a longer hospital stay compared to culture-negative patients, (Table 21).

Table 21. Comparison of duration of hospital stay

Culture	Mean	Std. Deviation	Unpaired T test	P Value
Positive	15.09	6.38	6.527	0.000
Negative	5.28	4.27	Difference is significant	

4.18. Comparison of ANC with platelet count

In Table 22, ANC with Mean & SD for analysing by one way ANOVA is significant with P<0.01.

Table 22. Comparison of ANC with platelet count

ANC	Mean	Std. Deviation	One way ANOVA test	
<10000	139.79	181.61	F Value	P-Value
10000 to 25000	246.39	226.55	3.683	0.009
25001 to 50000	290.83	216.44	Difference is significant	
50001 to 1 lac	204.61	190.75		
>1 lac	426.71	240.14		
Total	257.09	226.44		

4.19. Distribution of study group as per, outcome

In the present study, we analyzed the outcome of 76 patients, where 2 patients (2.7%) died and 74 patients (97.3%) were discharged, (Table 23).

Table 23. Outcome

Outcome	Percent
Dearth	2.63%
Discharge	97.37%
Total	100.00%

4.20. Comparison of outcome among study

In this study, the outcome was compared between patients with positive and negative cultures. It was found that 2 (18.2%) patients died and 9 (81.8%) were discharged in the group with positive cultures, while all patients in the negative culture group were discharged. The difference between the two groups was found to be significant with a significant p-value, (Table 24).

Table 24. Culture outcome

	Outcome		Total
Culture	Death	Discharge	
Positive	18.2%	81.8%	100.0%
Negative	0.0%	100.0%	100.0%
Total	2	74	76
	2.6%	97.4%	100.0%

Chi-Square test	df	P Value	Association is
Pearson Chi-Square	1	0.000	Sig
Fisher's Exact Test		0.019	Sig

5. Discussion

Febrile neutropenia is a life-threatening complication of hemato-oncological conditions, making it crucial to understand its clinical profile, etiology, and treatment outcomes. This study aims to review these aspects in patients with febrile neutropenia and aplastic anemia or hemato-oncological diseases.

Our study revealed that febrile neutropenia affects all age groups almost equally, with a mean age of 6.2 years and a median age of 5 years. Our findings are consistent with those of previous studies, including M.E. Santoliya *et al.,* [11] from Santiago, Chile, who reported a mean age of 7 years (range 7 months to 17 years), and Zarina Latiff *et al.,* [12] from Malaysia, who reported a mean age of 6.5 years and a median of 6 years. In terms of gender distribution, our study showed that 82.89% of patients were male, while 17.11% were female, with a male-to-female ratio of 4.84:1. This observation is consistent with previous studies from Karachi [13] and Maharashtra [14] that reported male predominance in febrile neutropenia cases.

Regarding the etiology of febrile neutropenia, our study found that pre-B cell acute lymphoblastic leukemia (44 patients, 57.89%) was the most common underlying disease, followed by acute myeloid leukemia (12 patients, 15.79%), aplastic anemia, and Hodgkin's lymphoma (4 patients each, 5.26%). Other diseases such as T-cell acute lymphoblastic leukemia, Wilms' tumor, and hemophagocytic lymphohistiocytosis accounted for 3.95% and below. These results are similar to those of previous studies conducted worldwide, such as those by Santoliya *et al.,* [11], Kuntegowdanahalli C Lakshmaiah *et al.,* [14], Timothy M. *et al.,* [15], Alam *et al.,* [16], and Elio Castagnola *et al.,* [14].

In terms of clinical presentation, our study showed that most patients (68.42%) presented with respiratory symptoms, while 31.58% presented with gastrointestinal symptoms. Only 5.26% of patients presented with symptoms of the skin and soft tissue. This finding is consistent with previous studies conducted worldwide, indicating that respiratory symptoms are the most common clinical presentation in patients with febrile neutropenia.

In our study, we observed that 5 out of 24 patients with GI symptoms had abnormalities on ultrasonography report of abdomen and KUB. These abnormalities included neutropenic enterocolitis in 3 patients, bilateral echogenic kidneys in 1 patient, and moderate hepatomegaly in 1 patient. Prasad M *et al.,* [17] reported that the focus of infection in febrile neutropenia was primarily found in the lung (41.4%), sinus/oral cavity (14.2%), skin/soft tissue (14.2%), intra-abdominal (10%), perianal (7.1%), catheter (4.2%),

and others. Our findings were similar to a study conducted by Nihal Ozdemir *et al.,* [18] from Istanbul, which reported that the cause of febrile neutropenia in 50% of cases was fever of unknown origin. The focus of infection was clinically defined in 66 patients (22%) (excluding bacteraemia), with pulmonary infection found in 25 patients (38%), gastrointestinal infection in 19 patients (29%), urinary tract infection in 12 patients (18%), otolaryngological or dental infection in 6 patients (9%), dermatological and soft tissue infection in three patients (4.5%), and meningitis in one patient (1.5%).

Chemotherapy is the mainstay of management for most cancers. In our study, 63 (82.9%) patients had received chemotherapy, while 13 (17.1%) had not. Patients who had not received chemotherapy included those with diagnoses of aplastic anemia, Fanconi's anemia, and HLH. Among patients who developed febrile neutropenia, 52 (68.4%) had received chemotherapy within the last 10 days, and 24 (31.6%) had not received chemotherapy in the last 10 days. Our findings suggest that the majority of patients with febrile neutropenia episodes experience them immediately after receiving chemotherapy. Additionally, most patients developed febrile neutropenia during the induction phase (48.7%) of chemotherapy, followed by the maintenance phase (22.4%), consolidation phase (17.1%), and pre-phase (2.7%). Elio Castagnola *et al.,* [19] found that the highest proportion of neutropenic periods occurred during aggressive treatment for acute leukemia or non-Hodgkin lymphoma (48%), and allogeneic hemopoietic stem cell transplantation (44%); the lowest proportion (9%) was observed during maintenance chemotherapy for acute leukemia. Other reports have also shown that febrile neutropenia occurs more commonly during induction chemotherapy than during consolidation and maintenance chemotherapy [20,21].

In our study, we started all patients empirically on ceftriaxone and amikacin. However, out of the 76 patients, 11 (14.4%) required piperacillin-tazobactam, 9 (11.8%) received vancomycin, 8 (10.5%) received metronidazole, 6 (7.9%) received fluconazole, and 5 (6.5%) received meropenem. Imipenem was required in two (2.6%) patients, while linezolid, ciprofloxacin, and colistin were each required in one patient based on sensitivity pattern of positive culture reports. From our study, we can conclude that most patients responded well to ceftriaxone and amikacin, with few patients requiring a change in antibiotics. Therefore, the combination of ceftriaxone and amikacin appears to be a good first-line empirical therapy in our institute. However, it is important to note that sensitivity patterns may differ among institutions, and it is wise to devise a hospital-based therapy. Studies have shown that different institutes use different antibiotics based on their sensitivity patterns. For example, Kuntegowdanahalli C Lakshmaiah et al. [14] conducted a study on cancer patients and found that cefoperazone-sulbactam was effective as a first-line empirical antibiotic. Similarly, Shogo Kobayashi et al. [22] conducted a study on febrile neutropenic patients in children and recommended empirical first-line antibiotics (cefepime or cefozopran + piperacillin + amikacin) in 206 (82%) cases, second-line antibiotics (piperacillin-tazobactam + carbapenem + amikacin + micafungin) in 73 (29%) cases, and third-line antibiotics (meropenem + glycopeptides + micafungin) in 24 (10%) cases. The overall response rates were 71.4%, 50.7%, and 62.5% for the first, second, and third-line antibiotic therapies, respectively.

In our study, we analyzed various blood parameters, including hemoglobin, platelet count, ANC count, temperature, duration of hospital stay, and duration of neutropenia. The mean hemoglobin was 8.5 g/dL, mean platelet count was 67,273/mm3, mean temperature was 101.70 F, mean ANC was 257 neutrophils/mm3, mean duration of hospital stay was 6.7 days, and mean duration of neutropenia was 5.5 days. In comparison, Santolaya et al. [11] reported a mean ANC (SD) of 190±173 neutrophils/mm3 and a mean temperature of 38.7^{o}C±0.5^{o}C in their study conducted in Chile.

In our study, all patients with febrile neutropenic episodes were admitted, and blood cultures were sent. Empirical treatment with ceftriaxone and amikacin was initiated. Out of 76 patients, 11 (14.5%) were culture-positive, with 7 (9.2%) having positive blood cultures and 5 (5.3%) having positive urine cultures. In 65 (85.5%) patients, no focus of infection was identified. Among the culture-positive patients, 7 (63.7%) had grown gram-negative organisms like Pseudomonas aeruginosa, Escherichia coli, and Salmonella typhi, while 4 (36.3%) had grown gram-positive organisms like coagulase-negative Staphylococci and Enterococcus. Our study shows that clinically documented infections, which are culture-positive, are seen in 11 (14.5%) patients, with gram-negative organisms (63.7%) being predominantly isolated from the culture, consistent with other studies worldwide.

A similar study conducted by M. E. Santolaya *et al.,* [11] from Chile reported that the most common organisms recovered were E. coli, S. aureus, coagulase-negative Staphylococcus species, and Klebsiella species.

Elio Castagnola, *et al.*, [19] reported that fever of unknown origin was the most frequent clinical diagnosis (in 79% of cases), followed by bacteremia (10%); invasive mycosis was diagnosed in only 2% of cases. Another study conducted by Bhojraja *et al.,* from India reported that the majority of organisms were gram-negative (52%), followed by gram-positive (40%), and 8% had fungal aetiology. The most common organism isolated was E. coli and coagulase-negative Staphylococcal aureus (CONS) in six episodes each, ESBL E. coli (extended spectrum beta-lactamases Escherichia coli) in three episodes; Methicillin-resistant Staphylococcus aureus (MRSA), Pseudomonas, Klebsiella and Candida species in two episodes each; Proteus vulgaris and Alpha haemolytic streptococci were found in one episode each. Kuntegowdanahalli C. Lakshmaiah *et al.,* [14] found that the most common organisms isolated were Gram-negative bacilli (63.64%), with Escherichia coli being the most frequent pathogen followed by Gram-positive cocci (GPC) (36.36%). The overall culture positivity was 29.62%.

Regarding our study, we compared the temperature of patients with culture-positive and culture-negative patients and found that the mean temperature was 102.1oF, which was higher in culture-positive patients as compared to the culture-negative patients, in which the mean temperature was 101.7oF. However, the p-value difference was not significant. We also compared the absolute neutrophil count (ANC) in culture-positive and culture-negative patients and found that the mean ANC in culture-positive patients was 168.7, whereas it was 272 in culture-negative patients. Although the ANC count was lower in culture-positive patients compared to culture-negative patients, the p-value difference was not significant.

We conducted a comparison of the duration of hospital stays between patients who tested positive for a culture and those who tested negative. We found that the mean duration of hospital stay for culture positive patients was 15.09 days, while it was 5.28 days for culture negative patients. Moreover, our analysis revealed that the difference in p-values was statistically significant.

In addition, we evaluated the outcome of patients with febrile neutropenia, specifically in terms of death or discharge. Our study showed that out of 76 patients, two (2.7%) patients died, while the remaining 74 (97.3%) were discharged. We further analyzed the death and discharge rates among patients who tested positive and negative for a culture. Among the 11 culture positive patients, two (18.2%) died, while the remaining nine (81.8%) were discharged. In contrast, all 65 culture negative patients were discharged. Our findings are consistent with the literature from various parts of the world, such as Bhojraja *et al.*, who reported a mortality rate of 13.75% in their study, and a study by Bothra M *et al.* that showed mortality occurred in 8 (5%) of patients.

6. Conclusion

In conclusion, this study sheds light on the clinical and investigative profile of children with febrile neutropenia. Our findings indicate that respiratory symptoms were the most commonly presented, followed by gastrointestinal and urinary tract symptoms. Acute lymphoblastic leukemia was the most common malignancy associated with febrile neutropenia, and most episodes occurred during the induction phase of treatment. Gram-negative bacteria, particularly Pseudomonas aeruginosa, were the predominant organisms, while coagulase-negative S. aureus was the most common gram-positive organism.

We also found that empirical therapy with ceftriaxone and amikacin resulted in satisfactory clinical outcomes, and the indiscriminate use of higher antibiotics must be avoided. Our study revealed a statistically significant difference in the duration of hospital stay between culture-positive and culture-negative patients, with culture-positive patients staying almost 10 days longer in the hospital. Additionally, the mortality rate was 2.6%, and all patients who died had positive cultures, with Pseudomonas sepsis being the cause of death.

Overall, our study highlights the importance of early identification of febrile neutropenia and the need for effective antibiotic therapy. Our findings could help in developing better strategies for the management of febrile neutropenia in children.

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