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Original Research Article

Study of Clinical and Microbiological Profile of Febrile Neutropenia in Adult Patients in Hematolymphoid Malignancies in Tertiary Care Centre

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Abstract

Introduction: Febrile neutropenia is a haematological emergency which develops as a result of treatment of haematological malignancies. The literature shows that life threatening infection is observed in 48 to 60% of patients with febrile Neutropenia. Cancer patients receiving antineoplastic therapy are susceptible to be adversely affected by chemotherapy-induced side effects such as myelosuppression or mucositis, which make them at risk for bacterial and fungal infections.

Material and Methods: This was cross sectional, observational, Descriptive study conducted in tertiary care centre & teaching institute. The study period was from March 2019 to March 2021. The present study included 100 patients with adult hemato-lymphoid malignancies who were receiving chemotherapy and who had developed febrile neutropenia.

Results: In this study majority of the patients were middle aged. Males were seen to be affected more than female. Fever and weakness was the common presentation of febrile neutropenic patients. A large number of patients were presented with clinical signs and symptoms suggestive of respiratory system involvement. Duration of neutropenia and fever were significantly associated with outcome. Gram negative infections especially pseudomonas aeruginosa species was a common cause of febrile neutropenia. The cases of AML and Hodgkin's lymphoma were common in the present study. In our study 16% patients died during the course of treatment.

Conclusion: Since inflammatory response is muted in neutropenic patients, a fever may be the earliest and the only sign of infection. It is, therefore, critical to recognize fever early in neutropenic patients and to initiate Empirical antibacterial therapy promptly to avoid progression to sepsis syndrome and possibly death.

Keywords: FN, Febrile Neutropenia, Chemotherapy, Hematolymphoid Malignancy, Sepsis Syndrome.

Introduction

Febrile neutropenia is a hematological emergency which develops as a result of treatment of hematological malignancies. The literature shows that life threatening infection is observed in 48 to 60% of patients with febrile Neutropenia [1]. Cancer patients receiving antineoplastic therapy are susceptible to be adversely affected by chemotherapy-induced side effects such as myelo suppression or mucositis, which make them at risk for bacterial and fungal infections. Since inflammatory response is muted in neutropenic patients, a fever may be the earliest and the only sign of infection. It is, therefore, critical to recognize fever early in neutropenic patients and to initiate antibacterial therapy promptly to avoid progression to sepsis syndrome and possibly death [2].

Febrile neutropenia (FN) prolongs hospital stay, increases health care costs, and compromises chemotherapy efficacy due to delays and dose reductions. Prompt initiation of adequate antimicrobial therapy is the backbone of FN treatment [3]. It is estimated to cause life-threatening events in 48–60% of patients. Empiric use of antibiotics has declined mortality due to febrile neutropenia from 75 to 10%[4].An infectious aetiology is documented in 30– 60% of the febrile neutropenia episodes in the setting of haematological malignancies; bacteremia being most common accounting for up to 25% of the cases [5]. Mortality rate as high as 11% is documented due to febrile neutropenia in some haematologic malignancies [6].

However, in recent years a trend back towards the higher incidence of gram-negative infection and sepsis has evolved due to the emergence of antibiotic resistance gram negative bugs [7]. In reality, despite availability of different international guidelines such as the Infectious Diseases Society of America (IDSA) and the 2013 American Society of Clinical Oncology (ASCO) guidelines, we are still facing many challenges in the management of patients with FN [8]. There are very few comprehensive reports available on FN incidence rate, complication, and its routine management. So, the present study was designed to determine precisely how FN is managed and what the characteristics of FN patients have and also risk factors associated with FN development.

Material & Methods

This was cross sectional, observational and descriptive study conducted in tertiary care centre & teaching institute, the study period was from March 2019 to March 2021. The present study included 100 patients with adult hemato-lymphoid malignancies who were on active chemotherapy,who had received chemotherapy previously and who had developed febrile neutropenia.This study was started after getting valid written permission from institutional ethical committee, total 100 patients of hematological malignancies with febrile Neutropenia were included in this study, inclusion criteria were Patients with hematological malignancies with single oral Temperature greater than or equal 100.4 ^{0} F (≥38.0°C) for greater than or equal to 1 hour or twice in 24 hours period or Any temperature greater than or equal to 101^0 F(≥38.3°C) , Patients with ANC less than 1500 cells/microliter, Patients more than or equal to 18 years of age. Exclusion criteria were Patients without fever on examination or by history, Patients with ANC more than 1500 cells/microliter and Patients not willing and refused to give consent.

Detail Procedure of study

After applying inclusion and exclusion criteria and after taking written valid informed consent study patients were enrolled. Data was collected using proforma.

Febrile Neutropenia was defined by the following criteria a single oral temperature measurement of greater than or equal to 101^0 F(≥38.3°C) or temperature greater than or equal to 100.4 ^{0} F (≥38.0°C) for 1 hour with ANC less than 500/cubic mm or ANC that was expected to decrease to less than 500/cubic mm during the next 48 hours. All febrile neutropenic patients with adult hematological malignancies were investigated for Complete Blood Count, Peripheral blood smear, Absolute Neutrophil Count, Liver function test, liver serum enzymes, Random Blood Sugar, Kidney function tests,serum electrolytes, Blood culture and sensitivity, Urine, sputum and pus samples whenever indicated, Chest x-ray, USG Abdomen & pelvis. Blood/urine/sputum/throat swab/pus specimens were collected whenever needed, skin lesions were cleaned with sterile normal saline and cotton. The crusts were removed with sterile needle.

The oozing pus was collected by 2 sterile cotton swab ram staining microscopy and culture and sensitivity and was done in required cases.Empirical antibiotics were used as per institutional antibiotic policy till the blood culture reports are available and then accordingly depending on the blood culture and sensitivity reports specific antibiotics were used. Complete blood count, routine investigations, any other required investigations and vitals were monitored.all aseptic precautions were taken. Temperature charting was repeated daily till the patients remains admitted in hospital or discharge or death.

Results

In our study Maximum study patients (22%) were from 18 to 30 and 31 to 40 years age group. The mean age and standard deviation of study patients was 46.11 ± 16.80. Males were 75% while females were 25% among all study patients.

Table 1: Distribution of patients according to clinical features.

Clinical Features	Number of patients (N)	Percentage (%)
Fever	100	100
Diarrhea	24	24
Vomiting	17	17
Weakness	35	35
Altered sensorium	11	11
Burning Micturition	19	19
Vertigo	16	16
Bleeding	19	19
Infection	7	7
Respiratory symptoms	32	32
Splenomegaly	18	18
Hepatomegaly	14	14

In this study all patients (100%) had fever, 24% were presented with diarrhea,17% were with vomiting, 35% had weakness, 11% were with altered sensorium, 19% had burning micturition, 16% felt vertigo, 19% had bleeding, 7% had infection, 32% presented with respiratory infections, 18% had splenomegaly, while 14% had hepatomegaly. on distribution of our study patients according to duration of neutropenia and fever we observed that 57% study patients had

neutropenia for less than 13 days while 43% had neutropenia for more than 13 days. While 58% had fever for less than 5 days and 42% had fever for more than 5 days.

In our study we found chest X-ray findings of LRTI in 31% of cases.

Table 2: Distribution of patients according to bacteria isolated on culture and antibiotics used

Bacteria Isolated	Number of cases (N)	Percentage (%)	Antibiotics used
Pseudomonas Aeruginosa	21	21	ceftazidime + Amikacin
Escherichia coli	15	15	Meropenam
Acinetobacter spp	9	9	Colistin
Klebsiella spp	20	20	Meropenam
Staphylococcus Aureus	4	4	Vancomycin
MRSA	4	4	Linezolid

In our study We found that 8% culture report shown gram positive bacteria, 65% shown gram negative bacteria while 27% reports were sterile

Table 3: Distribution of Patients according to diagnosis

Diagnosis	Number of cases (N)	Percentage (%)
ALL	14	14
AML	22	22
Burkitt's Lymphoma	2	2
CLL	11	11
DLBCL	20	20
HCL	2	2
Hodgkin's Lymphoma	29	29

In our study distribution of patients according hemolymphoid malignancies we observed that 22% of patients were of AML, followed by 20% cases of DLBCL, ALL cases were 14%, CLL cases were 11%, Hodgkins lymphoma cases were 29%, Burkitt's lymphoma and HCL cases were 2% each respectively. The patients in our study on active chemotherapy were 77% while 23% taken chemotherapy previously, Among all patients in our study patients 16% patients died during the course of treatment.

Discussion

In the present study of 100 patients we have studied the clinical and microbiological profile of febrile neutropenia in adult hemolymphoid malignancies. After distribution of study patients according to age we found that maximum study patients (22%) were from 18 to 30 and 31 to 40 years age group. Followed by 17% from 41 to 50 years age group.16% patients were from 51 to 60 years age group, 14% from 61 to 70 years age group and 9% were from more than 70 years age group.

The mean age of study population was 46.11 while median was 45. In the similar study done by Jacob LA *et al* 16 patients (29%) were aged 50 years or above. Taj M *et al* observed that the mean age of study population was 28.57 years while median was 20.Ghosh I *et al* stated that the median age was 33 years (range,8–70 years). Parodi R *et al* in their study observed that the mean age of study patients was 49 with range 34 to 60 years. Jamal A *et al* observed that mean age was 30.1 years. In our study males were

75% and females were 25%. Jacob LA *et al* in their study included 51% males and 49% females. In the study of Taj M *et al* 69% were males and 31% were females. Ghosh I *et al* included 148 males and 52 females out of 200 study patients. Parodi RL *et al* included 288 males and 227 females in their study. Jamal A *et al* study had included 61 males and 49 females.

In this study the most commonly seen clinical feature was fever. It was present in 100% study patients, Followed by weakness (35%) and respiratory symptoms (32%), Diarrhea in 24%, burning micturition in 19%, bleeding in 19%, splenomegaly in 18%,hepatomegaly in 14%, altered sensorium in 11% while infection was seen in 7% study patients. Taj M *et al* in their study observed that most frequent signs and symptoms at presentation were fever and generalized weakness followed by gastrointestinal and respiratory symptoms. Karimi *et al* performed general physical examination for all patients by emphasizing on sites most likely to be infected, including the skin, catheter sites, teeth, oropharynx and gingival surfaces, sinuses, lungs, abdomen, genitals, and perianal area.

Kapoor R *et al* analyzed the symptoms and revealed that 32% study patients had respiratory symptoms (cough,running nose, sore throat, breathlessness, and occasionally pleuritic chest pain) along with fever. About 8% study patients had symptoms involving the gastrointestinal tract in the form of nausea, vomiting, diarrhea, anorexia, and pain in abdomen. However, most patients had vague symptoms such as lethargy, irritability, polyarthralgia and bodyache. We had done laboratory investigations of all patients and we observed that mean and SD of HB was 6.35 ± 1.076, on urine routine pus cell PHPF was 38 ± 9.315, serum bilirubin was 0.87 ± 0.06, AST was 40.67 ± 6.197, ALT was 36.86 ± 4.71, alkaline phosphatase was 96.97 ± 28.62, blood urea was 34.79 ± 2.955, serum creatinine was 0.95 ± 0.45, platelet was 76605 ± 14349, TLC was 778 ± 150.3, ANC was 234.1 ± 112.8. Taj M *et al* in their research found that Mean haemoglobin was 9.3, mean absolute neutrophil count (ANC) was 0.96, and mean platelet count was 56 at the time of presentation.

Krishnamani K *et al* in the similar study stated that there was a significant association noted between mean serum bilirubin and outcome. Higher deaths were seen in patients having mean serum bilirubin more than 1.5 mg% (P = 0.000), odds ratio: 20.139). A mean serum creatinine >1.2 mg% resulted in higher deaths with statistical significance (16% vs. 1%) (P =0.000), odds ratio: 19.365 (95% confidence interval [CI] of mean: 4.066– 92.237). With regard to serum albumin there was no association with outcomes. Kapoor R *et al* in their study observed that, 4% study patients had profound neutropenia (ANC <100) while 58% of study patients had ANC more than 300. Only 10% of the study patients admitted with FN had associated severe anemia (<7.0 g/dl). Karimi F *et al* stated that the majority of patients suffered from severe neutropenia (ANC <500 cells/μL) with a mean neutrophil count of 0.30 ± 0.11 × 109/L. On distribution of study patients according to duration of neutropenia and fever we observed that 57% study patients had neutropenia for less than 13 days while 43% had neutropenia for more than 13 days. While 58% had fever for less than 5 days and 42% fever for more than 5 days. After correlating this duration with outcome we found that it was highly significant p value 0.0001. Similar findings were mentioned by Ghosh I *et al* in their study,they stated that there was significant association between duration of neutropenia and fever with outcome (p value 0.001). Karimi F *et al* observed that median duration of neutropenia (defined as an ANC <500 cells/μL) was 4 days, and the median duration of febrile episodes was 1 day.

While Kumar A *et al* concluded that there was negative correlation between duration of Neutropenia and fever. In patients with prolonged neutropenia, the duration of fever was also prolonged. In our study We found that 8% culture report shown gram positive bacteria, 65% shown gram negative bacteria while 27% reports were sterile. Kumar A *et al* observed that out of all positive cultures 70% was gram negative species, 28% were gram positive species.

Lakshmaiah KC *et al* observed that out of all positive cultures 63.64% were gram negative species while 36.36% were gram positive species. Cortés JA *et al* in their study observed that 52 Gram negative bacilli (46.4%) and 43 Gram-positive cocci (38.4%).Jamal A *et al* in their study stated that out of 163 microbiologically proven infectious episodes, gram-negative organisms accounted for 79% of infections whereas; gram positive organisms comprised 21% of all the infections. Jacob LA *et al* in their study observed that 56.25% of the positive cultures yielded Gram negative bacteria, 31.25% Gram positive and 12.5% mixed (both Gram positive and Gram negative). In our study we found that Pseudomonas aeruginosa accounted for infection in 21% cases and treated by ceftazidime + Amikacin, Eschericia coli accounted for 15% cases and treated by Meropenam, Acinetobacter accounted for 9% and treated by Colistin, Klebsiella accounted for 20% and treated by Meropenam, Staphylococcus aureus accounted for 4% and treated by Vancomycin while MRSA accounted for infection in 4% cases and treated by Linezolid. Jacob LA *et al* in their study observed that Among Gram negative isolates,100% sensitivity was observed for imipenem followed by meropenem and piperacillin+tazobactam (91.67%). 83.3% of the isolates were sensitive to cefoperazone+sulbactam and amikacin. Least sensitivity was observed for ceftazidime and cefotaxime (50%). Two (66.7%) of the *Klebsiella* and one of the *E. coli* (33.3%) isolates were extended spectrum beta lactamase (ESBL) producers.

Among Gram positive bacteria, both the isolates of Enterococci were resistant to Amikacin whereas the single Methicillin resistant *S. aureus* (MRSA) isolate was sensitive. All the Gram positive isolates were sensitive to linezolid, teicoplanin, and vancomycin. Taj M *et al* in their study observed that gram negative cultures included 27 Escherichia coli (40%), 12 Klebsiella pneumoniae (17.6%), 8 Klebsiella spp. (12%), 10 Pseudomonas aeruginosa (14.7%), and 8 Pseudomonas spp. (12%). Gram positive isolates had 8 Staphylococcus aureus (66%) out of which 4 were Methicillin resistant Staphylococcus aureus (MRSA) and 2 were Methicillin sensitive Staphylococcus aureus (MSSA), however 02 Vancomycin resistant Enterococci (VRE) were also isolated. The Escherichia coli strains were sensitive to piperacillin+tazobactam (48%), amikacin (88%), and carbapenem group (66.6%) while it was exhibiting very good sensitivity to cefoperazone+sulbactam (96%). Klebsiella pneumonia was 41% sensitive to piperacillin+tazobactam and 50% to amikacin. Klebsiella species was 87% sensitive to both piperacillin+tazobactam and amikacin. Pseudomonas aeruginosa was 100% sensitive to piperacillin+tazobactam and amikacin while Pseudomonas species was 75% sensitive to piperacillin+tazobactam and 50% to amikacin.

Among Gram positive isolates MRSA was 100% sensitive to vancomycin; however, 02 cases of vancomycin resistant enterococci were documented. Other routine Gram negative microorganisms were showing routine sensitivity pattern. Ghosh I *et al* in their study observed that Common Gram-negative organisms were Pseudomonas aeruginosa (12), Eschericia coli (11),

Acinetobacter spp. (10), and Klebsiella pneumoniae (10).Common Gram-positive bacteria were Staphylococcus aureus (Total-20, methicillin resistant-4), coagulase-negative staphylococcus (6), and Entercoccus spp. (8).

Highest sensitivity was seen to cefoperazone+sulbactam (84.1%), followed by piperacillin+tazobactam (65.9%), imipenem (63.7%), meropenem (59.1%), amikacin (48.8%), ticarcillin+clavulanate (44.7%), ciprofloxacin (39%), and amoxicillin+clavulanate (25%).Cortes JA *et al* in their study observed that The most frequent isolate was Escherichia coli (21) isolates in urine and 13 isolates in blood cultures, followed by Staphylococcus aureus (7 isolates in blood cultures) and Klebsiella pneumoniae (5 isolates in blood and 3 in urine cultures). Lakshmaiah KC *et al* in their study observed that Among Gram negative infections, Escherichia coli was the most common isolate (32.14%) followed by Klebsiella pneumoniae, Acinetobacter baumannii and Pseudomonas aeruginosa (25%, 21.43%, and 17.86%) respectively. Staphylococcus aureus was the most common isolate amongst Gram positive infections (three were methicillin resistant S. aureus [MRSA]).

Blood culture was positive in 21/108 (65.62% of all culture positive) episodes. In blood culture, 12 and 9 isolates were GNB and GPC respectively. GPC accounted for 42.86% of blood stream infection with S. aureus being the most common isolate. Sputum culture was positive in 7/108 (7.41%) of FN episodes. The most common isolate in sputum was P. aeruginosa and E. coli followed by K. pneumoniae, A. baumannii and S. aureus. Fungi were isolated in four sputum samples with two samples yielding Aspergillus species and two Candida species. No bacterial pathogens were isolated from urine. The antibiotic sensitivity among GNB was highest for imipenem (100%), followed by pipercillin+tazobactum (86.95%). Most of the E. coli isolates were resistant to cefoperazone+sulbactum, piperacillin+tazobactum. Gram positive isolates including MRSA were uniformly sensitive to vancomycin, teicoplanin, linezolid and levofloxacin.

With first line antibiotic (cefoperazone+sulbactum), 68.5% FN episodes showed an improvement, 26% episodes improved with second line (piperacillin+tazobactum with amikacin), another 5.5% required third line antibiotics (imipenem/cilastin or meropenem).

Additional vancomycin was required in 14.5% FN episodes, while 17% episodes required addition of antifungal agent on day 5 due to unresponsive fever. In our study we found chest X-ray findings of LRTI in 31% of cases. Krishnamani K *et al* stated that positive findings on chest X-ray resulted in higher deaths on univariate analysis which was significant (P =0.002). Odds ratio - 14.479 (95% CI of mean - 2.731–76.777).Karimi F *et al* found that presence of respiratory tract infections (6.95%) on chest X-ray. In our study distribution of patients according hemolymphoid malignancies we observed that 22% were of AML, followed by DLBCL cases 20%, ALL cases were 14%, CLL cases were 11%, Hodgkins lymphoma cases were 29%, Burkitt's lymphoma and HCL cases were 2% each respectively.

Jacob LA *et al* in their study found that acute myeloid leukemia (AML) was the most common diagnosis (28%) among HM, followed by diffuse large B cell lymphoma (DLBCL) (13.3%).Taj M *et al* found that the most frequent hematological disease documented was ALL 91 cases (40.3%), followed by AML 45 cases (19.9%), aplastic anemia 32 cases (14.2%), lymphoma 19 cases (8.4%), CML 13 cases (5.8%). Parodi RL *et al* found that Most FNEs (395) were secondary to chemotherapy, 291 of them due to on hematological malignancies, i.e., Non-

Hodgkins lymphoma (NHL), acute myeloid leukemia (AML), acute lymphocytic leukemia (ALL), and Hodgkin's lymphoma.

Karimi F *et al* in their study observed that ALL cases 14 (12.2%), AML cases 29 (25.5%), CLL cases15 (13%), Non-Hodgkin's lymphoma cases 4 (3.5%), CML cases 1 (0.9%) and other cases were 47 (40.8%). The patients in our study on active chemotherapy were 77% while 23% taken chemotherapy previously. Jacob LA *et al* in their study stated that rising incidence of Gram positive bacteremia in febrile neutropenic patients has been reported over the past three decades, especially from the developed countries. This has been attributed to the increasing use of aggressive chemotherapy regimens.

Taj M *et al* stated that Majority of cases developed neutropenia at the induction phase of chemotherapy in acute leukemia. Parodi RL *et al* observed that Neutropenia followed chemotherapy in 77% of cases, half of the cases due to hematological malignancies. Jamal A *et al* in their study stated that advent of aggressive chemotherapy has significantly improved the survival of patients suffering from haematological malignancies but at the stake of increased risk of bacterial infections and sepsis which are a major cause of morbidity and mortality. Among all patients in our study,16% patients died during the course of treatment. The mortality rate was 16%. Cortes JA *et al* in their study reported that 10 patients died from FN, which represents a 7.7% mortality rate (deaths per episode); 50% of patients who died received inappropriate empirical antibiotic therapies compared with only 13% in surviving patients. Krishnamani K *et al* reported 7 deaths among study patients during course of study. Most of the acute myeloid leukemia deaths (7/8) occurred during induction chemotherapy noted by Lakshmaiah KC *et al*.

Summary

In this study majority of the patients were middle aged group. Male was seen to be affected more than female. Fever and weakness was the common presentation of febrile neutropenic patients in this study. A large number of patients presented with clinical signs and symptoms suggestive of respiratory system involvement. Duration of neutropenia and fever were significantly associated with outcome. Gram negative infections especially pseudomonas aeruginosa species were a common cause of febrile neutropenia in this study. Lower respiratory tract infection and urinary tract infection was seen to be more common in febrile neutropenic patients.

Conclusion

The cases of AML and Hodgkins lymphoma were common in the present study. Active chemotherapy and hematolymphoid malignancies were significantly associated with febrile neutropenia.

Abbreviations

ALL: Acute Lymhoblastic Leukemia
AML: Acute Myeloid Leukemia
ANC: Absolute neutrophil count
CLL: Chronic lymphocytic Leukemia
DLBCL: Diffuse Large B cell Lymhoma
FN: Febrile Neutropenia
IDSA: Infectious Diseases Society of America
ASCO: American Society of Clinical Oncology
HM: Hemolymhoid malignancy
HCL: Hairy cell leukemia
NHL: Non-Hodgkins lymphoma
GNB: Gram negative bacilli
GPC: Gram positive cocci

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