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Research Article

Prevalence of Antimicrobial Resistant Bacterial Infections among Neutropenic Patients in Hiwa Cancer Hospital, Sulaimani, Iraq

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Abstract

Background: Febrile neutropenia is one of the most serious complications of cancer chemotherapies. Appropriate empirical antibiotics should be started immediately because delay in treatment may cause life-threatening consequences. ***Objective***: This study focuses on the common bacteria encountered at the Hiwa Hospital to review the current state of the hospital's antibiogram and recommendations for managing antimicrobial resistance. ***Method***: We retrospectively collected culture-confirmed febrile neutropenic cases from the system database of a tertiary care cancer hospital in Sulaimani, Iraq, from January 2021 to December 2022. ***Results***:144 culture-confirmed cases were collected during the study period, ninety-four of them from hematology wards and fifty from oncology wards. The participant age range was 2-79 years with a mean age of 34.8 years. Seventy-three of them were male with male to female ratio of 1:0.9. Gram-negative bacteria comprised 50.7% of total cases, 47.9% had gram-positive, while only 1.4% had fungal growth. The most common isolated pathogens were *Staphylococci* species (38.9%), *E. coli* (29.2%), *Klebsiella pneumonia* (9%), *Streptococcus* spp. (8.3%), and *Pseudomonas* spp. (8.3%). *Staphylococcus* spp. showed a significantly increased prevalence of resistance against amoxicillin/clavulanic acid, ceftriaxone, cefepime, and levofloxacin, while *E. coli* had it against ceftriaxone, ceftazidime, cefepime, ciprofloxacin, meropenem, and piperacillin/tazobactam. *Klebsiella* spp. had a significantly increased prevalence of resistance against amikacin, cefepime, and ciprofloxacin. MRS strains among *Staphylococci* spp. were 48.2%, MDR among gram-negative was 74%, and XDR was 12.3%. ***Conclusions***: We found a high prevalence of antibacterial resistance among cancer patients that contributes to quinolones-induced collateral damage.

Keywords: Antibiotic resistance, Collateral damage, Febrile neutropenia, MDR, MRS strains, XDR.

انتشار الالتهابات البكتيرية المقاومة لمضادات الميكروبات بين مرضى قلة العدلات في مستشفى هيوا للسرطان، السليمانية، العراق

الخلاصة

الخلفية: قلة العدلات الحموية (FN) هي واحدة من أخطر مضاعفات العلاجات الكيميائية للسرطان. يجب أن نبدأ المضادات الحيوية التجريبية المناسبة لمنع العواقب التي تهدد الحياة بسبب تأخير العلاج. **الهدف**: تسليط الضوء على البكتيريا الشائعة التي تصادف في مستشفى هيوا، والوضع الحالي للمضاد الحيوي للمستشفى وتوصيات للسيطرة على مقاومة العلاج. **الطريقة**: من يناير 2021 إلى ديسمبر 2022 ، جمعنا بأثر رجعي مرضى FN المؤكدين من الزرع البكتيري من قاعدة بيانات نظام مستشفى هيوا في السليمانية، العراق. **النتائج**: جمعنا 144 حالة مؤكدة من الزرع البكتيري، منها أربع وتسعون حالة من أجنحة أمراض الدم وخمسون حالة من أجنحة الأورام. تراوحت أعمار المشاركين بين 2-79 سنة. وكان ثلاثة وسبعون منهم من الذكور، وبلغت نسبة الذكور إلى الإناث 1: 0.9. شكلت البكتيريا سالبة الجرام 50.7٪ من إجمالي الحالات، و 47.9٪ كانت بكتيريا إيجابية الجرام، و 1.4٪ فقط نمو فطري. كانت مسببات الأمراض المعزولة الأكثر شيوعا هي أنواع المكورات العنقودية (38.9٪)، الإشريكية القولونية (29.2٪)، الكلبسيلة الرئوية (9٪)، العقدية النيابة (8.3٪)، والزائفة النيابة (8.3٪). كانت العديد من سلالات المكورات العنقودية مقاومة للأموكسيسيلين/حمض الكلافولانيك، سيفترياكسون، سيفيبيم، وليفوفلوكساسين. كانت الإشريكية القولونية مقاومة للسيفترياكسون، السيفتازيديم، السيفيبيم، سيبروفلوكساسين، ميروبينيم، وبيبيراسيلين/تازوباكتام. زاد انتشار مقاومة الأميكاسين والسيفيبيم والسيبروفلوكساسين بشكل ملحوظ بين Klebsiella spp. كانت هناك سلالات MRS بنسبة 48.2٪ بين المكورات العنقودية، و 74٪ سلالات مقاومة للأدوية المتعددة (MDR) بين السلالات سالبة الجرام، و 12.3٪ سلالات MDR بين السلالات المقاومة للأدوية (XDR) واسعة النطاق. **الاستنتاجات**: هناك انتشار كبير للمقاومة المضادة للبكتيريا بين مرضى السرطان، مما يساهم في الأضرار الجانبية التي يسببها الكينولون.

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INTRODUCTION

Infections in cancer patients constitute a significant contributor to morbidity, mortality, and substantial financial burdens [1]. It can present a significant obstacle to the efficacy of cancer treatment. The escalating global rise of antimicrobial resistance further exacerbates these challenges [1,2]. Febrile neutropenia is one of the most serious complications of cytotoxic myelosuppressive cancer chemotherapies and is associated with significant morbidity and mortality, it might necessitate chemotherapy holding or dose reduction which could impact the effectiveness of treatment [3,4]. The main function of neutrophils is to provide a host defense mechanism against infections, particularly bacterial and fungal infections [5,6]. Patients with neutropenic fever are particularly vulnerable to infections; the risk of infection increases with the severity and duration of neutropenia [7]. The severity of neutropenia is associated with the chemotherapy potency. The likelihood of progressive infections rises as the absolute neutrophil count (ANC) becomes lower than 1000/µL, and the risk of life-threatening infection increases as the (ANC) falls into the severely neutropenic range which is below <500/µL. Patients with agranulocytosis are highly susceptible to severe, life-threatening infections with opportunistic organisms which is characterized by an almost complete absence of neutrophils in the peripheral blood with ANC below 100/µL [8]. The incidence of febrile neutropenia varies according to malignancy, those patients who received chemotherapy for a hematological malignancy have a higher incidence compared to those with neoplastic therapy [7]. Patients with intermediate or high risk for developing febrile neutropenia are prophylactically treated with quinolones [5]. Upon diagnosis of severe febrile neutropenia, timely and appropriate action is necessary [5). Initial diagnostic approaches include a complete blood count with at least two sets of blood cultures followed by empirical antibiotic therapy [5,1]. Empirical antibiotic therapy is the initial administration of broad-spectrum antibiotics within 24 hours of admission due to the absence of information regarding the causative organism and it is antimicrobial susceptibility [9]. The goal of empirical antibiotic therapy is to offer sufficient coverage against common offending pathogens with minimal exposure to unnecessary antibiotics [10]. Selection of antibiotics should rely on patients' symptoms, previous culture, and the antibiogram data of the institution [11,1]. Empirical therapy must be followed by a target (adjusted) antibiotic therapy that uses antibiotics based on laboratory culture and sensitivity results [12]. Among microbes, bacteria stand as the predominant pathogens associated with febrile neutropenia [13,1]. The bacterial pathogens pattern differs both over time and across different countries or regions. Initially, gram-negative bacteria were more prevalent, but gram-positive bacteria later became more common [14,15,13). Recent trends show a resurgence of gram-negative bacteria in adults and gram-positive bacteria in pediatric patients [14]. Commonly implicated bacterial pathogens generally include aerobic gram negatives such as; *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*. Also, aerobic gram positives such as Staphylococcus aureus, coagulase-negative Staphylococci, viridans Streptococci, and Enterococci. Anaerobic bacteria and fungi are also possible but to a lesser extent [6,1,13]. The outlook is more unfavorable for individuals with confirmed bloodstream bacterial infections, especially rod-shaped gram-negative [16]. The mortality rate is 18% in cases of gram-negative bacteremia and 5% in instances of gram-positive bacteremia [17]. The World Health Organization (WHO) has warranted that the excessive and inappropriate use of antibiotics has resulted in the rise of antibiotic resistance, which poses a significant threat to global health security (7). Clinical practice guidelines from the Infectious Disease Society of America IDSA recommended empirical antibiotic monotherapy typically includes a beta-lactam antibiotic with antipseudomonal activity (cefepime, meropenem, imipenem, piperacillin/tazobactam) [1,13]. Unfortunately, the use of prophylactic antibiotics including extended-spectrum beta-lactamase (ESBL) contributed to the progression of resistance pathogens [1,6]. Infections caused by multi-drug-resistant (MDR) microorganisms contribute to higher mortality rates, increased demand for medical care, and increased treatment costs. Infections are among the most common causes of cancer patients' death, Unfortunately, the emergence of MDR pathogens threatens the efficacy of treatment and the survival of patients who rely on antibiotics for treatment success [7]. Variations in pathogen profiles by region emphasize the need for tailored management of febrile neutropenia in cancer patients, particularly given the global challenge of increasing antibiotic resistance [15]. However, few studies have been conducted in this hospital, and data on bacterial profile resistance in our region remains limited. This study focuses on the most common pathogens encountered in neutropenic patients at Hiwa Cancer Teaching Hospital to review the current state of the antibiogram of the hospital and enhance our understanding of the antimicrobial resistance and sensitivity patterns of the chosen agents. Additionally, the study aims to choose the most suitable antibiotic regimens for these patients. Moreover, it has the potential to pave the way for future investigation into this approach and may influence changes in the existing treatment guidelines of this hospital.

METHODS

Study design and setting

This cross-sectional study was conducted at Hiwa Cancer Teaching Hospital (tertiary care hospital) in Sulaimani, Iraq, with a secondary analysis of routinely collected hospital data. According to the hospital guidelines for any patient diagnosed and admitted with neutropenia routinely two sets of blood cultures are taken one from the central venous catheter and one from the peripheral vein, in cases where absent central catheter, two sets of peripheral vein puncture will be taken, a complete blood count test including differential leukocyte count will also be taken. The BD Phoenix fully automated system is used for rapid identification and bacterial susceptibility. Data was collected from the hospital patient information database between January 1, 2021 to December 31, 2021 compared to those of January 1, to December 31, 2022.

Inclusion criteria

Between 2021 and 2022, the Hiwa Hospital System database regularly recorded blood cultures with positive growth results for patients who developed FN between the ages of 2 years and older after receiving chemotherapy for an oncological or hematological malignancy.

Exclusion criteria

Those patients had neutropenia due to another cause, rather than chemotherapy. We excluded all patients with viral infections and those whose diagnoses were not documented at Hiwa Hospital, as these data were collected during the COVID-19 era.

Statistical analysis

We performed the statistical analysis using the Statistical Package for the Social Sciences (SPSS) version 26.0 (IBM Corp., Armonk, NY, USA). We present continuous variables as the mean and standard deviation (SD), and categorical variables as numbers and percentages. We used the chi-square test to estimate the difference between categorical variables. A *p-value of* <0.05 was considered significant.

RESULTS

A total of 144 blood cultures were collected during the study period from 1st January 2021, to 31st December 2022. Sixty-nine samples were obtained in 2021 and seventy-five in 2022. The participants' ages ranged from 2 to 79 years old with a mean age of 34.8±221 years. there were seventy-three males and seventy-one females resulting in a 1:0.9 male-to-female ratio. Ninety-four of the participants (65.3%) were admitted to hematological wards, while fifty (34.7%) were admitted to oncology wards (Table 1).

Table 1. Demographic and basic characteristics of the patients with neutropenic fever

Characteristics	Values
Age (year)	34.8±22.1
< 20 years	58(40.3)
20- 40 years	26(18.1)
41- 60 years	37(25.7)
>60 years	23(16.0)
Gender	
Male	73(50.7)
Female	71(49.3)
Ward	
Hematology	94(65.3)
Oncology	50 (34.7)
Years of collecting samples	
2021	69(47.9)
2022	75(52.1)
Total	144(100.0)

The values are expressed as frequencies, percentages, and means±SDs.

The incidence of bacterial growth for 2021 and 2022 were as the following subsequently; Gram-negative bacteria were detected among 50.7% (49.3%, 52%), whilst gram positive comprised 47.9% (47.8%, 48%) of all isolates, and only 1.4% (2.9%, 0%) were had fungal growth. The most common isolated organism were *Staphylococcu*s spp. 38.9% (40.6%, 37.3%), *E. coli* was the second highest by 29.2% (27.5%, 30.7%). *Klebsiella* came in third 9% (8.7%, 9.3%). This was followed by *Streptococci species* hemolyticus group 6.2% (4.3%, 8%), and non-hemolyticus *Streptococci* spp. or *Enterococcus* spp. 2.1% (2.9%, 1.3%), then *Enterobacter* spp.1.4% (1.4%, 1.3%) and lastly, *Truperella*, *Salmonella*, *Acinetobacter*, *Achromobacter, Stenotrophomonas* all were available in 0.7% (0%, 1.3%) (Table 2).

Table 2: Organisms isolated from febrile neutropenic patients

Microorganism isolated	2021	2022	Total
Gram-positive bacteria	33(47.8)	36(48.0)	69(47.9)
Staphylococcus	28(40.6)	28(37.3)	56(38.9)
Streptococcus hemolyticus	3(4.3)	6(8.0)	9(6.2)
Streptococcus nonhemolyticus	2(2.9)	1(1.3)	3(2.1)
Trueperella	0(0.0)	1(1.3)	1(0.7)
gram-negative bacteria	34(49.3)	39(52.0)	73(50.7)
E. coli	19(27.5)	23(30.7)	42(29.2)
Klebsiella	6(8.7)	7(9.3)	13(9.0)
Enterobacter	1(1.4)	1(1.3)	2(1.4)
Pseudomonas	8(11.6)	4(5.3)	12(8.3)
Salmonella	0(0.0)	1(1.3)	1(0.7)
Acinetobacter	0(0.0)	1(1.3)	1(0.7)
Achromobacter	0(0.0)	1(1.3)	1(0.7)
Stenotrophomonas	0(0.0)	1(1.3)	1(0.7)
Fungi	2(2.9)	0(0.0)	2(1.4)
Candida	2(2.9)	0(0.0)	
Total	69(48.0)	75(52.0)	144(100.0)

The values are expressed as frequencies and percentages.

Out of 142 positive samples with bacterial growth, only four showed sensitivities to all tested antibacterial (three gram-positive, one gram-negative). Among 94 hematological cases, 50 of them had gram-negative bacterial growth, while among oncological cases 23 had gram-negative bacterial growth (Table 3). Among 42 isolated *E. coli*, 83.3% of them were MDR, and 4.765 were XDR. Among 13 isolates of *K. pneumonia* 76.9% were MDR and 15.38 were XDR, while among 12 isolates of *P. aeruginosa*, 58.3% were MDR and 41.65 were XDR.

Table 3: Distribution of gram-negative vs gram-positive isolates among hematology and oncological malignancies

Ward	Gram-negative	Gram-positive	Fungi
Hematology (n=94)	50(53.2)	44 (46.8)	0(0.0)
Oncology (n=50)	23(46)	25(50)	2(4)
144	73	69	2

The values are expressed as frequencies and percentages.

Table 4: Gram-negative MDR strains over the two subsequent years

Bacteria	2021	2022	Total
E. coli	13	22	35(83.3)
K. pneumonia	4	6	10(76.9)
P. aeruginosa	5	2	7(58.3)
A. bumannii	0	1	1(100)
Stenotrophomonas spp.	0	1	1(100)
Total	22	32	54(74)

The values are expressed as frequencies and percentages. MDR: multidrug resistance.

Table 5: Gram-negative XDR over the two subsequent years

Bacteria	2021	2022	Total
E. coli	1	1	2(4.76)
K. pneumonia	1	1	2(15.38)
P. aeruginosa	3	2	5(41.6)
A. bumannii	0	0	0(0.0)
Stenotrophomonas spp.	0	0	0(0.0)
Total	5	4	9(12.3)

The values are expressed as frequencies and percentages. XDR: extensive drug resistance.

Table 4 and Table 5. MRS strains in 2021 were twelve (among 28 staphylococci species) which is 42.8%. In 2022 fifteen were isolated (among 28 staphylococci species) which accounts for 53.5% of them. In 2021 among two isolated Enterococci species, both of them were VRE, whilst only one Enterococci was found in 2022 and it was VSE (Table 6).

Table 6: Gram-positive MDR strains over the two subsequent years

Bacteria	2021	2022	Total
Staphylococcus spp.	12	15	27(48.2)
Enterococci spp.	2	0	2(66.6)

The values are expressed as frequencies and percentages. MDR: multidrug resistance.

We analyzed the common pathogens identified in this study and compared them with the antibiotics commonly utilized at Hiwa Cancer Teaching Hospital. Among gram negatives, a significantly increased prevalence of *E. coli* resistance was found against ceftriaxone, ceftazidime, cefepime, ciprofloxacin, meropenem, and, piperacillin/tazobactam. *Klebsiella* resistance against ceftazidime was 100% in both years, and it is prevalence of resistance was found to increase toward ciprofloxacin and cefepime. The resistance pattern of *pseudomonas* was only increased against ciprofloxacin (Table 7). In our study four isolates of gram-positive bacteria were isolated, fifty-six of them were *staphylococcus species* that showed a significantly increased prevalence of resistance to amoxicillin/clavulanic acid, ceftriaxone, cefepime, and levofloxacin. When the number of tested isolates is below four in one year, we did not calculate the *p*-value due to an imbalanced comparison between the two years (Table 8).

DISCUSSION

Cancer patients are highly susceptible to infections owing to either the myelosuppressive effect of chemotherapy or damage of primary host defense mechanism as mucosal membranes of the alimentary track that leads to normal flora translocations into the bloodstream and infection. In neutropenic patients; fever may be the only and early sign of infection due to diminished neutrophil-mediated inflammatory response. Early recognition of sever neutropenic fever and appropriate empirical systemic antibiotic therapy is crucial, thereby preventing the progression to sepsis and fatal outcomes [15]. Our results demonstrated that there was not a significant difference in the incidence of febrile neutropenia among the two genders. According to a recent study, they had a male ratio slightly higher than the female ratio but they could not find any statistically significant association between gender and febrile neutropenia [18]. In another study by Ali *et al*. [19], there was no notable variance in the incidence of febrile neutropenia between the two genders. Another study by Poveda *et al*. [20] reported a male-to-female ratio near our results. Consistent with existing literature, our data demonstrates a higher incidence of febrile neutropenia among hematological malignancies than those with solid tumors [6]. We had a hematology versus oncology rate of 65.3% to 34.7% respectively, this result is disproportionate to the data from Joudeh *et al*. [6] who got 84.7% among hematological cases. While Makhani *et al*. [18] had only 59.4% of hematological malignancies who experienced febrile neutropenia. However, another study in Iran by Vahedian-Ardakani *et al*. [14] yielded results that closely resemble our findings, they reported 63.3% cases in hematology and 37.7% in oncology. Over

the following twenty years, there was a notable shift in the causes of febrile neutropenia with a significant decrease in cases caused by gram-negative bacilli and a rise in those cases caused by gram-positive cocci.

Table 7: Antibiotic resistance in gram-negative isolates

Microorganisms	Year	Amikacin	Ceftriaxone	Ceftazidime	Cefepime	Colistin	Ciprofloxacin	Meropenem	piperacillin/ tazobactam
E. Coli	2021	1(6.3%) (n=16)	6 (42.9) (n=14)	8(50.0) (n=16)	1(12.5) (n=8)	0 (0.0%) (n=19)	3(27.3) (n=11)	3(16.7) (n=18)	0(0.0) (n=11)
	2022	1(4.3) (n=23)	20(87.0) (n=23)	19(82.6) (n=23)	19(82.6) (n=23)	0(0.0) (n=23)	20(87.0) (n=23)	8(34.8) (n=23)	12(54.5) (n=22)
	Total	2(5.1) (n=39)	26(70.3) (n=37)	27(69.2) (n=39)	20(64.5) (n=31)	0(0.0) (n=42)	23(67.6) (n=34)	11(26.8) (n=41)	12(36.3) (n=33)
	***p*-value**	**0.35**	**0.009**	**0.034**	**<0.001**	**>0.05**	**0.002**	**0.019**	**0.001**
Klebsiella	2021	3(50.0) (n=6)	5(83.3) (n=6)	6(100.0) (n=6)	3(75.0) (n=4)	0(0.0) (n=6)	2(50.0) (n=4)	3(50.0) (n=6)	3(75.0) (n=4)
	2022	1(14.3) (n=7)	6(100.0) (n=6)	7(100.0) (n=7)	7(100.0) (n=7)	0(0.0) (n=7)	5(83.3) (n= 6)	3(42.9) (n=7)	6(85.7) (n=7)
	Total	4(30.8) (n=13)	11(91.7) (n=12)	13(100.0) (n=13)	10(90.9) (n=11)	0(0.0) (n=13)	7(70.0) (n=10)	6(46.2) (n=13)	9(81.8) (n=11)
	***p*-value**	**0.016**	**0.363**	**>0.05**	**0.0103**	**>0.05**	**0.026**	**0.797**	**0.175**
Pseudomonas	2021	4(50.0) (n=8)	8(100.0) (n=8)	8(100.0) (n=8)	4 (80) (n=5)	0(0.0) (n=8)	1(20.0) (n=5)	5(62.5) (n=8)	2(50.0) (n=4)
	2022	1(25.0) (n=4)	4(100.0) (n=4)	2(50.0) (n=4)	2(50.0) (n=4)	0(0.0) (n=4)	2(50.0) (n=4)	2(50.0) (n=4)	1(25.0) (n=4)
	Total	5(41.7) (n=12)	12(100.0) (n=12)	10(83.3) (n=12)	6(66.7) (n=9)	0(0.0) (n=12)	3(33.3) (n=9)	7(58.3) (n=12)	3(37.5) (n=8)
	***p*-value**	**0.031**	**>0.05**	**0.009**	**>0.05**	**>0.05**	**0.016**	**0.577**	**0.018**

The data are expressed as numbers and percentages.

Table 8: Antibiotic resistance in gram-positive isolates

Microorganism	Year	Ampicillin	Amoxicillin/ clavulanic acid	Ceftriaxone	Cefepime	Levofloxacin	Vancomycin	Meropenem	Piperacillin/ tazobactam
Staphylococcus spp.	2021	14(93.3) (n=15)	8(57.1) (n=14)	9(39.0) (n=23)	7(58.3) (n=12)	5(21.7) (n=23)	0(0.0) (n=28)	8(61.5) (n=13)	11(44.0) (n=25)
	2022	25(92.6) (n=27)	13(81.25) (n=16)	17(80.95) (n=21)	15(83.3) (n=18)	21(75.0) (n=28)	0(0.0) (n=28)	13(68.4) (n=19)	13(72.2) (n=18)
	Total	39(92.9) (n=42)	21(70) (n=30)	26(59.1) (n=44)	22(73.3) n=30	26 (51.0) (n=51)	0(0.0) (n=56)	21(65.6) (n=32)	24(55.8) (n=43)
	***p*-value**	**0.420**	**0.017**	**0.015**	**0.022**	**<0.001**	**>0.05**	**0.05**	**0.066**
Streptococci nonhemolyticus	2021	0(0.0) (n=0)	0(0.0) (n=2)	1(33.3) (n=3)	1(50.0) (n=2)	0(0.0) (n=1)	0(0.0) (n=3)	0(0.0) (n=1)	0(0.0) (n=3)
	2022	2(66.7) (n=3)	2(50.0) (n=4)	2(66.7) (n=3)	2(50.0) (n=4)	1(20.0) (n=5)	0(0.0) (n=5)	2(33.3) (n=6)	2(40.0) (n=5)
	Total	2(66.7) (n=3)	2(33.3) (n=6)	3(50) (n=6)	3(50.0) (n=6)	1(16.6) (n=6)	0(0.0) (n=8)	2(28.6) (n=7)	2(25.0) (n=8)
	***p*-value**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**
Streptococci hemolyticus	2021	0(0.0) (n=2)	2(100.0) (n=2)	1(50) (n=2	2(100) (n=2)	0 (0.0) (n=2)	2(100) (n=2)	1(50) (n=2)	0(0.0) (n=1)
	2022	0(0.0) (n=2)	1(100) (n=1)	1(100) (n=1)	1(100) (n=1)	0(0.0) (n=2)	0(0.0) (n=2)	1(100) (n=1)	0(0.0) (n=0)
	Total	0(0.0) (n=4)	3(100.0) (n=3)	2(66.7) (n=3)	3(100.0) (n=3)	0(0.0) (n=4)	2(50.0) (n=4)	2(66.7) (n=3)	0(0.0) (n=1)
	***p*-value**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**

The data are expressed as numbers and percentages. N/A: not calculated due to low isolate.

This shift can be attributed to various factors including widespread administration of chemotherapy leading to substantial oral mucositis, the near-universal presence of central venous catheters among these patients, and frequent use of prophylactic antibiotics primarily targeting gram-negative bacilli as quinolones [21,22,6]. Another factor for gram-positive shifts back is the excessive consumption of H2 receptor antagonists and those drugs that suppress gastric acid secretion among these patients [23]. A study from Tanzania [24] showed that all their cases had gram-positive bacterial growth. However, in recent years several studies highlighted a notable revert in the epidemiology of febrile neutropenia, indicating a shift back from gram-positive to gram-negative, additionally, there has been a significant emergence of MDR prevalence [21,22,25]. A similar trend was reported by Vahedian-Ardakani *et al*. [14] they recorded 84.9% gram-negative. However recent data from a study in the Middle East shows gram positives are more predominant [6]. Our results showed that among culture-

positive cases, 73 (50.7%) of them were gram-negative 34 (49.6%) in 2021 and 39 (53.4%) in 2022 and 69 (47.9%) were gram-positive 33 (47.8%) in 2021 and 36 (52.2%) in 2022. Among hematological cases, 53.2% of them had gram-negative growth. However, most investigators reported an incidence of gram-negative bacteria among hematological cases higher than what we reported [14,15], this can be attributed to many factors, as we followed our patients' drug history from the hospital database, almost all cases who admitted at hematological wards they had received prophylactic doses of quinolones that can decrease gram-negative incidence and protect most of those with hematological malignancy against bacteremia post-chemotherapy [17]. However, many centers reported comparable rates of gram-positive and gram-negative incidence of bacteremia in FN [22,17]. Fungal infection in our hospital was %1.4 which is comparable to another Middle Eastern country study 1% [17]. Regarding the most common offending pathogen, our findings show predominance of *Staphylococci* spp., *E. coli*, *Streptococci* spp., *Klebsiella*, and *Pseudomonas* spp. A similar trend was also reported by Parodi et al. [22]. *Staphylococci spp*. was the most frequently isolated bacteria by 38.9%, with 28 isolates each year. 42.8% of *Staphylococci spp*. were MRS strains and this value increased to 53.5% in 2022. That represents 18.7% of total cases and 48.2% of all *Staphylococci spp*. This value is lower than a study conducted in Venezuela by Morris *et al*. [26], who found that 89.3% of Staphylococcus aureus spp were MRSA and it is higher than a recent study from a developed country by Joudeh *et al*. [6] they reported only 1.6% MRSA. Lubwama *et al*. [25] from Uganda reported that all *Staphylococcus spp*. in their study were MRSA. *Staphylococcus spp*. in our study had a significantly increased prevalence of resistance to amoxicillin/clavulanic acid, ceftriaxone, cefepime, and levofloxacin. It has an overall resistance rate of 92.9% to ampicillin, 70% to amoxicillin/clavulanic acid, 59.1% to ceftriaxone, 73.3% to cefepime, 51% to levofloxacin, 65.6% to meropenem, and 55.8% to piperacillin/tazobactam. Among 12 Streptococci spp. nine of them were *Streptococci hemolyticus* group (6.2%) and three were non hemolyticus group (*Enterococci spp*. 2.1%). The non-hemolyticus group in 2021 was 100% susceptible to ampicillin, amoxicillin/clavulanic acid, levofloxacin, vancomycin, meropenem, and piperacillin/tazobactam. It is total resistance to ampicillin was 66.7%, amoxicillin/clavulanic acid and ceftriaxone 33.3%, cefepime 50%, levofloxacin 16.6%, meropenem 28.6% and, piperacillin/tazobactam was 25%. Among two Enterococci spp in 2021, both of them were VRE, while in 2022 only one species was isolated and it was VSE. Totally they were 100% susceptible to piperacillin/tazobactam, levofloxacin, and ampicillin. In the Joudeh *et al*. [6] study they were resistant to piperacillin/tazobactam by 42.9% and to ampicillin by 33.3%, and they reported Enterococci as the predominant pathogen while it was not found as a dominant pathogen in our results and VRE prevalence was not increased over the two subsequent years. Among gram-negative pathogens, E. coli represents the most frequently isolated bacteria 19 in 2021 and 23 in 2022. That is 29.2% of total cases, this finding is consistent with a review [21], which reported it is range from 10.1%-53.6%. In 2021 among 11 isolated *E. coli* samples, tested for piperacillin/tazobactam susceptibility, all of them were sensitive to it, but in 2022 (54.5%) of 22 isolated tests became resistant to it. It is total resistance rate over the two subsequent years was 5.1% to amikacin, 70.3% to ceftriaxone, 69.23% to ceftazidime, 64.5% to cefepime, 67.6% to ciprofloxacin, 26.8% to meropenem and 36.3% to piperacillin/tazobactam. A study from Iran by Vahedian-Ardakani *et al*. [14] reported 50% resistance to ciprofloxacin, 31% to amikacin, 20% to meropenem, and another study from Vietnam by Bhat *et al*. [27] reported that 82.9% of E. coli were resistant to quinolones,42.8% to aminoglycosides, 15.6% to carbapenems. Over the two subsequent years, there were 13 isolates of Klebsiella pneumonia, which represents 9% of total pathogens, six in 2021 and seven in 2022. This result is consistent with a review [21] that included 24 studies, and Klebsiella pneumonia isolation range was mentioned as 9.7%-44.5%. In our study, Klebsiella pneumonia was highly resistance to ceftazidime and ceftriaxone in 2021, which means the prevalence of resistance did not significantly increase since it was already high in 2021 (100% and 83%) to 100% and 100%, respectively. Overall *Klebsiella pneumonia* in our study was resistant to Amikacin by 30.8%, ceftriaxone by 91.7%, ceftazidime by 100%, cefepime by 90.9%, ciprofloxacin 70%, meropenem 46.2% and piperacillin/tazobactam 81.8%. while in the Joudeh *et al*. [6] study it was resistance to cefepime by 40%, ceftriaxone by 50%, ceftazidime piperacillin/tazobactam, and ciprofloxacin 60%. Another study by Lubmawa *et al*. [25] reported Klebsiella pneumonia resistance against ceftazidime and ceftriaxone was 100%, piperacillin/tazobactam and ciprofloxacin were 85.7%. Pseudomonas aeruginosa accounted for 8.3% of our results 8 in 2021 and 4 in 2022. This finding is consistence with the Trecarichi & Tumbarello [21] review, who recorded it is frequency in 7%-44.5%. In 2021 it has 50% resistance to amikacin,100% to ceftazidime, 80% to cefepime, 20% to ciprofloxacin, 62.5% to meropenem and 50% to piperacillin/tazobactam. In 2022 it showed a significant prevalence of increased resistance against ciprofloxacin, whilst it decreased significantly toward amikacin, piperacillin/tazobactam, and ceftazidime. Joudeh *et al*. [6] results showed that Pseudomonas aeruginosa resistance to meropenem was 66.7%, and 50% to ciprofloxacin, ceftazidime, and cefepime while in our study it is mean resistance rate over the two subsequent years was 41.7% to amikacin, 83.3% to ceftazidime, 66.7% to cefepime, 33.3% to ciprofloxacin, 58.3% to meropenem and 37.5% to piperacillin/tazobactam. MRS strains and VRE are usually considered MDR among gram-positive [1]. Our cumulative data showed the dominance of Staphylococcus spp. and among them, 48.2% were MRS strains. However, 66% of isolated *Enterococci spp*. were VRE, but Enterococci prevalence in our results was not high, it

represented only 2.1% of all isolates. Among gram-negative bacteria, in 2021 64.7% were MDR, and in 2022 it increased to 82%. Overall MDR prevalence was 74% of gram-negative in the two years. 12.9% of our patients had XDR and this value is higher than Vahedian-Ardakani *et al*. [14] result, who found 10% XDR. The high prevalence of MRS strains and the high quinolone resistance rate among gram-negative rods indicate quinolone-induced collateral damage. Quinolones and cephalosporins are implicated to cause collateral damage, which is increased susceptibility to opportunistic infections, and emergence of MDR in non-targeted bacteria. The type of collateral damage depends on the type of antibiotic used. In the case of cephalosporins; it can lead to VRE, ESBL-Klebsiella Pneumonia, Beta-lactam resistance Acinetobacter, and C-difficile infections. While quinolone overuse has been associated with quinolone resistance among gram-negative bacilli and, increases the incidence of MRSA infections [28]. This is in line with our results because sustained use of quinolones among cancer patients. Many guidelines as IDSA, NCCN, and ASCO recommend quinolones as prophylaxis for those cases who received intermediate and high-intensity chemotherapy as they are expected to experience severe and long-lasting neutropenia [5,29]. Among gram positives, all MRS strains were susceptible to vancomycin which makes it an appropriate drug of choice for cases diagnosed with it. VRE was an uncommon pathogen which makes it unnecessary to cover it in empirical therapy. The aforementioned two points indicate that; vancomycin remained with a high susceptibility rate in Hiwa Hospital. Regarding it is role as a component in empirical therapy; glycopeptides are only recommended in high-suspicion gram-positive infection and in institutions with high MRSA prevalence [30] however many guidelines provided wide ranges of recommendations for their indications, but they had poor clinical outcomes [31]. colistin showed no resistance in our data.

Conclusions

Our findings demonstrated a high prevalence of antimicrobial resistance among febrile neutropenic patients at Hiwa Cancer Teaching Hospital, which was mostly caused by quinolone-induced collateral damage. It is crucial that the empirical antibiotics employed at Hiwa Cancer Teaching Hospital efficiently treat multidrug-resistant Gram-negative bacteria. Given the high prevalence of cephalosporin resistance, we must employ carbapenems such as meropenem or imipenem as empirical therapy for severe neutropenic patients. Furthermore, the hospital must develop and update an antibiogram on a regular basis, as the rate of resistance to most antibiotics has increased dramatically.

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Conflict of interests

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Supplementary data can be shared with the corresponding author upon reasonable request.

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