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ORIGINAL ARTICLE

Antimicrobial resistance in febrile neutropenia. Are we left with some options?

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ABSTRACT... Objective: To assess the pathogenic organisms, antibiotic sensitivity and resistance patterns in patients with FN having hematological malignancies. **Study Design:** Prospective Cross-sectional study. **Setting:** National Institute of Blood Diseases and Bone Marrow Transplantation. **Period:** February 2023 to July 2024. **Methods:** Samples from 650 febrile neutropenia patients of either gender were collected adopting non-probability consecutive sampling technique. As per Clinical and Laboratory Standards Institute (CLSI) recommendations the organisms were isolated and identified by routine biochemical tests. The antibiotic sensitivity profile was determined by Kirby Bauer method. **Results:** Microbiologically confirmed infectious events were recorded in 311 cultures. The majority (232; 74.6%) of the patients had infections due to Gram negative bacteria (GNB). The most prevalent GNB was Escherichia coli (37.5%) followed by Klebsiella pneumonia (15.5%). Overall 16 (5.1%) bacterial isolates were XDR and 15(4.8%) were MDR. Most MDR and XDR strains were GNB and E. coli appeared as the most resistant in blood and urine cultures. Furthermore, E. coli were highly resistant to Fosfomycin (87.5%) and Amox-Clav (79.5%) whereas good sensitivity to colistin (79.5%), and amikacin (61.36%) was observed. Pan resistance was exhibited by 2 hypervirulent isolates of K. pneumoniae. In blood cultures, high resistance to methicillin (56.6%) was observed with S. epidermidis making it a clinically significant pathogen. **Conclusion:** Most bacterial isolates were resistant to penicillin, cephalosporins and quinolones used as part of empirical treatment of febrile neutropenia. Prudent use of antibiotics may be the best preventive strategy to the spread and emergence of antibiotic resistant GNBs.

Key words: E.coli, Febrile Neutropenia, Klebsiella Pneumoniae, Pseudomonas.

INTRODUCTION

Febrile neutropenia (FN) is a medical emergency specifically influenced by the duration and intensity of neutropenia.[1] FN frequently complicates the course of disease in cancer patients, affecting about 80% of patients with hematological malignancies. FN is primarily caused by infections, which not only cause treatment delays but also have a substantial effect on morbidity and mortality rates.[2-4] Profound neutropenia increases the risk of bacteremia, which exacerbates the severity of the condition.[5]

The mucosal linings and barriers, such as those in the sinuses and gastrointestinal system, are essential for protecting the body against infections. These host defenses can be weakened by chemotherapy and radiation treatment, which raises the possibility of microbial invasion.[6] Central venous lines, on the other hand are potentially other source for invasion into the body. Gram-negative aerobic bacteria have historically accounted for the majority of FN isolates. Nonetheless, throughout the past 40 years, a notable shift in the range of microorganisms responsible for FN has been noted.[7] Methicillin-resistant Staphylococcus aureus and vancomycin-resistant Enterococci are the most common multidrug-resistant Gram-positive bacteria (GPB).[8] Gram-negative bacteria (GNB) that are resistant to at least three of the following antibiotic classes such as carbapenems, cephalosporins, and anti-pseudomonal penicillin are known as multi-drug resistant bacteria.[8,9]

According to the incidence and trends of resistance, the misuse of broad spectrum antibiotics has resulted in the formation of resistant microbes.

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Therefore, while carefully planning antibiotic regimens, it is important to evaluate the institutional regulations regarding the use of empirical antibiotics in patients with febrile neutropenia, as well as the prevalence of bacteria and their sensitivity pattern.[10]

Bacterial resistance is alarmingly increasing, according to global data, which makes managing FN more difficult. The dynamic nature of antibiotic resistance makes it difficult to use conventional regimens for patients with FN, even if there are defined criteria for its evaluation and treatment.[11,12] To inform effective practical treatment techniques, it is essential to take into account recent data on the local epidemiology of the most common infections and the patterns of resistance inside the institution.[13] Since the advent of empirical antibiotic treatment, the mortality rate from FN in cancer patients has decreased from 75% to less than 10%and have enabled the utilization of aggressive chemotherapeutic regimens.[14,15]

This study was done to evaluate the patterns of antibiotic sensitivity, resistance, and pathogenic microbes in FN patients with hematological malignancies. There have been extensive studies on FN from western nations, but limited literature is available from Pakistan on the infectious pathogens, empirical antibiotics use and implications. The need of rapidly delivering empirical antimicrobial therapy for FN patients is highlighted by the major effect that the severity of FN and the time frame of infection have on main treatment results. The local bacterial spectrum and susceptibility patterns must be kept in mind by healthcare practitioners in order to maximize patient treatment.

METHODS

This prospective cross sectional study was conducted at National Institute of Blood Diseases and Bone Marrow Transplantation (NIBD-BMT) Karachi, Pakistan from February 2023 to July 2024. FN was defined as single oral temperature greater than or equal to 101 ˚F (38.3˚C) or a temperature greater than or equal to 100.4 ˚F (38˚C) for at least an hour, with an absolute neutrophils counts (ANC) of less than 1500 cells/ microliter.[16]

Adopting non-probability consecutive sampling technique, patients of either gender with hematological malignancies (as per medical record) having FN (as per operational definition) and undergoing microbiological culture evaluation (as per operational definition) were included. The patients not meeting the diagnostic criteria for FN, as defined above or those who had hematological disorders other than blood cancer, drug-induced FN or liver disease were excluded.

Approval from the institutional ethical committee was taken with IRB no: NIBD/IRB-240/10-2022. Informed and written consent were acquired from parents or guardians of the children participating in the study. Patients fulfilling inclusion and exclusion criteria were analyzed. Blood and other body fluids were sent for culture analysis to the institutional laboratory. The BACTEC blood culture system was used for the analysis of blood samples while urine, pus and sputum samples were inoculated on different enriched and selective agar culture plates following the CLSI recommendations. Organisms were identified according to routine bacteriological procedures and Kirby-Bauer disc diffusion method was used for interpreting antibiotic susceptibility by measuring zone of inhibition. The results were recorded as sensitive, intermediate or resistant based on the CLSI and EUCAST cutoff for each tested antibiotic.[17] The colistin and vancomycin were labeled as resistant by the microtitre tube dilution method. All positive cultures were observed within 16 hours were considered as true bacteremia. Multidrug -resistance (MDR) was defined as non-susceptibility to ≥1 agent in ≥3 antimicrobial categories; extensively drug-resistant (XDR) as susceptibility limited to ≤2 categories; pan drug resistance (PDR), as non-susceptibility to all agents in all antimicrobial categories. All positive cultures observed within 16 hours were considered as bacteremia. For urine cultures, two consecutive samples were taken from females and one from male. The CFU $>10^4$ were correlated clinically as true microbiologically confirmed urine isolates. The infections were labeled by assessing the quantity

of the organism grown, the presence of a specific pathogen associated with the symptoms, and repeating cultures usually at 24-48 hours to verify consistency in findings.

Statistical Analysis

Data was analyzed by IBM-SPSS Statistics, version 26.0. Frequencies and percentages were calculated for the categorical variables while mean and standard deviation (SD) were computed for quantitative variables. Chi-square and *Fisher's exact test* were utilized to compare data considering p <0.05 as statistically significant.

RESULTS

In a total of 650 patients, positive cultures were found in 311(47.8%) subjects. The frequencies of types of hematological malignancies are shown in table 01 and demographical characteristics shown in table 02. Out of 650, 382 (58.8%) were male. The mean age was 46.84±16.25 years. The most common type of specimen used for culture and sensitivity analysis was blood in 116 (37.3%) while urine specimen in 97 (31.2%) cases (Figure-1).

Type of Hematological Malignancy	FN Patients(n)	Percentage (%)
AML	210	32.30
ALL	185	28.46
HL	86	13.23
CML	84	12.92
NHL	80	12.30
Burkitt's lymphoma	05	0.76

Table-I. Frequency of types of hematological malignancy in FN patients:

N: Number of patients, %: Percentage, AML: Acute Myeloid Leukemia, ALL: Acute Lymphoblastic Leukemia, HL: Hodgkin's Lymphoma, CML: Chronic Myeloid Leukemia, NHL: Non-Hodgkin's Lymphoma

In a total of 311 positive culture specimens, 232 (74.6%) were found to be gram negative and 79 (25.4%) were gram positive. The most prevalent microorganism in gram negative isolates were E.coli (n=87; 37.5%) followed by Klebsiella pneumoniae (n=36; 15.5%), Pseudomonas species (n=25; 11.2%) and Pseudomonas aeruginosa (10.3%), the details are shown in Figure-2(a). In gram positive isolates, Staphylococcus epidermidis (62%), and Micrococcus species (20.3%) were the most prevalent isolates and the details are depicted in Figure-2(b). However, both of these could be a contaminated normal skin flora. In gram negative organisms, Acinetobacter species, Burkholderia cepacia, Citrobacter species and Moraxella species were identified by the routine bacteriological technique substantially which were not previously prevalent. In gram positive organisms, Micrococcus species was reported for the first time at our center.

Parameters	n (%)
Age mean±SD (years)	46.84±16.25
Gender	
Male	382(58.76)
Female	268(41.23)
ANC grading	
Grade 0(≥ 2000 cells/mm^3)	27(4.15)
Grade 1(≥ 1500-<2000 cells/mm^3)	302(46.4)
Grade 2 ≥ 1000-<1500 cells/mm^3)	260(40)
Grade 3 ≥500-<1000 cells/mm^3)	55(8.46)
Grade 4 <500 cells/mm^3)	06(0.92)
Type of organism(n=311)	
Gram-positive organism	79(25.4%)
Gram-negative organism	232(74.6%)
Reason of hospitalization	
Chemotherapy	515(79.2)
Infection	479(73.6)
Disease Progression	24(3.69)
Others	25(3.84)
Co morbidities	
None	05(0.79)
Cardiovascular	433(66.6)
Respiratory	172(26.4)
Others	40(6.15)

Table-II. Demographic characteristics of FN patients:

N: Number of patients, %: Percentage, ANC: Absolute Neutrophils Counts, SD: Standard deviation

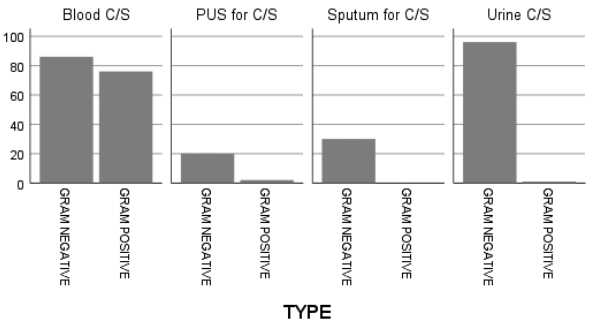

Figure-1. Frequency of type of specimen with culture and sensitivity analysis

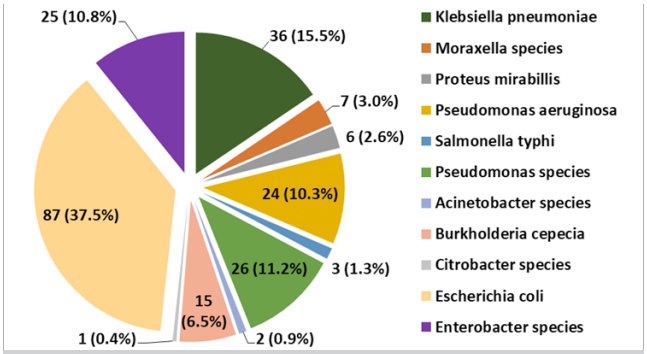

Figure-02 (a). Distribution of gram negative isolates (n=232)

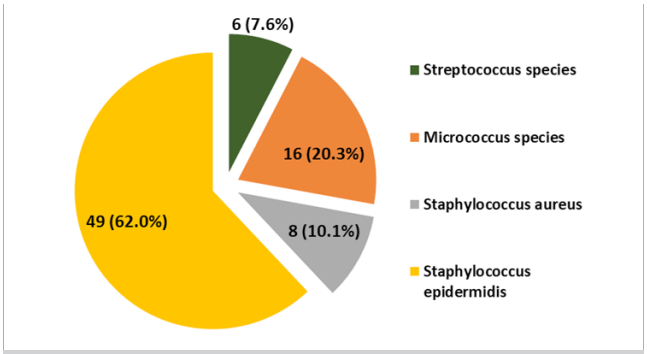

Figure-02 (b). Distribution of gram positive isolates (n=79)

Gram negative were mostly reported in urine cultures 96 (41%) whereas gram positive organisms were found in blood cultures 76 (96%).

The frequency of gram positive and gram negative with specimen types were found (p<0.001) as shown in Table-III.

The most effective antibiotic was colistin (79.5%) against E. coli isolates in blood and other specimens (urine and sputum), followed by amikacin (61.36%), while highest resistance was noted for Amox-Clav (88.6%) and fosfomycin (87.5%). Among the samples, the urine cultures had the highest resistance with 43(48.8%) for Amox-Clav.

For Klebsiella pneumoniae, the highest sensitivities were observed for fosfomycin (81.57%) and colistin (73.68%) whereas highest resistance was seen for ceftriaxone (83.3%) and Co-Trimoxazole (80.5%). Twelve (33.3%) sputum cultures showed the highest resistance. For Staphylococcus epidermidis, vancomycin (98.1%), linezolid (98.1%) and amikacin (86.7%) were the most sensitive drugs while highest resistance patterns were seen for Co-Trimoxazole (75.47%). The higher rates of resistance and sensitivity patterns of antibiotics against most frequent gram positive and gram negative isolates are revealed in Table-IV.

	Type of samples			
Gram Negative (n=232)	**Blood C/S n(%)**	**PUS C/S n(%)**	**Sputum C/S n(%)**	**Urine C/S n(%)**
Acinetobacter species	0(0)	0(0)	2(0.86)	0(0)
Burkholderia cepacia	14(6.03)	0(0)	0(0)	1(0.43)
Citrobacter species	0(0)	0(0)	0(0)	1(0.43)
E. coli	30(12.93)	7(3.01)	3(1.29)	47(20.25)
Enterobacter species	3(1.29)	2(0.86)	0(0)	20(8.62)
Klebsiella pneumonia	8(3.44)	5(2.15)	14(6.03)	9(3.87)
Moraxella catarrhalis	2(0.86)	0(0)	5(2.15)	0(0)
Proteus mirabilis	0(0)	2(0.86)	0(0)	4(1.72)
Pseudomonas species	18(7.75)	1(0.43)	2(0.86)	5(2.15)
Pseudomonas aeruginosa	8(3.44)	3(1.29)	4(1.72)	9(3.87)
Salmonella typhi	3(1.29)	0(0)	0(0)	0(0)
Gram positive(n=79)				
Micrococcus species	16(20.25)	0(0)	0(0)	0(0)
Staphylococcus aureus	6(7.59)	2(2.53)	0(0)	0(0)
Staphylococcus epidermidis	49(62.0)	0(0)	0(0)	0(0)
Streptococcus species	5(6.32)	0(0)	0(0)	1(1.26)

Table-III. Frequency of gram negative or gram positive species in different specimen from FN patients (n=311)

n (%)= number(percentage), Fisher's exact test, p=<0.05

Antibiotics	Gram Negative Organisms										Gram Positive Organisms			
	Escherichia coli(88)		Enterobacter species(29)		Klebsiella pneumonia(36)		Pseudomonas aeruginosa(24)		Pseudomonas species(26)		Staphylococcus epidermidis(53)		Staphylococcus aureus(10)	
	S (n)	R (n)	S (n)	R (n)	S (n)	R (n)	S (n)	R (n)	S (n)	R (n)	S (n)	R (n)	S (n)	R (n)
Penicillin														
Amox-Clav	4	70	12	17	9	24	--	--	--	--	--	--	--	--
Oxacillin	--	--	--	--	--	--	--	--	--	--	17	33	2	8
Pipercillin/ Tazobactam	19	54	5	2	19	18	20	4	14	4	--	--	--	--
Cephalosporin														
Ceftriaxone	7	61	3	6	8	30	0	5	11	10	--	--	--	--
Glycopeptide														
Vancomycin	--	--	--	--	--	--	--	--	--	--	52	1	10	0
Monobactam														
Aztreonam	17	66	5	4	10	28	8	14	8	14	--	--	--	--
Carbapenem														
Meropenem	37	28	4	3	15	18	15	9	16	5	--	--	--	--
Aminogylcosides														
Amikacin	54	16	6	3	6	12	18	6	8	18	46	4	7	3
Quinolones														
Ciprofloxacin	6	82	5	22	6	32	16	7	17	9	24	26	--	--
Others														
Fosfomycin	7	77	13	10	31	5	--	--	--	--	--	--	--	--
Co-Trimoxazole	15	66	2	6	7	29	0	19	18	8	13	40	5	5
Linezolid	--	--	--	-	--	--	--	--	1	0	52	1	9	1
Colistin	70	8	9	0	28	6	20	4	15	11	--	--	--	--

Table-IV. Resistance and sensitivity patterns of antibiotics against most frequent gram positive and gram negative isolates

S=Sensitive; R=Resistant; --= Not required

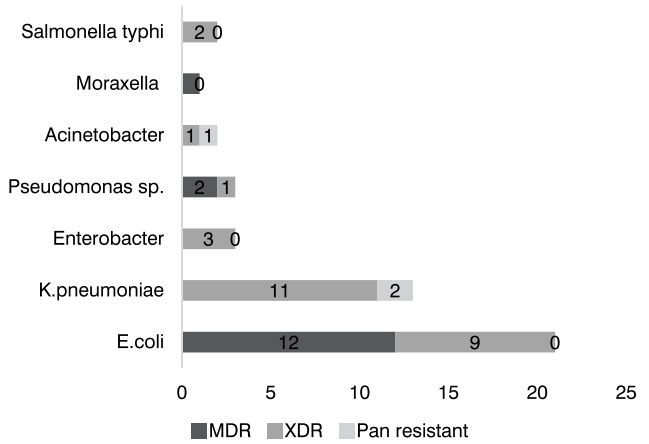

Figure-3. Distribution of MDR, XDR and PDR in Gram negative isolates

The frequency of methicillin resistant Staphylococcus aureus (MRSA), methicillin resistant Staphylococcus epidermidis (MRSE), XDR, CRE, MDR, PDR and VRE was 10(%), 30(9.6%), 16(5.1%), 16(5.1%), 15(4.8%), 3(0.96%) and 2(0.64%) respectively (Table-V and Figure-3). Blood stream infections due to resistant bacteria were frequent but pan resistant Acinetobacter sp. and K. pneumoniae were isolated from sputum and pus samples. (Table-V and Figure-3)

DISCUSSION

Infections are arguably the leading cause of death among cancer patients, especially those with hematologic malignancies, accounting for about 60% of reported deaths in this population.[18,19] The heightened vulnerability to infections can be ascribed to various factors originating from the patient's primary disease as well as their therapeutic implications.

	Blood(c/s) n(%)	Sputum(c/s) n(%)	Pus(c/s) n(%)	Urine(c/s) n(%)
MRSA(n=10)	8(2.57)	0(0)	2(0.64)	0(0)
MRSE(n=30)	30(100%)	0(0)	0(0)	0(0)
MDR(n=15)	5(1.6%)	2(0.64)	1(0.32)	7(2.25)
XDR(n=16)	9(2.89)	1(0.32)	2(0.64)	4(1.28)
CRE(n=16)	8(2.57)	1(0.32)	4(1.28)	4(1.28)
PDR(n=3)	0(0)	2(0.64)	0(0)	1(0.32)
VRE(n=2)	0(0)	0(0)	0(0)	2(0.64)

Table-V. Frequency of resistance according to the types of specimens

MDR: Multi Drug Resistant, XRD: Extensively Drug-Resistant, PDR: pan drug resistance, CRE: Carbapenem-Resistant Enterobacteriaceae, VRE: Vancomycin Resistant Enterococci, Methicillin-resistant Staphylococcus aureus

These infections may be caused by a variety of pathogens, including bacteria, fungi, viruses, and others. Interestingly, bacteria are the most common cause of infections among these microbiological offenders, followed by fungi.[19]

This trend emphasizes the significance to comprehend and treat bacterial infections in the context of cancer therapy since they pose a serious risk to these patients. According to the current study, gram-negative organisms represented predominance over gram-positive ones (74.6% vs. 25.4%), and the most prevalent gram-negative bacterial isolates among patients with FN who had hematological malignancies were Klebsiella pneumoniae and E. coli. Notably, a study from Palestine evaluating patients of hematological malignancies noted 45.8% gram negative bacteria and 39.6% gram positive isolates in patients with hematological malignancies.[20]
Similar to the current study, a study by John et al. from India found that gram-negative bacterial infections were more prevalent among cancer patients with FN, and that the most common bacterial isolates among these patients were Klebsiella pneumoniae (32.8%) and E. coli.[21] The results of another local investigation, which indicated that gram-positive and gram-negative isolates were detected in 75% and 25% of patients with hematological disorders and neutropenia, respectively, are in line with our findings about the pronounced preponderance of gram-negative isolates among FN cases (74.6%).[10]

In contrast to the study, which indicated that E. coli and Klebsiella pneumoniae were the most prevalent gram-negative isolates, our study found that E. coli was the most common bacterial isolate, followed by Pseudomonas aeruginosa and Klebsiella pneumoniae.[21] Similar findings were made by a prior national study of a juvenile cohort of chemotherapy-induced FN, which showed that gram-negative bacterial infections were present in 92% of cases (mostly Klebsiella, followed by Pseudomonas and E. coli).[22] The most common pathogen found in our gram-positive isolates was Staphylococcus epidermidis. Despite the fact that both S. epidermidis and Micrococcus species may contaminate normal skin flora, it is concerning as S. epidermidis isolates have a high level of methicillin resistance. Moreover, considering that S. epidermidis has been shown to have a major role in central line-related blood stream infections, these results highlight the variety of infections that cause FN in this cohort of patients.

Our study's patterns of antibiotic sensitivity and resistance showed that vancomycin and linezolid regularly showed high sensitivity rates as gram-positive bacteria, making them dependable therapeutic choices. Nonetheless, the sensitivity differences across gram-negative species, including ciprofloxacin's comparatively low sensitivity, were comparable to those found in the earlier study.[10] Moreover, our study reveals that resistance to widely used antibiotics like ciprofloxacin and fosfomycin is increasing. This emphasizes how crucial it is to choose antibiotics carefully. It has been observed that gram-negative organisms are becoming more resistant to carbapenems worldwide.[8,23]

According to an earlier study from our center,

the sensitivity against gram positive isolates was generally high (80%).[10] However, the current data indicates that the resistance patterns against gram positive isolates are significantly increased with regard to Co-Trimoxazole against staphylococcus epidermidis, which has become a serious problem in hospitals due to its resistance to several antibiotics.[24,25] Moreover, the present study also endorses restricting or discouraging the use of fluoroquinolone prophylactic due to the absence of conclusive evidence for increased survival. Furthermore, it is concerning that we found comparatively increased meropenem resistance patterns against E. coli in blood cultures.

Our study's limitations include the single center data and limited sample size. To provide more reliable conclusions, however, further thorough research is required following the implementation of antibiotic stewardship. Nevertheless, the study provides insights for the microbial profiles and antibiotic sensitivity in hematological malignancy patients with FN. Our findings emphasize the need for judicious antibiotic selection based on local resistance patterns, individualized patient characteristics and establishment of antibiotic stewardship which needs to be established at our center. To maximize treatment approaches and enhance patient outcomes in this population, ongoing field research and monitoring, along with the establishment of national statistics, are crucial.

CONCLUSION

FN is potentially a detrimental consequence in patients with hematological malignancies that increases the morbidity and mortality rates and also impairs the treatment outcomes. The recent investigation revealed a worrying rise in resistance to conventional antimicrobials in addition to the antibiotics that are frequently used in FN. While there has been progress in supportive care, more multicenter research is required to assess antibacterial and antifungal agents in both therapeutic and prophylactic settings, as well as to use biomarkers and risk prediction guidelines in the clinical setting to reduce the use of antimicrobial agents without compromising patient safety.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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3	**Samina Naz Mukry:** Contributed in manuscript writing.
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7	**Nida Anwar:** Conception of the study, designed, edited, critically reviewed and approved the final version of the manuscript.