Microbiological Profile and Clinical Outcomes of Febrile Neutropenia in Cancer Patients at a Tertiary Care Centre in Nepal

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ABSTRACT

Introduction: Febrile Neutropenia (FN) from chemotherapy raises mortality (10%) and healthcare burden. Immediate broad-spectrum antibiotics are vital, highlighting the importance of personalized antibiotic choices for FN.

Methods: This prospective observational study, conducted at Bir Hospital and Bhaktapur Cancer Hospital from 2023 to 2024, investigated 200 cases of chemotherapy-induced febrile neutropenia. From the patients with chemotherapy induced febrile neutropenia, blood and relevant samples were cultured for antibiotic sensitivity. Initial antibiotic therapy followed Infectious Diseases Society of America guidelines (IDSA), later adjusted based on cultures. Granulocyte colony-stimulating factor was used until neutrophil recovery. Outcomes, including mortality and hospital stay, were recorded. Analysis, using Statistical Package for the Social Sciences (SPSS), considered various factors presenting results as mean ± standard deviation or frequency and percentage and significance at $P<0.05$, using T-test and Fisher's-exact test.

Results: Among 200 cases of febrile neutropenia with mean age of 49.41 years, only 2.5% had severe neutropenia. Cultures were positive in 9.5% cases primarily from blood (42.1%) and urine (15.8%) with predominance of Gram-negative bacteria (Escherichia coli and Klebsiella). Most bacterial isolates were sensitive to antibiotics like amikacin, tazobactam-piperacillin, imipenem, and meropenem, tigecycline and resistance to oral ciprofloxacin and cefotaxime was in significant number of cases. The mean hospital stay was 5.82 days and only 4 deaths were recorded. Advanced age and comorbidities correlated with increased mortality rates.

Conclusion: Timely empirical antibiotics reduce mortality in febrile neutropenia and should be customized according to local pathogen and sensitivity patterns. Advanced age and comorbidities are linked to increased mortality thus require careful management.

Keywords : Chemotherapy; Febrile Neutropenia; Microbiology.

INTRODUCTION

Febrile Neutropenia (FN), a severe chemotherapy complication, leads to increased morbidity and mortality.[1] It affects 10%-50% of solid tumor patients and over 80% with blood malignancies. It is linked to increased costs and nearly a 10% mortality rate, posing a substantial healthcare and economic burden.[2] Over time, the bacterial profile in febrile neutropenia has shifted, with increased prevalence of gram-positive organisms, particularly staphylococcal species (22%). Methicillin-resistant Staphylococcus aureus (MRSA) increased from 5% to 14%. Pseudomonas aeruginosa ranked second but showed low prevalence in the later period and enterococcal species had an 8% prevalence.[3]

To prevent life-threatening complications, guidelines advise prompt administration of broad-spectrum antibiotics within one hour of documented fever.[4] Moreover, use of broad spectrum antibiotics has resulted in emergence of multi-drug resistant bacteria.[5] The choice of antibiotics depends on local pathogen and resistance pattern which can change from time to time and place. This study identifies recent bacterial patterns, susceptibility, and clinical variables in FN patients with solid tumors at our institute.

METHODS

This prospective observational study conducted at NAMS included 200 cases of chemotherapy-induced febrile neutropenia from 2023 to 2024. Institutional review board approval was obtained, and relevant data were collected with informed consent. The patients >18 years old with histologically proven malignancy undergoing chemotherapy, meeting febrile neutropenia criteria, admitted to the hospital, and providing informed consent were included in the study. Febrile Neutropenia was defined as an absolute neutrophil count (ANC) of < 500 cells/mm3 or an ANC that is expected to decrease to < 500 cells/mm3 during the next 48 hour and fever was defined as a single oral temperature of ≥ 38.3°C (101°F) or temperature of ≥ 38.0°C (100.4°F) sustained over a 1- hour period.[6] Profound neutropenia is defined as ANC ≤ 100. Data collection involved comprehensive patient information, cancer diagnosis, staging, chemotherapy details, and various tests. MASCC risk calculation was done, and patients with a score <21 were admitted. Blood and relevant samples were cultured, and antibiotic sensitivity testing was performed. Blood culture was carried out aseptically; 10 mL of blood was drawn, directly added to the culture media, and cultured using a Bactex-FX 200 BD instrument (Becton and Dickinson, Franklin Lakes, NJ). Antibiotic sensitivity testing was performed by the Kirby-Bauer disc diffusion method. Fungal culture was not done due to lack of facility and cost issues. Comprehensive metabolic panel: complete hemogram with differentials and estimation of ANC, Renal Function Test, Liver function test, chest X-ray, and urine routine and microscopic examination was done. Initial empirical antibiotic therapy followed Infectious Diseases Society of America guidelines (IDSA) guidelines, with adjustments based on culture reports. Besides antibiotics, patients received short-acting granulocyte colony-stimulating factor until neutrophil recovery. Outcomes, including mortality, hospital stay, and microbiological reports, were recorded on the proforma. Data analysis using Statistical Package for the Social Sciences (SPSS) included stratification by various factors, and results were presented as mean ± standard deviation or frequency and percentage. Statistical significance was considered at P<0.05 using T-test and Fisher exact test.

RESULTS

This study conducted at Bir Hospital and Bhaktapur Cancer Hospital for one year documented 200 instances of febrile neutropenia among 175 patients, with an average age of 49.41±16 years. The distribution of age was fairly balanced; with 103 cases (51.5%) being over 50 years old and 97 cases (48.5%) less than 50 years old. Nearly equal numbers of male (101, 50.5%) and female (99, 49.5%) patients participated in the study. Only 25 cases (12.5%) presented with severe neutropenia (≤100), while 38 cases (19%) had concurrent comorbidities at the time of diagnosis. Among the 200 cases of febrile neutropenia, 75.5% did not receive prophylactic granulocyte colony-stimulating factor (GCF), whereas 24.5% experienced febrile neutropenia despite prophylactic GCF use as shown in Table 1.

Table 1: Characteristics of patients with FN

Characteristics	Number of febrile neutropenia episodes (%)
Age in years	
<50	97 (48.5%)
≥50	103 (51.5%)
Sex	
Male	101(50.5%)
Female	99 (49.5%)
Comorbidites	
Yes	38 (19%)
No	162 (81%)
Severity of neutropenia	
≤100 ANC	25 (12.5%)
>100 ANC	175
Duration of neutropenia	
≤7days	197 (98.5%)
>7days	3 (1.5%)
Use of prophylactic GCSF	
Yes	49 (24.5%)
No	151 (75.5%)

Out of the 200 cases, 19 (9.5%) exhibited positive cultures, with blood and urine being the common source of bacterial isolates, constituting 42.1% and 15.8%, respectively, as outlined in Table 2. Predominantly, Gram-negative bacteria were isolated, with notable instances of Escherichia coli and Klebsiella pnemoniae, identified in 8 and 6 cases, respectively. Additional bacterial strainsincluded Acinetobacter baumannii (1 case), Citrobacter freundii (2 cases), and Pseudomonas aeruginosa (1 case), as delineated in Fig 1 . An analysis of susceptibility patterns indicated that a majority of bacterial isolates responded favorably to antibiotics such as amikacin, tazobactam-piperacillin, imipenem, and meropenem, with no instances of resistance observed against

tigecycline. Conversely, oral ciprofloxacin and cefotaxime displayed resistance in a significant number of cases, with 14 and 10 cases exhibiting resistance, respectively, as illustrated in Fig 2.

Table 2: Details of culture

Culture result	Number (percentage)
Positive	19 (9.5%)
Negative	81 (90.55)
Organism	
Gram positive	1
Gram negative	18
Source of culture positivity	
Blood culture	8 (42.1%)
Urine culture	8 (42.1%)
Sputum culture	3 (15.8%)

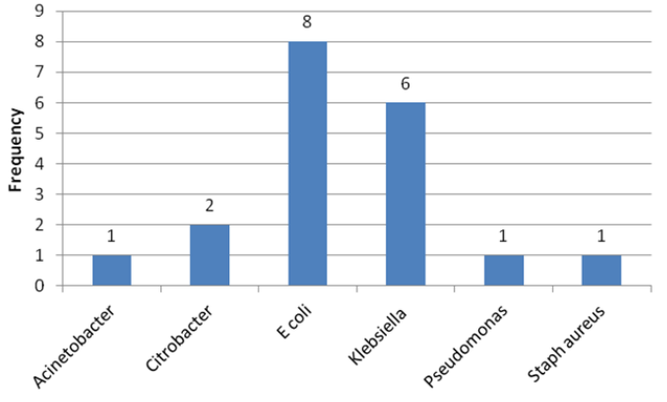

Figure 1. Organism isolated from positive culture

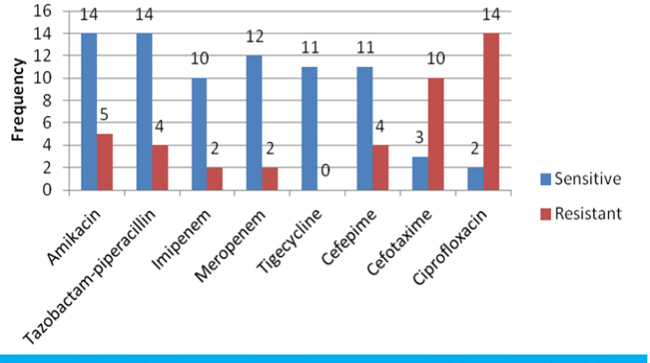

Figure 2. Antibiotic sensitivity pattern of bacterial isolates

The clinical prognosis for febrile neutropenia generally proved favorable, with only 4 fatalities documented, and mean hospitalization duration of 5.82±2.3 days, as depicted in Table 3. Notably, among the 4 deceased patients, only one exhibited a positive culture result. Advanced age (p=0.04) and the presence of comorbidities (p=0.001) were markedly linked to increased mortality rates in cases of febrile neutropenia. Furthermore, the duration of hospital stay was prolonged among febrile neutropenia patients, averaging 12±2.5 days (p=0.038), as illustrated in Table 4.

Table 3: Clinical outcome of febrile neutropenia

Clinical variables	Number (percentage)
Mortality	
No	196 (98%)
Yes	4 (2%)
Length of hospital stay (mean±SD)	5.82±2.3

Table 4: Relationship between mortality and clinical parameters

Characteristics	Alive	Death	P value
Age (Mean±SD)	49.14±16.1	62.25±8	0.04*
Sex			
Male	99	2	0.68†
Female	97	2	
Comorbidites			
Yes	34	4	0.001†
No	162	0	
Severity of neutropenia			
≤100 ANC	24	1	0.41†
>100 ANC	172	3	
Duration of neutropenia			
≤7 days	193	0	0.94†
>7 days	3	4	
Use of growth factors			
Yes	49	0	0.32†
No	147	4	
Length of stay (Mean±SD)	5.69±2,18	12±3.5	0.038*
Culture positive			
Yes	18	1	0.33†
No	178	3	
ANC	329.40 ±179.3	334.75 ±203.3	0.96*

ANC= Absolute neutrophil count, p value <0.05 is statistically significant

** Student t-test, † Fisher's exact test*

DISCUSSION

Febrile neutropenia is a serious concern for cancer patients with increased morbidity and mortality with range of 6.8%-20%.[7] Appropriate empirical antibiotic is very important in treating febrile neutropenia and preventing deaths. The choice of empirical antibiotic should be based on the prevalence of microbial pathogens and the antibiotic sensitivity which vary over time and place. Therefore, conducting regular studies to understand these patterns is vital for treatment decisions. In our institute, we

primarily rely on guidelines from the Infectious Diseases Society of America (IDSA) for selecting empirical antibiotics, rather than solely relying on local data.

Our study findings illuminate key aspects of febrile neutropenia (FN) in cancer patients. We noted a relatively modest rate of positive cultures, with only 9.5% of cases showing positive results, predominantly from blood and urine samples. This result is similar to the findings of study done in India by Jacob et al. which revealed overall positive culture rate of 21.3%, with 8% positivity in solid malignancies.[8] Another investigation by Babu et al. detected microbial isolates in 15% of cases, encompassing both hematological and solid malignancies, with a lower positive culture rate in solid malignancies (4%).[9] Maria et al. study demonstrated a 34.9% positive culture rate, with 17.5% positivity in blood cultures.[10] The variability in culture positivity may stem from differences in bacterial culture methodologies and lack of exclusive enrolment of solid malignancy cases as most of the studies incorporated both solid and haematological malignancies.

There has been a trend in shift of organism from gram negative to gram positive organisms in recent years. Study by Hilmar et al. in the United States showed that 61% of bacteremia were caused by gram positive organisms and 27% were caused by gram negative organisms.[11] However in our study we found that predominant organism isolated were gram negative bacteria with staph aureus isolates in only one instances. Among gram negative bacteria, E coli and klebsiella pneumoniae were predominant organisms. As guidelines for empirical treatment of febrile neutropenia emphasizes the need of antipseudomonal and MRSA coverage, our study showed lower rate of culture positive for pseudomonas and staph aureus. However, our result aligns with the study done in India where gram negative bacteria is the chief isolates with low positivity for pseudomonas.[8] Another Study done in India showed predominant gram negative bacteria with Klebsiella spp. being the most common.[12]In a study done in Saudi Arabia, equal frequency of both gram positive and gram

In a study done in Saudi Arabia, equal frequency of both negative organisms were found among positive culture in 13.5% cases.[13] The emergence of gram positive organism can be attributed to the placement of indwelling catheters in many cancer patients for chemotherapy delivery while our patients due to financial constraints can't afford indwelling catheter and none of our patients had indwelling catheters. This can be the reason of lower positivity of gram positive organisms. The antibiotic susceptibility patterns for both gram positive and gram negative bacteria revealed favorable responses to antibiotics such as amikacin, tazobactam-piperacillin, imipenem, and meropenem, with tigecycline showing universal efficacy. The antibiotic sensitivity pattern was similar to study done by Jacob et al. in India.8 However, resistance to oral ciprofloxacin and cefotaxime was prevalent among a significant subset of cases. Schelenz et al. showed higher incidence of gram negative isolates with higher rate of ciprofloxacin resistance which can be attributed to the increased use of fluoroquinolone prophylaxis in cancer patients during chemotherapy.[14]

Notably, our study documented a favorable clinical outcome for FN, with a mere 2% mortality rate among the 200 cases analyzed with the mean hospital stay of 5.82 days. Advanced age and the presence of comorbidities emerged as significant predictors of increased mortality, emphasizing the importance of considering patient demographics and medical history in treatment decisions. The rate of hospital mortality was 5.3% in study done by Hamidreza et al. where older age was associated with increased mortality which is similar to our study.[15] Study done in Saudi Arabia showed the mortality rate was 11.2% and it was significantly associated with the presence of bacteremia.[13] Mortality rate observed in study done by Jacob et al was 12.5% in solid malignancies where presence of comorbodities was significantly associated with increased mortality.[8] The lower mortality rate among our patients compared to other studies reflects the efficacy of empirical antibiotics and lack of extended resistance against antibiotics as we didn't observe the resistance to empirical antibiotics used.

CONCLUSION

Because of dynamic nature of FN epidemiology, there is the need for ongoing surveillance to inform empirical treatment strategies. Furthermore, our study contributes to the understanding of antibiotic resistance patterns and treatment outcomes of FN in cancer patients highlighting the importance of tailored management strategies informed by both local data and global research trends.

REFERENCES

1. De Naurois J, Novitzky-Basso I, Gill MJ, Marti Marti F, Cullen MH, Roila F. Management of febrile neutropenia: ESMO Clinical Practice Guidelines. Ann Oncol. 2010 May;21(SUPPL. 5):v252–6. [Full Text] [Pubmed] [DOI]

2. Klastersky J. Management of Fever in Neutropenic Patients with Different Risks of Complications. Clin Infect Dis. 2004 Jul 15;39(s1):S32–7. [Full Text] [Pubmed] [DOI]

3. Kanamaru A, Tatsumi Y. Microbiological Data for Patients with Febrile Neutropenia. Clin Infect Dis. 2004 Jul 15;39(s1):S7–10. [Full Text] [Pubmed] [DOI]

4. Flowers CR, Karten C. Communicating Safe Outpatient Management of Fever and Neutropenia. J Oncol Pract. 2013 Jul;9(4):207–10.[Full Text] [Pubmed] [DOI]

5. P. Bodey G. Infectious complications in the cancer patient. Curr Probl Cancer. 1977 Jun;1(12):1–63. [Full Text] [Pubmed] [DOI]

6. Freifeld AG, Bow EJ, Sepkowitz KA, Boeckh MJ, Ito JI, Mullen CA, et al. Clinical Practice Guideline for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer: 2010 Update by the Infectious Diseases Society of America. Clin Infect Dis. 2011 Feb 15;52(4):e56–93. [Full Text] [Pubmed] [DOI]

7. Lyman GH, Michels SL, Reynolds MW, Barron R, Tomic KS, Yu J. Risk of mortality in patients with cancer who experience febrile neutropenia. Cancer. 2010 Dec 1;116(23):5555–63. [Full Text] [Pubmed] [DOI]

8. Jacob L, Lakshmaiah K, Govindbabu K, Suresh T, Lokanatha D, Sinha M, et al. Clinical and microbiological profile of febrile neutropenia in solid tumors and hematological malignancies at a tertiary cancer care center in South India. Indian J Cancer. 2014;51(4):464.[Full Text] [Pubmed] [DOI]

9. Babu KG, Lokanatha D, Lakshmaiah KC, Suresh Babu MC, Jacob LA, Bhat GR, et al. Bloodstream infections in febrile neutropenic patients at a tertiary cancer institute in South India: A timeline of clinical and microbial trends through the years. Indian J Med Paediatr Oncol. 2016 Jul 12;37(03):174–82. [Full Text] [Pubmed] [DOI]

10. Bachlitzanaki M, Aletras G, Bachlitzanaki E, Messaritakis I, Koukias S, Koulouridi A, et al. Evaluation of Febrile Neutropenia in Hospitalized Patients with Neoplasia Undergoing Chemotherapy. Microorganisms. 2023 Oct;11(10). [Full Text] [Pubmed] [DOI]

11. Wisplinghoff H, Seifert H, Wenzel RP, Edmond MB. Current Trends in the Epidemiology of Nosocomial Bloodstream Infections in Patients with Hematological Malignancies and Solid Neoplasms in Hospitals in the United States. Clin Infect Dis. 2003 May 1;36(9):1103–10.[Full Text] [Pubmed] [DOI]

12. Paul M, Bhatia M, Rekha US, Omar BJ, Gupta P. Microbiological Profile of Blood Stream Infections in Febrile Neutropenic Patients at a Tertiary Care Teaching Hospital in Rishikesh, Uttarakhand. J Lab Physicians. 2020 Aug;12(2):147–53. [Full Text] [Pubmed] [DOI]

13. Al-Tawfiq JA, Hinedi K, Khairallah H, Saadeh B, Abbasi S, Noureen M, et al. Epidemiology and source of infection in patients with febrile neutropenia: A ten-year longitudinal study. J Infect Public Health. 2019 May;12(3):364–6. [Full Text] [Pubmed] [DOI]

14. Schelenz S, Nwaka D, Hunter PR. Longitudinal surveillance of bacteraemia in haematology and oncology patients at UK cancer centre and the impact of ciprofloxacin use on antimicrobial resistance. J Antimicrob Chemother. 2013 Jun 1;68(6):1431–8. [Full Text] [Pubmed] [DOI]

15. Hatamabadi H, Arhami Dolatabadi A, Akhavan A, Safari S. Clinical Characteristics and Associated Factors of Mortality in Febrile Neutropenia Patients; a Cross Sectional Study. Arch Acad Emerg Med. 2019;7(1):39. [Full Text] [Pubmed]

16. Flowers CR, Seidenfeld J, Bow EJ, Karten C, Gleason C, Hawley DK, et al. Antimicrobial Prophylaxis and Outpatient Management of Fever and Neutropenia in Adults Treated for Malignancy: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol. 2013 Feb 20;31(6):794–810. [Full Text] [Pubmed] [DOI]