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Original Article

Bacterial spectrum and antimicrobial resistance pattern in cancer patients with febrile neutropenia

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Abstract: Background: Bloodstream infections are serious complications in neutropenic cancer patients. There has been a universal pickup in multidrug resistant (MDR) strains. For individuals who are at high risk for infections caused by MDR bacteria, a novel de-escalation strategy has been developed. Determine the bacterial spectrum and antibiotic resistance pattern in febrile neutropenic cancer patients was the goal of this investigation. Materials and Methods: From 2019 to 2020, 60 cancer patients with febrile neutropenia who were sent to Isfahan's Omid Hospital were included in this retrospective analysis. Experiments were done on the antimicrobial susceptibility of isolated bacterial infections. Results: The patients' average age was 43.35±15.59 years. Ninety-one percent (55/61) of the 60 patients had hematologic malignancies, and 8.3 percent (5/61) had solid tumors. The majority of the germs were gram-negative bacteria (66.7 percent). E. coli was the pathogen that was isolated the most frequently (26.7%), followed by Klebsiella (16.7 percent). In addition, the most prevalent identified Gram-positive bacteria was Staphylococcus epidermidis (21.7 percent). Third-generation cephalosporin (ESBL-E) resistance was present in 50% of E. coli, along with 50% resistance to cotrimoxazole, ciprofloxacin, and piperacillin, 31% resistance to amikacin, and 20% resistance to meropenem (CRE). They had an 80% sensitivity to amikacin and a 70% sensitivity to ciprofloxacin. Ten percent of our patients had antibiotic resistance in the antibiogram (XDR). Conclusion: In summary, most bacterial infections were resistant to different medications. The emergence and spread of Gram-negative bacteria that are resistant to antibiotics can be stopped by prudent antibiotic use.

Keywords: Antibiotic resistance, bacteria, cancer, febrile neutropenia

Introduction

Due to the sort and escalated treatment and other risk factors, numerous cancer patients encounter a diminish in the components of the safe frameworks that make them more susceptible to various infectious diseases. One sort of blood component whose number commonly decreases amid cancer is the group of neutrophils, which constitutes the primary line of the body's resistance against maladies. Fever-related neutropenia is a reduction in neutrophil counts (FN) [1]. Neutropenia is a cancer emergency that can have significant adverse effects, including death and severe infection complications [2]. The primary neutrophil count is less than 1000 cell/L, or the absolute neutrophil count (ANC) is less than 500 cells/L. The ANC drops to less than 500 cell/L within 48 hours. The condition is known as febrile neutropenia (FN), defined as a single oral temperature reading of less than 38.3°C or a sustained oral temperature of less than 38°C for more than an hour [3]. Due to the widespread use of monoclonal antibodies and other biologic agents, the adoption of intensive chemotherapy protocols, the rising average age of cancer patients, and the frequent presence of multiple comorbidities, the management of neutropenic cancer patients is currently more difficult than in previous decades. Thus, even if the cancer population's overall survival rate has increased, clinicians still regularly deal with infectious consequences [4, 5].

When it comes to infectious consequences during neutropenia, bacterial bloodstream infections (BSIs) are in the first place and sepsis is a substantial cause of death in this situation due to the inadequacy of the inflammatory response

[6]. Because it has been linked to lower morbidity and mortality, febrile neutropenia should be treated as a medical emergency and urgent empirical antibiotic therapy must be administered [7]. Antimicrobial resistance is reported by the clinical breakpoints advised by the US Food and Drug Administration, the Clinical and Laboratory Standards Institute (CLSI), and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) (FDA). There have been many different definitions of MDR pathogens. Still, a collaborative endeavor by the ECDC and CDC expert panel defined multidrug resistance as acquired non-susceptibility to at least one agent in three or more antimicrobial categories that are pertinent for a specific species [8]. The selection of an appropriate empirical therapy or prophylaxis is significantly impacted by the rise in resistant bacteria in cancer patients [9].

Drug resistance in the area is noteworthy; however, antibiotic resistance can be remarkably effectively combated by limiting needless antibiotic exposure [10]. The effectiveness of appropriate empirical antibiotic therapy has significantly reduced mortality and morbidity. Based on antibiotic susceptibility patterns in the same area, type of underlying disease, clinical presentation, length of time since chemotherapy, history of infection, length of hospital stay or the number of hospitalizations, and antibiotics used, the best empirical antimicrobial agent is selected [11]. To avoid unnecessary antibiotics and aid patients in improving their general condition, antibiotic therapy must be reevaluated as soon as feasible after 48 to 96 hours based on the antibiogram [12]. Previous studies have reported controversial data on the prevalence of antibiogram results in patients with febrile neutropenia [2, 13]. On the other hand, there is a lack of information regarding the bacterial range and antibiotic resistance pattern of bacteria in Iran cancer patients and people with febrile neutropenia. This study aimed to identify the bacterial spectrum and antibiotic resistance trend in bacteria isolated from cancer patients with febrile neutropenia.

Materials and methods

Study population and design

This is a retrospective descriptive analysis on 60 febrile neutropenic cancer patients. This study was conducted between March 2019 and March 2020. The study protocol was approved by the Ethics Committee of Isfahan University of Medical Sciences (ethics code: IR.MUI.MED.REC.1400.779).

Inclusion and exclusion criteria

The inclusion criteria were age of more than 180 years, diagnosis of cancer of any type, being under treatments for stages 1, 2, or 3 of cancer, admission to our medical center due to febrile neutropenia, and signing the written informed consent to participate in this study. When the absolute neutrophil count (ANC) was less than 500 cells/mm^3 or when the ANC was predicted to fall to 500 cells/mm^3 within the next 48 hours, febrile neutropenia was defined as a fever with a single oral temperature measurement of less than 38.3°C or a temperature of less than 38.0°C sustained over 1 hour. The exclusion criteria were the patient's will to exit the study and be in the remission phase.

Data gathering

The study indicators were: Demographic information, medical history, including any underlying conditions, prior treatments for infections, treatment options, laboratory investigation results, microbiological results with blood cultures, microorganism identification, drug susceptibility patterns, and adjustments to antibiotic therapy based on blood culture results were evaluated.

These data were extracted from patient's files.

Microbiological definition

The term "extended-spectrum-lactamase-producing enterobacterales" (ESBLs) refers to enzymes that may hydrolyze extended-spectrum cephalosporin produced by certain bacteria. Gram-negative bacteria that have developed no susceptibility to at least one agent in three or more antimicrobial categories are MDR Gram-negative pathogens. Carbapenem-resistant Gram-negative bacteria resistant to an antibiotic from the carbapenem class are referred to as gram-negative microorganisms [14]. Resistance to Hard-to-Treat Medicine (DTR) When P. aeruginosa exhibits complete resistance to all of the following, it is said to be pseudomonas. Ciprofloxacin, levofloxacin, imipenem-cilastatin, aztreonam, cefepime, cef-

Table 1. Demographic data of 60 patients with febrile neutropenia

Patient characteristics	Number (%)
Age, years (median, range)	
Male	36 (Mean; 43.78)
female	24 (Mean; 42.71)
Underlying diseases	
Hematologic malignancy	55 (91.7)
Solid tumor	5 (8.3)

Table 2. Causative microorganisms from 60 patients

Microorganisms	Number	%
Gram-negative bacteria		
Escherichia coli	16	26.7
Klebsiella pneumoniae	10	16.7
Acinetobacter baumannii	7	11.7
Pseudomonas aeruginosa	3	5
Enterobacter spp.	3	5
Gram-positive bacteria		
Coagulase-negative Staphylococci	13	21.7
Staphylococcus aureus	4	6.7
Enterococcus	3	5
Streptococcus pneumonia	1	1.7

tazidime, and piperacillin-tazobactam [15]. Methicillin-resistant Staphylococcus aureus (MRSA), methicillin-resistant coagulase-negative Staphylococci (MRCoNS), and vancomycin-resistant Enterococci (VRE) were defined as antibiotic-resistant Gram-positive bacteria [14].

Statistical analysis

We coded the data using SPSS 25 and conducted a descriptive statistical analysis. For quantitative variables, mean and standard deviation, as well as tests like the chi-square and independent T-test, there are numbers and percentages for descriptive variables. We regarded a nominal *P*-value of 5% or less as significant.

Results

Study population

From March 2019 and March 2020, there were a total of 538 admissions with fever and had at least two blood cultures before starting antibiotics. We included 60 admissions due to febrile neutropenia.

Demographic data

As a result, 60 individuals who experienced febrile neutropenia during the study period were included. The mean age of the male patients was 43.78±16.93 years, the mean age of the female patients was 42.71±13.67 years, and the median age of the enrolled patients was 43.35±15.59 years. Thirteen percent of the patients were in the 20-25 age group. Additionally, 24 (40%) are female and 36 (60%) are men. Fifty-five patients (91.7%) had a hematologic malignancy (AML, ALL, CLL, CML, lymphoma, M.M.) as the underlying condition, and five patients (8.3%) had a non-hematologic malignancy (breast, ovary, colon, pancreas cancer). These patients were all receiving chemotherapy. **Table 1** displays the patients' demographic characteristics. The mean absolute neutrophil count (ANC) was 217.25±294.834 in females and 205.06±284.091 in males. In 43 patients (70%), the absolute neutrophil count (ANC) was less than 200 cells/mm^3. Characteristics of Febrile Neutropenia Episodes: there were 39 bacteremias caused by a single Gram-negative microorganism (66.7%), E. coli 26.7% was the most frequently isolated agent of primary bacteremia, followed by staphylococcus epidermis 21.7% and Klebsiella pneumonia 16.7%.

Microbiology results

Causative microorganisms from 60 patients are shown in **Table 2**. We examined the data on bacterial illnesses that are resistant to antibiotics. All antibiotics are ineffective for 30% of patients. Unfortunately, 10% of our patients had antibiotic resistance in the antibiogram (XDR). Acinetobacter and Enterococcus made up the majority of XDR (35 percent each), followed by Pseudomonas (15 percent) and Klebsiella pneumonia (15 percent). Approximately 50% of E. coli were found to be resistant to a third-generation cephalosporin (ESBL-E), 50% of E. coli were found to be resistant to cotrimoxazole, ciprofloxacin, piperacillin, and 31% of them were found to be resistant to amikacin, and 20% of them were found to be resistant to meropenem (CRE). Fifty percent of K. pneumoniae had ESBL resistance to third-gen-

Table 3. The proportion of drug-resistant bacterial

Name of bacteria	Sensitive to all	Resistance to all	MRP	AK	CMX	CPR	VCM	PIP	TZC	Levo	IMP	N
Pseudomonas	1	1	0	0	0	0	0	1	1	0	0	3
Klebsiella pneumoniae	5	1	1	3	0	2	1	0	0	1	1	10
E. coli	7	0	6	4	1	1	0	1	0	1	7	16
Enterobacter aerogenes	0	0	1	1	1	0	0	2	2	0	1	3
Acinetobacter	3	2	0	0	0	0	0	0	0	1	1	7
Staph aureus	0	0	0	0	4	1	0	0	0	0	0	4
Staph epidermidis	3	0	1	1	7	6	1	0	0	1	1	13
Enterococcus	0	2	0	0	0	0	1	0	0	1	0	3
Strep pneumoniae	0	0	0	0	0	0	1	0	0	1	0	1
Total	18	6	9	9	13	10	4	4	3	6	11	60
Percentage	30	10	15	15	21.7	17	7	7	5	10	18.5	100

MRP = Meropenem, AK = Amikacin, CMX = cotrimoxazole, CPR = Ciprofloxacin, VCM = Vancomycin, PIP = Piperacillin, TZC = Tazocin, Levo = Levofloxacin, IMP = imipenem.

Table 4. Changes in antibiotics

Variable	change	Not change	Total
pseudomonas	1	2	3
Klebsiella pneumonia	7	3	10
E. coli	10	6	16
Enterobacter aerogenes	1	2	3
Acinetobacter	3	4	7
Staphylococcus aurous	1	3	4
Staphylococcus epidermis	2	11	13
Enterococcus	1	2	3
Streptococcus pneumonia	1	0	1
Total	27	33	60

eration cephalosporins, and forty percent had carbapenem resistance (CRE). Of all Klebsiella pneumonia cases, 50% were drug-responsive. They had an 80% sensitivity to amikacin and a 70% sensitivity to ciprofloxacin. P. aeruginosa was resistant to carbapenem in 50% of cases (DTR). Piperacillin/tazobactam was sensitive to P. aeruginosa in 50% of cases. Furthermore, 90 percent of the A. baumannii in this investigation were resistant to amikacin, carbapenem, piperacillin/tazobactam, and a third-generation cephalosporin. According to our research, 23% of Staphylococcus epidermis samples were responsive to all antibiotics, whereas 65% of methicillin-resistant coagulase-negative Staphylococci (MRCoNS) were discovered. Cotrimoxazole (77%) and Ciprofloxacin (70%) were more effective medications against staphylococcus epidermis. Methicillin-resistant Staphylococcus aureus (MRSA) accounted for forty of the first Staphylococcus aureus cases, but all of them were susceptible to cotrimoxazole. Of the enterococcus, 67 had vancomycin resistance. We only have one blood culture *Streptococcus pneumonia*, which was only susceptible to vancomycin and levofloxacin. The proportion of drug-resistant bacterial infections is shown in **Table 3**.

Antibiogram results

Further analysis of the data on antibiotic changes based on antibiogram results showed that, of the 55 percent of patients in our data (33 patients), 45 percent (27 patients) changed their empiric antibiotics as a result of the antibiogram. In other instances, the prescription empiric antibiotic was the same as the antibiogram result for susceptible antibiotics. These patients are categorized as susceptible antibiotic change patients according to antibiogram. **Table 4** displays whether to change antibiotics.

Discussion

A frequent side effect of treatment in oncologic patients is febrile neutropenia. According to this study, gram-negative bacteria accounted for more than 60% of the patients and were the most prevalent causal pathogens. Ten percent of Gram-negative bacterial infections were carbapenem-resistant and 19% were XDR (resistance to all antibiotics in the antibiogram).

The most often detected pathogen in febrile neutropenia episodes with microbiologic docu-

mentation was bacteria (74 percent). Similar to earlier studies conducted in Thailand and other Asian nations [16, 17], the majority were Gram-negative bacteria (48.6%), followed by Gram-positive bacteria (23.4%), and viruses (15%). However, studies conducted in western nations revealed that up to 60-70% of all microorganisms were Gram-positive bacteria. This finding may be related to more aggressive chemotherapy regimens that increase the risk of mucositis, frequent use of central venous catheters, and antibiotic prophylaxis during neutropenia [18, 19]. In our investigation, E. coli (26.7%), staphylococcus epidermis (21.7%), and Klebsiella pneumonia were the most frequently isolated bacteria (16.7 percent). Regarding the type and frequency of pathogens, our findings about the causal pathogens differ from those of other investigations. Therefore, medicines that act against Gram-negative and Gram-positive bacteria should be used as empirical antibiotic therapy in febrile neutropenia, and they should be modified based on the primary causal pathogen in each treatment facility. The majority of positive cultures were from blood cultures, similar to the previous studies [19, 20]. The proportion of antibiotic-resistant bacteria tends to increase among Gram-negative and Gram-positive bacterial infections. In comparison to earlier studies' findings of 34% and data from the National Antimicrobial Resistant Surveillance, Thailand (NARST), which revealed a 30% resistance rate, it was discovered that nearly 50% of E. coli were resistant to third-generation cephalosporin. However, it was found that 50%, 70%, and 80% of E. coli were susceptible to piperacillin/tazobactam, amikacin, and carbapenem, respectively. In comparison to earlier studies (30-40%), the percentage of K. pneumoniae resistance to third-generation cephalosporins increased (by 50%) [21, 22].

Of all Klebsiella pneumonia cases, 50% were drug-responsive. Forty percent were resistant to meropenem, 80 percent were sensitive to amikacin, and 70 percent were susceptible to ciprofloxacin. Over 15% of P. aeruginosa in the study of the NARST were drug-resistant, and 50% of P. aeruginosa were sensitive to piperacillin/tazobactam, which was similar to the previous studies [20, 23]. P. aeruginosa was resistant to all antibiotics in the antibiogram (XDR), similar to the previous studies. The proportion of A. baumannii that was resistant to every antibiotic listed in the antibiogram (XDR) from this study was 35%, and 90 percent of A. baumannii were found to be sensitive to third-generation cephalosporin, piperacillin/tazobactam, amikacin, and carbapenem, which was higher than the 70-80 percent found in earlier studies in Thailand [24, 25].

Similar to the percentages of MDR organisms (12-39%) and carbapenem-resistant organisms (16%) in the other research [25, 26], there were 25% of MDR Gram-negative germs and 20% of carbapenem-resistant Gram-negative microorganisms. According to our research, the proportion of antibiotic-resistant Gram-positive bacterial infections (MRSA 40%, MRCoNS 65%, and VRE 67%) was higher than the percentage of resistant microorganisms in the NARST study (MRSA 0.1%) but similar to that in a prior study conducted in the United States (MRSA 30-53%) [27]. Numerous patients with febrile neutropenia and negative blood cultures. Most likely, a sizable number of false-negative tests that happened for two reasons contributed to the problem. Several individuals received oral or intravenous antibiotics before receiving a blood culture. Another possibility is that we lacked sufficient BACTEC Culture, and infections do not thrive well in typical blood cultures. As demonstrated, 55% of our patients did not receive the antibiotics recommended by an antibiogram. As a result, initiatives for optimal antibiotic therapy should focus on the rise in bacterial infections that are resistant to antibiotics. Our study's findings provided important information regarding the pathogens that cause febrile neutropenia and the prevalence of bacteria that are resistant to antibiotics, which helped us formulate treatment recommendations.

Here we had a retrospective evaluation of the patient's documents. The limitations of this study were that this study could have unknown potential confounders, we used the data initially collected for these purposes, not all the relevant information, and we also had a low level of evidence compared with prospective studies. We also had a local study population compared to some former studies, suggesting that more studies on larger populations should be performed. Furthermore, we should explain that the prevalence of antibiotic-resistant bac-

teria, which varies between each community and hospital, impacts how antibiotic-resistant organisms are distributed and how susceptible they are to treatment. This study did not assess whether the prescribed antibiotics and the selection of antibiotics for each patient were suitable, which could impact the clinical outcomes. It is recommended that further multicentric research should be conducted on larger study populations to evaluate possible associated factors.

Conclusion

Neutropenic patient care presents new clinical difficulties. Today's proliferation of resistant bacteria across numerous nations emphasizes the necessity of surveillance, improved local epidemiological knowledge, and global infection control. Every cancer center should develop antimicrobial stewardship programs to optimize antibiotic therapies in terms of drug selection, dosage, and administration time, with the ultimate goal of enhancing patient outcomes. Secondary objectives are to reduce the negative impacts and expenses related to MDR infections and their treatment. Individualized empirical therapy options for febrile neutropenia are required. The effectiveness of the de-escalation strategy needs robust confirmation and should be investigated in large trials involving neutropenic patients. Bacteria are the predominant causative pathogen in febrile neutropenic patients. From our study, it was found that Gram-negative bacteria were the most common isolated pathogen. Antibiotic-resistant bacterial infections are associated with significant morbidity and mortality; therefore, surveillance of microorganism distribution and strategies for reducing the occurrence of an antibiotic-resistant bacterial infection should be established.

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Disclosure of conflict of interest

None.

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