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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 (FN) is one of the most serious complications of cancer chemotherapies. To avoid life-threatening complications from treatment delays, appropriate empirical antibiotics treatment should be initiated. ***Objective***: To highlight the common bacteria encountered at Hiwa Hospital, the current state of the hospital's antibiogram and recommendations for resistance management. ***Method***: From January 2021 to December 2022, we retrospectively collected culture-confirmed FN cases from the Hiwa Hospital system database in Sulaimani, Iraq. ***Results***: We collected 144 culture-confirmed cases, with ninety-four from hematology wards and fifty from oncology wards. The participants' ages ranged from 2–79 years. Seventy-three of them were male, with a male-to-female ratio of 1:0.9. Gram-negative bacteria comprised 50.7% of the total cases, 47.9% had gram-positive bacteria, and only 1.4% had fungal growth. The most common isolated pathogens were *Staphylococci species* (38.9%), *E. coli* (29.2%), *Klebsiella pneumoniae (*9%), *Streptococcus spp.* (8.3%), and *Pseudomonas spp.* (8.3%). A large number of *Staphylococcus* spp. were resistant to amoxicillin/clavulanic acid, ceftriaxone, cefepime, and levofloxacin. In contrast, *E. coli* was resistant to ceftriaxone, ceftazidime, cefepime, ciprofloxacin, meropenem, and piperacillin/tazobactam. Klebsiella spp. exhibited significantly higher levels of resistance to amikacin, cefepime, and ciprofloxacin. MRS strains were found in 48.2% of Staphylococci spp., 74% of gram-negative bacteria, and 12.3% of extensive drug-resistant (XDR) isolates. ***Conclusions***: There is a high prevalence of antibacterial resistance among cancer patients, which contributes to quinolone-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 cause severe morbidity, death, and cost burdens [1]. It can significantly reduce cancer treatment efficacy. The growing global prevalence of antibiotic resistance exacerbates these issues [1,2]. Febrile neutropenia is one of the most serious side effects of cytotoxic myelosuppressive cancer chemotherapy, resulting in significant morbidity and mortality. It may prompt a chemotherapy pause or dose reduction, affecting therapeutic efficacy [3,4]. Neutrophils serve as the host's primary defense mechanism against infections, notably bacterial and fungal infections [5,6]. Patients with neutropenic fever are especially susceptible to infections; the risk of infection increases with the severity and duration of neutropenia [7]. The potency of chemotherapy influences the severity of neutropenia. Lowering the absolute neutrophil count (ANC) below 1000/µL increases the risk of progressive infections, whereas ANC levels below <500/µL increase the risk of potentially fatal infections. Patients with agranulocytosis are especially prone to serious, life-threatening infections caused by opportunistic organisms. This is defined as an almost complete lack of neutrophils in the peripheral blood with an ANC ≤ 100/µL [8]. Patients who are at intermediate or high risk of developing febrile neutropenia are treated prophylactically with quinolones [5,6]. The frequency of febrile neutropenia varies by malignancy; patients who had chemotherapy for a hematological malignancy had a higher prevalence than those who underwent neoplastic therapy [7]. Following a diagnosis of severe FN, prompt and appropriate intervention is required. Initial diagnostic approach includes a full blood count and 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 a lack of information about the underlying organism and its antimicrobial susceptibility [9]. The goal of empirical antibiotic therapy is to provide enough coverage against common offending pathogens while minimizing exposure to unneeded medicines [10]. The selection of antibiotics should be based on the patients' symptoms, past culture, and the institution's antibiogram data [11,1]. Empirical therapy must be followed by target antibiotic therapy, which employs antibiotics based on laboratory culture and sensitivity findings [12]. Bacteria are the most common pathogens linked with febrile neutropenia [13,1]. The bacterial pathogen pattern varies over time and among countries or areas. Gram-negative bacteria were more numerous at first, but Gram-positive bacteria became more widespread with time [14,15,13]. Recent trends indicate a return of Gram-negative bacteria in adults and of Gram-positive bacteria in pediatric patients [14]. Bacterial pathogens frequently include aerobic Gram-negative bacteria such as *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*. Furthermore, aerobic Gram-positive bacteria like *Staphylococcus aureus*, coagulase-negative Staphylococci, Viridans, Streptococci, and Enterococci can also be present. Anaerobic bacteria and fungi are also possible, but to a lesser extent [6,1,13]. Individuals with confirmed bloodstream bacterial infections, particularly rod-shaped Gram-negative bacteria, have a less favorable outlook [16]. In cases of Gram-negative bacteremia, the mortality rate is 18%, while in cases of Gram-positive bacteremia, it is 5% [17]. The World Health Organization (WHO) has noted that excessive and inappropriate antibiotic usage has led to increased antibiotic resistance, posing a serious danger to global health [7]. The Infectious Disease Society of America (IDSA) clinical practice guidelines suggest empirical antibiotic monotherapy, which commonly comprises a beta-lactam antibiotic with antipseudomonal activity (cefepime, meropenem, imipenem, piperacillin, or tazobactam) [1,13]. Unfortunately, the use of prophylactic antibiotics, such as extended-spectrum beta-lactamase (ESBL), has contributed to the spread of resistant pathogens [1,6]. Infections caused by multidrug-resistant (MDR) germs increase mortality rates, the need for medical attention, and treatment costs. Infections are one of the leading causes of death among cancer patients. Unfortunately, the advent of MDR microorganisms puts treatment efficacy and patient survival at risk [7]. Variations in pathogen profiles by area highlight the need for individualized care for FN patients, especially considering the global challenge of antibiotic resistance [15]. However, our facility has not conducted many studies, and there is a scarcity of information on bacterial profile resistance in our region. This study focused on the most prevalent pathogens encountered in neutropenic patients at Hiwa Cancer Teaching Hospital, with the goal of reviewing the hospital's current antibiogram and improving our understanding of the antimicrobial resistance and sensitivity patterns of the chosen drugs. Furthermore, this study sought to identify the most appropriate antibiotic regimens for these patients. Furthermore, this study has the potential to pave the way for future research into this strategy as well as influence modifications in this hospital's current treatment recommendations.

METHODS

Study design and setting

This cross-sectional study was carried out at the Hiwa Cancer Teaching Hospital (a tertiary care facility) in Sulaimani, Iraq, and included a secondary analysis of routinely gathered hospital data. According to hospital protocols, for any patient identified and admitted with neutropenia, two sets of blood cultures are usually

obtained, one from the central venous catheter and one from the peripheral vein. If the central catheter is not present, we will perform two sets of peripheral vein punctures and a complete blood analysis, including a differential leukocyte count. Those patients had neutropenia due to another cause, rather than chemotherapy. Those patients had diagnoses not documented at Hiwa Hospital and all cases with viral infections were excluded since the results were collected during the COVID-19 era. The data were acquired from the hospital patient information database between January 1, 2021, and December 31, 2021, as opposed to January 1, 2021, to December 31, 2021.

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 <0.05 was considered significant.

RESULTS

Between January 1, 2021, and December 31, 2022, we collected 144 blood cultures in total. We collected 69 samples in 2021 and 75 samples in 2022. The participants' ages ranged from 2 to 79 years, with a mean of 34.8±22.1 years. There were 73 males and 71 females, resulting in a male-female ratio of 1:0.9. Hematological units admitted 94 participants (65.3%), while cancer wards admitted 50 (34.7%) (Table 1). In 2021 and 2022, bacterial growth incidence was as follows: 50.7% (49.3%, 52%) of all isolates were Gram-negative bacteria, 47.9% (47.8%, 48%) were Gram-positive bacteria, and only 1.4% (2.9, 0%) were fungi.

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 most often isolated microbes were *Staphylococcus species* (38.9%, 40.6%, and 37.3%), with *E. coli* ranking second at 29.2% (27.5%, 30.7%). *K. pneumoniae* ranked third at 9% (8.7%, 9.3%). *Klebsiella* ranked third with 9% (8.7%, 9.3%). The *Streptococci hemolyticus* group came in second at 6.2% (4.3%, 8%), followed by the non-hemolyticus *Streptococci* species or *Enterococcus* species at 2.1% (2.9%, 1.3%), and then by the *Enterobacter* species. Finally, *Truperella*, *Salmonella*, *Acinetobacter*, *Achromobacter*, and *Stenotrophomonas* were all present in 0.7% (1.4%, 1.3%).

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.

In Table 2, of the 142 positive samples exhibiting bacterial growth, only four were sensitive to all the evaluated antibacterial agents. We observed Gram-negative bacterial growth in 50 of the 94 hematological patients and in 23 of the oncological patients (Table 3). Among 42 isolated *E. coli* strains, 83.3% were MDR, while 4.765 were XDR. Among the 13 *K. pneumoniae* isolates, 76.9% were MDR and 15.38 were XDR, whereas among the 12 *P. aeruginosa* isolates, 58.3% were MDR and 41.65 were

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.

In 2022, we isolated 15 of the 28 *Staphylococci* species, accounting for 53.5% of them. In 2021, we isolated two *Enterococci* species, both of which were vancomycin-resistant *Enterococci* (VRE), but only one vancomycin-sensitive *Enterococci* spp. (VSE) was identified in 2022 (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 frequent bacteria found in this study and compared them to antibiotics commonly used at Hiwa Cancer Teaching Hospital. The Gram-negative strains of *E. coli* showed significantly high prevalence of resistance to ceftriaxone, ceftazidime, cefepime, ciprofloxacin, meropenem, and piperacillin/tazobactam. We discovered 100% resistance of *Klebsiella* to ceftazidime in both years, as well as a rise in resistance to ciprofloxacin and cefepime. Only ciprofloxacin increased the *Pseudomonas* resistance pattern (Table 7). Four types of Gram-positive bacteria were found in this study.

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.

Of these, 56 species of *Staphylococcus* showed significantly higher prevalence of resistance to amoxicillin/clavulanic acid, ceftriaxone, cefepime, and levofloxacin. We did not calculate the *p*-value when there were fewer than four tested isolates in a single year due to an uneven comparison between the two years (Table 8).

DISCUSSION

Cancer patients are more likely to get infections because chemotherapy can weaken or impair the body's primary defensive mechanism, such as the mucosal membranes of the digestive tract, allowing normal bacteria to enter the

bloodstream and cause infections. Fever may be the only early symptom of infection in neutropenic individuals due to a reduced neutrophil-mediated inflammatory response. Early identification of severe neutropenic fever and proper empirical systemic antibiotic therapy are critical in preventing the condition from advancing to sepsis and eventually mortality [15]. Our findings showed that the incidence of FN was not significantly different between the sexes.

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.

According to a recent study, the male ratio was somewhat higher than the female ratio, although there was no statistically significant link between gender and FN [18]. In another study, Ali *et al*. [19] found no significant difference in the incidence of FN between the two sexes. Poveda *et al*. [20] found a male-female ratio similar to ours. Consistent with the existing literature, our findings showed that individuals with hematological malignancies had a higher incidence of FN than those with solid tumors [6]. The hematology and oncology rates varied from 65.3% to 34.7%, respectively. This result is disproportionate to the findings of Joudeh *et al*. [6], who collected 84.7% of hematological cases. Makhani *et al*. [18] found that FN occurred in only 59.4% of individuals with hematological malignancies. Another study in Iran by Vahedian-Ardakani *et al*. [14] produced results that are very similar to ours; they recorded 63.3% of cases in hematology and 37.7% in oncology. Over the next two decades, the etiology of FN shifted dramatically, with Gram-negative bacilli accounting for fewer instances and Gram-positive cocci accounting for more. This shift can be attributed to a variety of factors, including widespread chemotherapy administration, which results in significant oral mucositis, the near-universal presence of central venous catheters among these patients, and the frequent use of prophylactic antibiotics primarily targeting Gram-negative bacilli, such as quinolones [21,22,6]. Another explanation for these Gram-positive shifts is that the patients are using too many H2 receptor antagonists and medicines that inhibit stomach acid production [23]. A study from Tanzania found that all of their cases exhibited Gram-positive bacterial growth [24]. However, multiple investigations in recent years have revealed a significant reversal in the epidemiology of FN, showing a shift from Gram-positive to Gram-negative cases. In addition, the prevalence of MDR strains has significantly increased [21,22,25]. Vahedian-Ardakani *et al*. [14] found a similar trend, with 84.9% Gram-negative. However, a recent study in the Middle East found that Gram-positive bacteria are more prevalent [6]. Our results revealed that 73 (50.7%) of the culture-positive patients were Gram-negative. Overall, 34 (49.6%) patients in 2021, 39 (53.4%) in 2022, 69 (47.9%) in 2021, 33 (47.8%) in 2021, and 36 (52.2%) in 2022 tested positive for Gram stain. Of the hematological patients, 53.2% exhibited Gram-negative growth. However, most investigators have indicated that the prevalence of Gram-negative bacteria among hematological patients is higher than our findings [14,15]. There are numerous things that contribute to this. Our patient drug histories from the hospital database show that almost all patients admitted to hematological wards received prophylactic doses of quinolones, which can reduce the incidence of Gram-negative bacterial infections and protect most patients with hematological malignancies from bacteremia after chemotherapy [17]. However, numerous centers have observed similar rates of Gram-positive and Gram-negative bacteremia in patients with FN [22,17]. Our hospital had a fungal infection rate

of 1.4%, which was similar to the 1% reported in another Middle Eastern country study [17]. Regarding the most common offending pathogen, our findings show the predominance of *Staphylococci* species, *E. coli*, *Streptococci spp*., *Klebsiella*, and *Pseudomonas spp*. Parodi *et al*. report a similar trend [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 accounts for 18.7% of total cases and 48.2% of all *Staphylococcus* spp. Morris *et al*. [26] did a study in Venezuela and found that 89.3% of *Staphylococcus aureus* were methicillin-resistant *Staphylococci* (MRSA), but Joudeh *et al*. [6] found just 1.6% MRSA in a developed country. Lubwama *et al*. [25], from Uganda, found that all *Staphylococcus* spp. in their investigation were MRSA. In our investigation, *Staphylococcus* spp. had significantly increased prevalence of resistance to amoxicillin/clavulanic acid, ceftriaxone, cefepime, and levofloxacin. The total resistance rates were: 92.9% for ampicillin, 70% for amoxicillin/clavulanic acid, 59.1% for ceftriaxone, 73.3% for cefepime, 51% for levofloxacin, 65.6% for meropenem, and 55.8% for piperacillin/tazobactam. Nine of the 12 *Streptococci* spp. were in the hemolyticus group (6.2%), whereas three were in the nonhemolyticus Enterococci spp. group (2.1%). In 2021, the nonhemolyticus group was completely susceptible to ampicillin, amoxicillin/clavulanic acid, levofloxacin, vancomycin, meropenem, and piperacillin/tazobactam. The overall resistance to ampicillin was 66.7%; amoxicillin/clavulanic acid and ceftriaxone were 33.3%; cefepime was 50%; levofloxacin was 16.6%; meropenem was 28.6%; and piperacillin/tazobactam was 25%. In 2021, researchers isolated two VRE *Enterococci* spp., but in 2022, they only isolated one VSE. Overall, the strains were completely responsive to piperacillin/tazobactam, levofloxacin, and ampicillin. Joudeh *et al*. [6] discovered that 42.9% and 33.3% of isolates were resistant to piperacillin/tazobactam and ampicillin, respectively. They reported that *Enterococcus* was the major pathogen, which we did not validate, and the prevalence of VRE did not increase during the next two years. *E. coli* is the most common Gram-negative pathogen, with 19 isolated in 2021 and 23 in 2022. This statistic represents 29.2% of total cases and is similar with a prior assessment [21], which revealed a range of 10.1% to 53.6%. In 2021, all 11 isolated *E. coli* samples examined for piperacillin/tazobactam sensitivity were sensitive, but by 2022, 54.5% of the 22 isolates were resistant. The total resistance rates during the next two years were 5.1% for amikacin, 70.3% for ceftriaxone, 69.23% for ceftazidime, 64.5% for cefepime, 67.6% for ciprofloxacin, 26.8% for meropenem, and 36.3% for piperacillin/tazobactam. Researchers in Iran [14] discovered that 50% of *E. coli* bacteria were resistant to ciprofloxacin, 31% to amikacin, and 20% to meropenem. Researchers in Vietnam [27] discovered that 82.9% of *E. coli* bacteria were resistant to quinolones, 42.8% to aminoglycosides, and 15.6% to carbapenems. *Klebsiella pneumoniae* isolates totaled 13 over the next two years, accounting for 9% of all pathogens—six in 2021 and seven in 2022. This finding is consistent with a review [21] of 24 research, which found Klebsiella pneumoniae isolation rates ranging from 9.7% to 44.5%. In our study, *Klebsiella pneumoniae* was highly resistant to ceftazidime and ceftriaxone in 2021, indicating that the prevalence of resistance did not considerably rise because it was already high (100% and 83% to 100% and 100%, respectively). Some of the *Klebsiella pneumoniae* bacteria examined were 30.8% resistant to amikacin, 91.7% resistant to ceftriaxone, 100% resistant to ceftazidime, 90.9% resistant to cefepime, 70% resistant to ciprofloxacin, 46.2% resistant to meropenem, and 81.8% resistant to piperacillin/tazobactam. Joudeh *et al*. [6] found resistance to 40% cefepime, 50% ceftriaxone, 50% ceftazidime, piperacillin/tazobactam, and 60% ciprofloxacin. Lubmawa *et al*. [25] found that all *Klebsiella pneumoniae* strains were resistant to ceftazidime and ceftriaxone, and 85.7% were resistant to piperacillin/tazobactam and ciprofloxacin. *Pseudomonas aeruginosa* accounted for 8.3% of our strains—eight in 2021 and four in 2022. This finding is similar with the Trecarichi and Tumbarello [21] review, which found a frequency range of 7% to 44.5%. In 2021, half of the isolates were resistant to amikacin, 100% to ceftazidime, 80% to cefepime, 20% to ciprofloxacin, 62.5% to meropenem, and 50% to piperacillin/tazobactam. Ciprofloxacin resistance increased dramatically in 2022, but declined greatly when amikacin, piperacillin/tazobactam, and ceftazidime were present. According to Joudeh *et al*. [6], *Pseudomonas aeruginosa* resistance to meropenem was 66.7% and 50% for ciprofloxacin, ceftazidime, and cefepime. In our analysis, over the next two years, those rates averaged 41.7% for amikacin, 83.3% for ceftazidime, 66.7% for cefepime, 33.3% for ciprofloxacin, 58.3% for meropenem, and 37.5% for piperacillin/tazobactam. MRS strains and VRE are commonly classified as MDR among Gram-positive bacteria [1]. Our total data revealed the dominance of *Staphylococcus* spp., with 48.2% being MRS strains. However, whereas 66% of the isolated *Enterococci* spp. had VRE, the prevalence of *Enterococci* in our investigation was low, accounting for only 2.1% of all isolates. In 2021, 64.7% of Gram-negative bacteria were MDR, and by 2022, this had risen to 82%. For two years, the overall MDR prevalence was 74%. Vahedian-Ardakani *et al*. [14] reported an XDR of 10%, but our total of 12.9% had XDR. The presence of various MRS strains and Gram-negative rods that are resistant to quinolones

indicates that quinolones cause damage to other cells. Researchers believe that quinolones and cephalosporins cause collateral harm, increasing susceptibility to opportunistic infections and the establishment of MDR strains in nontargeted bacteria. The sort of collateral damage varies with the antibiotic employed. Cephalosporins can cause VRE, ESBL-*Klebsiella pneumonia*, beta-lactam resistance in *Acinetobacter*, and *C. difficile* infections. Overuse of quinolones has been associated to Gram-negative bacilli becoming resistant to them and an increase in MRSA infections [28]. This is consistent with our findings because cancer patients frequently use quinolones. Many guidelines, including those from the IDSA, NCCN, and the American Society of Clinical Oncology (ASCO), advocate quinolones as prophylaxis for patients receiving intermediate- and high-intensity chemotherapy, as they are predicted to develop severe and long-lasting neutropenia [5,29]. Among Gram-positive strains, MRS strains were sensitive to vancomycin, making it an excellent therapy of choice for individuals with this condition. In our results, VRE is rare infection, hence it is unnecessary to include it in empirical therapy. These two points imply that vancomycin still has a high susceptibility rate in Hiwa Hospital. Only high-risk Gram-positive infections and institutions with a high MRSA occurrence prescribe glycopeptides as part of empirical therapy [30]. However, many guidelines offer a wide range of recommendations for specific indications, but their clinical outcomes are poor [31]. In our data, we do not report resistant strains to colistin.

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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