BJHS
Birat Journal of Health Sciences

ISSN:
2542-2758 (Print) 2542-2804 (Online)

ARTICLE INFO:
Received Date: 2024-08-02
Acceptance Date: 2024-12-08
Published Date: 2025-01-01

KEYWORDS:
Culture, Febrile Neutropenia, Hematology, Infection Site, Micro-organism

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Access the article online

DOI: https://doi.org/10.62065/bjhs582

CITATION:
Karki B, Sah MK, Bajracharya N, Acharya D, Gelal S, Shrestha NM, Thakuri HC, Sangroula RK, Paudel B, Poudyal BS. Sites of Infections and Types of Organisms in Patients with Febrile Neutropenia in Hematological Ward in Civil Service Hospital. Birat J. Health Sci. 2024;9(2):14-20.

Sites of Infections and Types of Organisms in Patients with Febrile Neutropenia in Hematological Ward in Civil Service Hospital

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ABSTRACT

Introduction: The risk of developing a significant infection increases as the neutrophil count falls below 500 cells/µL, particularly in cases of prolonged neutropenia lasting more than seven days. The site of infections and organisms causing those infections are helpful in diagnosis and that ultimately helps in judicial use of antimicrobials and helps to prevent antimicrobials resistant.

Objective: The objective of the study was to document the current sites of infection in patients with febrile neutropenia, pattern of bacterial growth and antibiotic susceptibility.

Methods: A prospective observational study was conducted from August 2023 to July 2024 at Civil Hospital, Kathmandu. A total 108 neutropenic cases with positive culture were enrolled in this study. This study involved a comprehensive evaluation of patients admitted to the Hematology Department, focusing on demographic and clinical data collection.

Results: Mean age of presentation was 31.96 years. Acute Myeloid Leukemia (52.8%) and Acute Lymphocytic Leukemia (21.3%) were the most common underlying hematological disorder, followed by Aplastic Anemia (13.9%), Multiple Myeloma (5.6%), Non-Hodgkin Lymphoma (4.6%), and Hodgkin Lymphoma (1.8%). Urine Samples yield the highest percentages of culture positivity (52%) followed by blood sample (18%). Gram-negative bacteria yield the highest positivity of 98.1% among which Escherichia coli(E-Coli) being the most common with 44.4% positivity followed by Kleibsella which was isolated in 38.9% of sample.

Conclusions: The Urinary Tract Infection(UTI) is most common site of infection, Gram-Negative microorganisms (98.1%) being the frequent cause. Female are more prone to have UTI. E-coli being the most common infecting microorganism.

INTRODUCTION

Fever in Neutropenia is defined as a single oral temperature ≥38.3°C (101°F) or sustained temperature ≥38.0°C (100.4°F) over an hour .[1] Neutropenia is defined as ANC <1500 cells/µL; severe at ANC <500 cells/µL, profound at ANC <100 cells/µL. Risk of infection increases significantly with ANC <500 cells/µL, especially if fever lasting

over seven days .[2]

Febrile Neutropenia is a major cause of morbidity, mortality, and high healthcare costs in cancer patients .[3] Mortality risk is higher in patients with hematologic malignancies and complications such as bacteremia and pneumonia.[4,5]

Causes of infections in febrile neutropenia may be due to chemotherapy effects, immune deficiencies from malignancy, or immunosuppressive treatments .[6] 20-30% of episodes have identifiable infections, mostly from endogenous flora mostly bacterial infections .[7]

Evaluation of neutropenic fever requires thorough history, physical exam, and diagnostic studies. Infection symptoms may be atypical; prompt evaluation is essential.[8] It includes complete blood count, liver function tests, serum creatinine, urinalysis, cultures, and imaging (preferably CT scans) .Prompt broad-spectrum antibiotics recommended for all cancer patients with neutropenic fever .[9,10] Early antibiotic intervention is critical for survival, akin to acute stroke or myocardial infarction management .[11] Guidelines recommend immediate evaluation and broad-spectrum antibiotics for all neutropenic fever cases, even without confirmed infection to improve outcomes.[1,12,13] Initiate antibiotics within 60 minutes of presentation to reduce mortality .[10,11,14]

Neutropenic patients are liable to various infections. If we are able to diagnose the site of infections and organisms causing those infections, it will be of great help for the management of the patient. Knowing organisms and their susceptibility to antimicrobial will lead to judicial use of antimicrobials and helps to prevent antimicrobials resistant.

METHODOLOGY

A prospective observational study was conducted at Civil Service Hospital in the department of Hematology from August 2023 to July 2024. Samples were collected from patients with neutropenic fever. The study population comprised of neutropenic patients who are 14 years and above, and those who are able to give written informed consent for participation. The Exclusion criteria were fever occurring during or within 12 h of transfusion of blood and blood products which responded to anti-pyretic and patients refusing to give consent. All the patients, fulfilling the eligibility criteria were enrolled in the study after written informed consent. Patient's clinical history, treatment course, the laboratory reports were recorded from the patient's case sheets either from out-patient department records or the discharge summary sheet. Standardized Proforma were used to record the data in accordance with the protocol's instructions.

The sample size was calculated using the following formula.

Considering prevalence of gram-negative cultures obtained from febrile neutropenic patient as 63.3%, Level of significance kept at 95% and absolute error(d)= 10%

Sample size calculation(n)

$n=z_{\alpha}^{2}(PQ)/d^{2}$

Q=100-P, zα=1.96, P=63.3 and d=10

n= 89.24 (approx. 90)

considering 10% of non-response, the minimal sample size was adjusted to 99

However, in this study 108 sample was taken for analysis.

This study involved a comprehensive evaluation of patients admitted to the Hematology Department, focusing on demographic and clinical data collection. The demographic data, including age and gender, along with additional information such as ethnicity, socio-economic status, and geographical location, were noted. The clinical data encompassed medical history, current medications, and any co-existing conditions.

Patients eligible for the study, who were admitted during the study period, were enrolled after an initial clinical evaluation to judge their eligibility based on specific inclusion and exclusion criteria. During this evaluation, detailed history was obtained, including chief complaints, underlying disease, onset of symptoms, and the duration of neutropenia. Symptoms that might relate to an underlying site of infection, such as cough, sinus pain, pain at the cannula site, diarrhea, dysuria, and perianal pain, were also recorded. A thorough clinical examination was conducted to identify any potential sites of infection and check for signs of infection or complications. Investigations included laboratory tests like complete blood count (CBC), covering white blood cell count, differential count, absolute neutrophil count (ANC), hemoglobin level, and platelet count.

Microbiological investigations involved culture and sensitivity tests for samples collected from blood, urine, sputum, or pus, to identify organisms and note their sensitivity to antimicrobials.

Informed written consent was obtained from all participants after explaining the study's purpose and procedures. Data were collected using a standardized proforma to ensure consistency and adherence to the protocol's instructions for data entry and management. Patient records were regularly updated and maintained throughout the study to ensure accurate diagnosis and effective monitoring of treatment outcomes. As per Infectious Disease Society Of America (IDSA) guideline, FN is defined as a single oral temperature measurement of >38.3^{0}C (101 ^{0}F) or a temperature of >38.0^{0}C (100.4^{0}F) sustained over a 1-h period with an Absolute Neutrophil Count (ANC) of <500 cells/mm^{3} or an ANC that is expected to decrease to <500 cells/mm^{3} during the next 48 hours.[17]

Analyses of data were performed upon completion of the study. Data were entered in MS Excel and analyzed using descriptive statistical methods SPSS-version-20. Frequency, percentage, mean and standard deviation were used to show descriptive results

RESULTS

The age distribution of the patient cohort shows that the majority are younger adults, with 65 out of 108 individuals (60.2%) falling within the 14-30 years age group. Comparatively, fewer patients are in the middle-aged bracket of 31-60 years, accounting for 35 individuals (32.4%). Only a small proportion of patients are

over 60 years old, with 8 individuals (7.4%). The mean age of the group is 31.96 years, with a wide standard deviation, indicating considerable age variability, ranging from 14 to 71 years.

Gender distribution within the study is skewed slightly toward males, who represent 59.3% (64 out of 108) of the patient population, whereas females make up 40.7% (44 out of 108). This suggests a higher prevalence or reporting of conditions among male patients in this cohort.

When examining the types of diagnoses, Acute Myeloid Leukemia (AML) is the most common diagnosis, affecting 57 patients (52.8%). This is followed by Acute Lymphoblastic Leukemia (ALL), which is present in 23 patients (21.3%). Aplastic Anemia (AA) affects 15 individuals (13.9%), while Multiple Myeloma (MM) and Non-Hodgkin Lymphoma (NHL) are less common, found in 6 (5.6%) and 5 (4.6%) patients, respectively. Hodgkin Lymphoma (HL) is the least prevalent diagnosis, seen in only 2 patients (1.8%).

Gender-Based Distribution of Infections:

The site of infection varies notably between male and female patients. Urinary tract infections are almost equally prevalent between the sexes, with 33 male patients (51.56%) and 32 female patients (72.71%) affected, although the percentage is higher among females. Blood infections, however, are more common in males, with 15 cases (23.44%) compared to 7 cases (15.91%) in females. Sputum samples show that infections are more frequent in males (18.75%) than in females (11.36%). Notably, pus infections are found only in males, with 4 cases reported.

The distribution of infectious organisms also shows some gender differences. Escherichia coli is the most frequently identified organism, found in 28 male and 20 female patients. Klebsiella is similarly distributed, with 22 male and 20 female cases. Pseudomonas and Citrobacter are found in both genders, though with slight differences in frequency. Acinetobacter, Staphylococcus, and Proteus are notably absent in female patients but are present among males.

Drug Sensitivity Patterns:

The drug sensitivity patterns reveal concerning levels of resistance among the isolated organisms. For Amikacin, a significant portion of the cases (65 out of 108) are resistant, with only 43 cases showing sensitivity. Similarly, resistance to Fluoroquinolones is even more pronounced, with 85 cases resistant and just 23 cases sensitive. This trend continues with Imipenem and PipTaz, where resistance is observed in 80 and 82 cases, respectively, compared to 28 and 26 sensitive cases.

Conversely, Polymyxin B shows a more favorable sensitivity profile, with 92 cases being sensitive compared to 16 resistant cases. Tiegecycline and Colistin also demonstrate relatively higher sensitivity, with 58 and 78 sensitive cases, respectively, though resistance is still a concern in a significant number of cases.

Table 1: Socio-Demographic Table

Characteristics	Category	Frequency (Percentage) N=108	Remarks
Age (in Yrs)	14-30	65	Age(mean years±SD) 31.96+/-17.02 Range: 14 Yrs-71 Yrs
	31-60	35	
	>60	8	
	Total	108 (100%)	
Sex	Male	64 (59.3%)	
	Female	44 (40.7%)	
	Total	108 (100%)	
Diagnosis	Acute Myeloid Leukemkia (AML)	57(52.8%)	
	Acute Lymphoblastic Leukemia (ALL)	23(21.3%)	
	Aplastic Anemia (AA)	15(13.9%)	
	Multiple Myeloma (MM)	6(5.6%)	
	Non Hodgkin Lymphoma (NHL)	5(4.6%)	
	Hodgkin Lymphoma (HL)	2(1.8%)	
	Total	108 (100.0%)	

Table 2: Gender Based Distribution

Characteristics	Sex	
	Male	Female
Site of infection		
Urine	33 (51.56%)	32 (72.71%)
Blood	15 (23.44%)	7 (15.91%)
Sputum	12 (18.75)	5 (11.36%)
Pus	4	0
Organism		
Escherichia coli	28	20
Klebsiella	22	20
Pseudomonas	3	3
Acinetobacter	4	0
Staphylococcus	2	0
Citrobacter	4	1
Proteus	1	0

Table 3: Drug Sensitivity

	Medicines	Organisms							Total
		Escherich-ia coli	Kleib-sella	Pseudomonas	Acineto-bacter	Staphylococcus	Citrobacter	Proteus	(n=108)
Amikacin	Resistant	22	38	1	1	1	2	0	65
	Sensitive	26	4	5	3	1	3	1	43
Fluoroquinolones	Resistant	38	40	1	1	2	2	1	85
	Sensitive	10	2	5	3	0	3	0	23
Imipenem	Resistant	36	39	0	1	1	2	1	80
	Sensitive	12	3	6	3	1	3	0	28
PipTaz	Resistant	34	41	1	1	2	2	1	82
	Sensitive	14	1	5	3	0	3	0	26
Polymyxin B	Resistant	4	2	2	3	2	2	1	16
	Sensitive	44	40	4	1	0	3	0	92
Tiegecycline	Resistant	21	17	4	2	2	3	1	50
	Sensitive	27	25	2	2	0	2	0	58
Colistin	Resistant	12	8	2	2	2	3	1	30
	Sensitive	36	34	4	2	0	2	0	78
Vancomycin	Resistant	_	_	_	_	1	_	_	1
	Sensitive	_	_	_	_	1	_	_	1
Teicoplanin	Resistant	_	_	_	_	0	_	_	0
	Sensitive	_	_	_	_	2	_	_	2

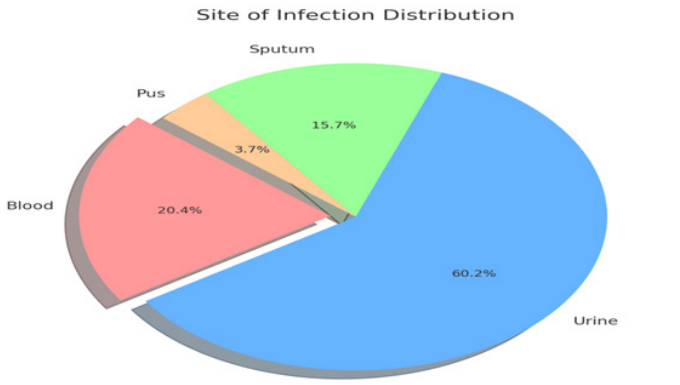

Fig 1: Pie chart representing the distribution of infection sites:

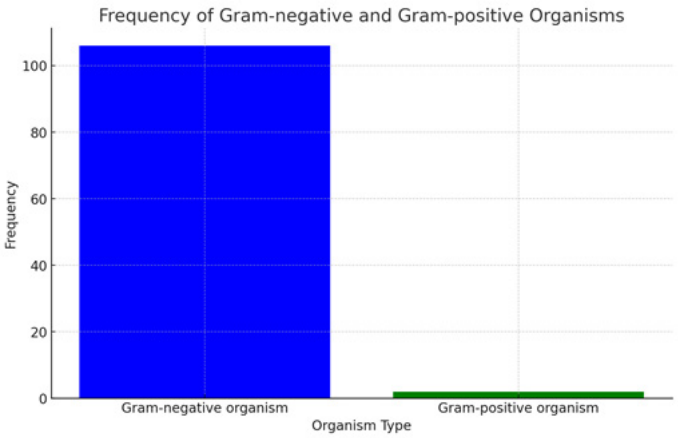

Fig 2: Type of micro-organisms

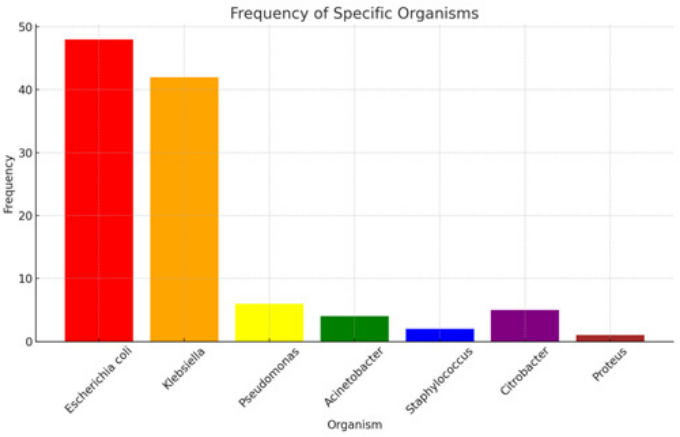

Fig 3: Specific Organism

DISCUSSION

The analysis of infection sites reveals that urinary tract infections (UTIs) are the most common, affecting both males and females, with a slightly higher incidence among females. This finding is consistent with the general population, where UTIs are more prevalent in women due to anatomical and physiological factors. However, the nearly equal distribution of UTIs between genders in this cohort may reflect the immunocompromised state of the patients, which could mitigate the typical gender differences seen in the general population.

Bloodstream infections are more frequent in male patients, which could be indicative of more severe or systemic infections in this group. This is concerning given the higher mortality rates associated with bloodstream infections, particularly in immunocompromised patients such as those with hematological malignancies. The presence of infections in sputum and pus samples, predominantly in males, suggests a greater susceptibility to respiratory and wound infections, possibly due to factors like smoking, chronic lung conditions, or more invasive procedures.

The distribution of microorganisms shows that Escherichia coli and Klebsiella are the predominant pathogens, which is consistent with other studies involving immunocompromised patients. These organisms are known to cause a wide range of infections, particularly in hospital settings where nosocomial infections are a significant concern. The absence of certain organisms like Acinetobacter and Staphylococcus in female patients could reflect differences in exposure or infection control practices between genders.

The observed antibiotic resistance patterns are alarming, particularly the high levels of resistance to commonly used antibiotics such as Fluoroquinolones, Imipenem, and PipTaz. These findings highlight the growing challenge of antibiotic resistance in clinical practice, especially in managing infections in immunocompromised patients. The increasing resistance pattern to the antibiotics drugs suggests that alternative treatment strategies, including the use of newer antibiotics or combination therapies, may be necessary.

Conversely, the relatively higher sensitivity observed with Polymyxin B and Colistin provides some hope for treating resistant infections. However, the use of these drugs must be approached with caution due to their potential for nephrotoxicity and other adverse effects. The varying sensitivity to Tiegecycline also suggests that while it may be effective against certain organisms, its role in treating infections in this patient population needs further exploration. S Basit et al.[15] in a cross-sectional study found Staphylococcus aureus (16%), E. coli (14.5%), Pseudomonas (8.5%), and Klebsiella (15.5%) in severe neutropenia patients over 15 years old. In a cross-sectional study, K Fatemeh et al.[16] observed that meropenem (91.3%) and vancomycin (47.82%) were the most prescribed antibiotics in 115 oncology patients with febrile neutropenia. Empiric antifungals were used in 20.86% of cases, with Gram-positive bacteria being the most common. M Mohsen et al.[17] in a cross-sectional study classified 77.3% of 375 patients as FUO and 22.7% as sepsis. Only 2.6% had positive blood cultures. Common antibiotics were ceftazidim and amikacin, with gentamicin used more in sepsis.G Mucahit et al.[18] conducted a retrospective study and found pneumonia, invasive aspergillosis, sepsis, typhlitis, mucormycosis, and UTIs common in 124 patients with 250 febrile neutropenia episodes. Pathogens included Gram-positive cocci (52%), Gram-negative bacilli (42%), and yeasts (6%).

Y Davood et al.[19] in a retrospective study identified E. coli,

Pseudomonas aeruginosa, Acinetobacter baumannii, Klebsiella pneumoniae, and staphylococci as common pathogens in neutropenic patients with nosocomial fever, with gram-negative organisms being most common. S Ahu et al.[20] in a prospective study detected invasive aspergillosis and candidemia in febrile neutropenic patients using microscopy, cultures, ELISA, and PCR. M K Prakas et al.[21] conducted a prospective study and found that Pseudomonas aeruginosa as the most common in febrile neutropenia, followed by MRSA, Acinetobacter, coagulase-negative staphylococci, Klebsiella pneumoniae, E. coli, and Candida spp.

MD Nattamol et al.[22] found a hospital mortality rate of 17.3% and a 30-day mortality rate of 20.5%, with a median length of stay (LOS) of eight days. Hematologic malignancies were present in 66.1% of patients. In-hospital mortality was linked to longer fever duration, abnormal liver function tests, ICU admission, and positive cultures. Thirty-day mortality was associated with abnormal liver enzymes, ICU admission, and fever lasting more than four days. A LOS greater than eight days was linked to hematologic malignancies, longer fever, and neutropenia exceeding five days. N Alaadin et al.[23] In a prospective observational study found that the respiratory tract was the most common infection site (52%), followed by the urinary tract (18%), and 16% had no clear infection focus. Gram-negative microorganisms (62.9%) were mostly sensitive to Aminoglycosides, while Gram-positive microorganisms (29.6%) were generally sensitive to vancomycin.

CONCLUSION

Younger adults and males were more frequently affected by these conditions, with AML being the most common diagnosis. Urinary tract infections were prevalent across genders, while bloodstream infections were more common in males. Escherichia coli and Klebsiella were the dominant pathogens, and concerning levels of antibiotic resistance were observed, particularly to Fluoroquinolones, Imipenem, and Vancomycin. These findings underscore the need for tailored treatment strategies, vigilant infection control, and careful antibiotic use to manage infections in this vulnerable population effectively.

LIMITATION OF THE STUDY

1. Only bacterial culture is done in this study. Viral and Fungal culture is not done.

2. This study is conducted in a single hospital and thus generalization of result of this study should be more useful for similar hospital.

ACKNOWLEDGEMENTS

We acknowledge the Departmentof Hematology Civil Service Hospital, Kathmandu, Nepal.

CONFLICT OF INTEREST

There is no competing interests among the authors.

FINANNCIAL DISCLOSURE

There is no funding for this study.

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