

# THE CURRENT SPECTRUM OF INFECTIONS IN CANCER PATIENTS WITH CHEMOTHERAPY RELATED NEUTROPENIA

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## ABSTRACT

**Background:** New cancer treatments have improved patient survival but also bring side effects like weakened immunity and higher infection risk. The present study aimed to assess the pattern of blood stream infections and antimicrobial resistance in blood isolates of neutropenic patients.

**Material and Methods:** This Cross-sectional, observational study was conducted at Department of Oncology, Jinnah Postgraduate Medical Centre, Karachi, Pakistan between August 2019 to August 2020. Malignant patients who underwent chemotherapy and presented with fever, neutropenia, and positive bacterial blood culture were enrolled in the study. Patients with a recent history of blood transfusion were excluded. The spectrum of bacterial infections and the antimicrobial resistance patterns of causative organisms isolated from blood were studied. The CLSI standard antimicrobial panel was used for each microorganism. Findings were presented in tabular form.

**Results:** During the study period 95 organisms were isolated from the blood cultures. Strains of *E. Coli*, *Klebsiella*, *Pseudomonas*, *S. Aureus*, *S. Pneumoniae*, were found in 27 (28.4%), 18 (18.9%), 13 (13.7%), 17 (17.9%), and 2 (2.1%) patients, respectively. 44.0% of *E. coli*, 68.8% of *Klebsiella*, and 38.5% of *Pseudomonas* were resistant to tazobactam. 92.6% of *E. coli*, 88.2% of *Klebsiella*, 100% of *Pseudomonas* were resistant to Co-amoxiclav. 52.9% of *Staph aureus* were resistant to methicillin. 23 (92.0%) strains of *E. coli*, 15 (83.3%) strains of *Klebsiella*, 6 (46.2%) strains of *Pseudomonas*, and 11 (68.8%) of *Staph aureus* were resistant to ciprofloxacin.

**Conclusion:** Resistance to the majority of the commonly used antimicrobial drugs was noted. Continuous antimicrobial resistance surveillance of the everchanging spectrum of causative organisms and their characterization is very important to treat the bloodstream infections (BSI) in cancer patients with chemotherapy induced neutropenia.

**Keywords:** Neutropenia Infection, Fever, Antimicrobial resistance, Chemotherapy.

## BACKGROUND

With the advancement in cancer treatment, many novel chemotherapeutic drugs have been introduced which have significantly improved the survival rate of cancer patients.<sup>1</sup> However, these potent cytotoxic chemotherapeutic drugs can result in several side effects including substantial immunosuppression thereby, an increased risk of infection.<sup>2</sup> Neutropenia is defined as

neutrophil concentration of less than or equal to 1500 of the total leukocytes (WBC Count). Patients with neutropenia are highly susceptible to infections which are associated with significant morbidity and mortality.<sup>3</sup> Chemotherapy-induced neutropenia is one of the most common and dangerous complications seen in cancer patients all over the world.<sup>4</sup>

Neutropenia related to chemotherapy is a serious hematologic toxicity which limits the doses and duration of treatment that can be tolerated by the patient.<sup>4,5</sup> Infections in cancer patients with neutropenia related to chemotherapy is associated with a poor patient outcome if not timely treated with appropriate antibiotics.

Even though the overall cancer survival rate has improved in the last decade owing to the adoption of a more aggressive approach particularly the use of monoclonal antibodies against cancer cells, the risk for

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**This article can be cited as:** Ashfaq M, Haider G, Ather T, Ahsan M, Khan ME, Seher S. The current spectrum of infections in cancer patients with chemotherapy related neutropenia. *Infect Dis J Pak.* 2023; 32(4): 147-153. DOI: 10.61529/idjp.v32i4.265

Receiving date: 31 Oct 2023  
Revision date: 23 Nov 2023

Acceptance Date: 29 Nov 2023  
Publication Date: 29 Dec 2023



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neutropenia among patients has elated significantly. Hence, it has become more difficult to treat and manage patients with chemotherapy related neutropenia especially if the patients are elderly or have multiple comorbidities.<sup>6</sup>

Gram negative *bacilli* and *staphylococcus aureus* or else are the most frequently isolated organisms from neutropenic cancer patients. Age of patient, type of chemotherapeutic medicine being used, and its duration are some of the risk factors associated with the infections among these patients.<sup>7-9</sup>

A local study by Saghir *et al.*, reported *pseudomonas aeruginosa* to be the most frequently isolated bacterial strain with a rate of 38%, followed by *E. coli* with a frequency of 25%, *Klebsiella*, *Proteus*, and *Shigella* with a frequency of 20%, 10%, and 7%, respectively.<sup>9</sup> Recent trends have shown an increased antimicrobial resistance in the gram-negative bacteria. A review of literature showed that resistance to amoxicillin was present in 44% cases of *E. coli* in 2004 which increased to 56% a year later ( $P=0.01$ ). Similarly, the rate of *E. coli* resistance to piperacillin was 11 percent by 2004 and increased to 38% in 2005 ( $P<0.001$ ).<sup>7</sup>

*Pseudomonas* isolates were resistant to several antibiotics including cefepime (60%), ciprofloxacin (80%), meropenem (13%), ceftriaxone (67%), cefoperazone (90%), tobramycin (40%), and imipenem (10%).

However, the local literature is more than a decade old and outdated. Due to the ever-changing spectrum of infection in cancer patients and the rise in multiple drug resistant bacteria, it is of the utmost importance to perform regular antimicrobial resistance surveillance studies and assess the change in characterization of the microbes. Studies have shown that empirical antibiotic therapy is associated with reduced morbidity and mortality among cancer patients with systemic infection. Therefore, it is vital to have an updated knowledge about the common most infectious agents in our community so that empirical as well as therapeutic antibiotic doses can be administered.<sup>8,9</sup>

Unfortunately, there is a scarcity of local literature on the subject. Therefore, the current study was undertaken. The goal of the study was to evaluate the spectrum of bloodstream infections (BSI) and study the

antimicrobial resistance in cancer patients with chemotherapy induced neutropenia.

## MATERIAL AND METHODS

A cross-sectional, observational study was conducted at the oncology department, Jinnah Postgraduate Medical Centre, Karachi, Pakistan between August 2019 to August 2020. The study was approved by the ethical committee board and an institutional review board (IRB) letter with reference number NO. F-81-IRB/2019-GENL/32729/JPMC was issued prior to the study.

Cancer patients who underwent chemotherapy (inpatient or day care) within the last 15 days and presented with a documented fever, neutropenia ( $ANC \leq 1500$ ) and a subsequent positive bacterial blood culture were enrolled in the study. Patients receiving chemo >15 days back, had a drug reaction, had a recent history of blood transfusion were excluded. Urine, sputum, and pus cultures were excluded. Positive fungal/viral cultures were also excluded. Blood cultures were sent according to standard lab protocols.

Fever due to non-infectious causes was ruled out before enrolling participants in the study. An informed written consent was obtained from all patients. A non-probability convenience sampling technique was applied to select participants for the research.

All sociodemographic parameters including age, gender, occupation, comorbidities, and residence were recorded using a predefined structured pro forma. Data regarding duration of symptoms, blood cell counts (including WBC and ANC), chemotherapy regimen, and type of malignancy was recorded. A normal white blood cell count was defined as a concentration between 4.5 to 11.0  $\times 10^9/L$ .<sup>10</sup> Neutropenia was classified as mild, moderate, or severe, based on the absolute neutrophil count (ANC). Mild neutropenia was defined as ANC between 1000-1500 cells/ $\mu L$ , moderate neutropenia was labeled as ANC of 500-1000/ $\mu L$ , while severe neutropenia was tagged as ANC of lower than 500 cells/ $\mu L$ .<sup>11</sup> Fever was defined as a single oral or axillary temperature of  $\geq 38.30$  Centigrade for more than one hour.<sup>12</sup>

The antimicrobial resistance patterns of causative organisms were studied. Various culture media including nutrient broth, nutrient agar, blood agar, etc.

were prepared to isolate and grow the causative agent. Blood samples were taken and sent to the laboratory using standard lab protocols.

A total of 95 microorganisms including both gram negative and positive bacteria were isolated and studied for their susceptibility pattern. 5 ml of blood was immediately added to brain heart infusion (BHI) broth and 8–9 ml of thioglycolate broth for anaerobes following collection. The blood culture vials were cultured at 37 C for seven days. A blood culture was deemed positive if an organism developed in at least one dish. The isolates were identified using Gram staining and common biochemical testing. The modified Kirby-Bauer disc diffusion method was used for assessing the susceptibility of microbes to various antibiotics. All standard biochemical tests were performed according to the Manual of clinical microbiology to detect and identify the bacterial isolates (as discussed with the microbiology team).

To study the antimicrobial sensitivity several groups of antibiotics including the Penicillins, Carbapenems, Cephalosporins, and Aminoglycosides were used. The results of antimicrobial sensitivity were recorded after 24 hours of incubation at 37°C. The data was entered and analyzed using SPSS (Statistical Package for the Social Sciences). The results were presented using mean and frequency or percentages. The continuous variables were presented as mean and standard deviation like age of the patients. Categorical variables like gender, residence, etc were presented as frequency and proportions.

## RESULTS

The mean age with standard deviation of patients was  $48 \pm 27.5$  years. There was a total of 95 patients who fulfilled the eligibility criteria. 43 (45.3%) were male while 52 (54.7%) were female patients and mostly  $n=65$

(68.4%) belonged to the urban area. The majority of the female participants were home makers. The median duration of symptoms before presenting to the hospital was 3.41 weeks. The most common presenting symptom of infection in cancer patients was fever which was documented in 95 (100%) patients. Cough was found in 20 (21.1%) patients while diarrhea and shortness of breath were found in 14 (14.7%) and 9 (9.5%) patients, respectively. The mean white blood cell count was  $2.235 \times 10^9/L$ .

The frequency of isolated strains of bacteria are presented in Table-1. Strains of *E. Coli*, *Klebsiella*, *Pseudomonas*, *S. Aureus*, *S. Pneumoniae*, were found in 27 (28.4%), 18 (18.9%), 13 (13.7%), 17 (17.9%), and 2 (2.1%) patients, respectively.

Table-2 demonstrates the pattern of antimicrobial resistance of the isolated agents in our study. 11 (44.0%) *E. coli*, 11 (68.8%) *Klebsiella*, and 5 (38.5%) *pseudomonas* were resistant to tazobactam. 25 (92.6%) *E. coli* and 15 (88.2%) of *Klebsiella*, were resistant to Co-amoxiclav. 23 (92.0%) strains of *E. coli*, 15 (83.3%) strains of *Klebsiella*, 6 (46.2%) strains of *Pseudomonas*, and 11 (68.8%) of *staph aureus* were resistant to ciprofloxacin. Carbapenem resistance was most seen in *Klebsiella*, followed by *E. coli* and *Pseudo*. MRSA was isolated from 9 (52.9%) isolates. Most isolates were resistant to amoxiclav followed by cephalosporins and quinolone.

Cyclophosphamide plus doxorubicin (AC) and Docetaxel, cisplatin and fluorouracil (TPF) were the most common regimes causing neutropenia with a frequency of 12 (12.63%) patients in each regime. 33 (34.7%) patients were admitted to ward for the management of neutropenia related to chemotherapy. The mean hospital stay of patients was two days. 62 (65.2%) were managed in the outpatient's department.

**Table-1: The sociodemographic characteristics of study participants (n=95).**

<b>Mean Age (<math>\pm</math> SD) in years</b>	<b>48.0 (<math>\pm</math>27.5)</b>
<b>Gender</b>	
Male	43 (45.3%)
Female	52 (54.7%)
<b>Residence</b>	
Rural	30 (31.6%)

<i>Urban</i>	65 (68.4%)
<b>Occupation</b>	
<i>Homemaker</i>	39 (41.1%)
<i>Labourers</i>	14 (14.7%)
<i>Farmers</i>	7 (7.4%)
<i>Others</i>	27 (28.4%)
<i>Unemployed or retired</i>	8 (8.4%)
<b>Presenting symptoms</b>	
<i>Fever</i>	95 (100%)
<i>Cough</i>	20 (21.1%)
<i>Shortness of breath</i>	9 (9.5%)
<i>Diarrhea</i>	14 (14.7%)
<b>Isolated Bacterial Strains</b>	
<i>E. Coli (gram -ve)</i>	27 (28.4%)
<i>Klebsiella (gram -ve)</i>	18 (18.9%)
<i>Pseudomonas (gram -ve)</i>	13 (13.7%)
<i>S. Aureus (gram +ve)</i>	17 (17.9%)
<i>S.Pneumoniae (gram +ve)</i>	2 (2.1%)
<i>Others</i>	18 (18.9%)
<b>Severity of neutropenia</b>	
<i>Mild</i>	24 (25.3%)
<i>Moderate</i>	50 (52.6%)
<i>Severe</i>	21 (22.1%)
<b>Organ of Malignancy</b>	
Breast	14 (14.7%)
Gastrointestinal tract	6 (6.3%)
Genitourinary tract	10 (10.5%)
Hematological malignancy	39 (41.1%)
Others	26 (27.4%)

**Table-2: Pattern of antimicrobial resistance of the isolated organisms in the study.**

Antimicrobial Drug	Isolated Microorganism			
	<i>E.coli</i>	<i>Klebsiella</i>	<i>Pseudomonas</i>	<i>S. Aureus</i>
Tazobactam	11 (44.0%)	11 (68.8%)	5 (38.5%)	NA
Co-amoxiclav	25 (92.6%)	15 (88.2%)	NA	NA
Methicillin	NA	0 (0.0%)	NA	9 (52.9%)
Ciprofloxacin	23 (92.0%)	15 (83.3%)	6 (46.2%)	11 (68.8%)
Amikacin	5 (20.8%)	3 (21.4%)	3 (23.1%)	0 (0.0%)
Imipenem	7 (26.9%)	11 (64.7%)	5 (38.5%)	NA
Cefixime	23 (92.0%)	16 (94.1%)	NA	NA
Ceftriaxone	23 (92.0%)	14 (87.5%)	NA	NA
Fosfomycin	1 (6.3%)	2 (16.7%)	NA	NA
Cotrimoxazole	14 (73.7%)	13 (86.7%)	NA	1 (9.1%)
Tetracycline	8 (66.7%)	6 (66.7%)	NA	6 (42.9%)

## DISCUSSION

Despite the continuous advancement in the management of cancer patients with introduction of newer chemotherapeutic drugs, neutropenia is still considered as one of the most dreadful adverse effects of cytotoxic chemotherapy.<sup>13</sup> Febrile neutropenia is a serious medical condition which can complicate the disease course of cancer patients and is associated with considerable financial burden. Since 1980, the spectrum of bacterial infections has drastically changed from gram-negative to gram-positive organisms owing to the fluoroquinolone prophylaxis being administered in most settings.<sup>14</sup>

However, more recently a further change in the spectrum of organisms causing the bacterial infections in neutropenic patients is being observed. In a study by Carvalho *et al.*, a trend towards gram-negative bacteria was observed.<sup>15</sup> Similarly, another local study by Jamal *et al.*, reported a trend towards gram-negative bacteria with a frequency of 79% in patients with febrile neutropenia. *E. coli* and *Staphylococcus aureus* were the most commonly reported causative agents.<sup>16</sup>

We have also reported a higher frequency of gram-negative isolates in our study, *E. coli* being the most common, findings which are in accordance with the study quoted above. These findings further consolidate the notion that there is indeed a shift from gram positive bacteremia towards multidrug resistant gram-negative bacterial infections in neutropenic patients with malignancy.

We identified numerous strains of bacteria that were multidrug resistant. The increasing trend towards multidrug resistant gram-negative bacterial infections can be attributed to the injudicious and inadequate use of antibiotics.<sup>17</sup>

A study conducted to evaluate the incidence of bloodstream infections in 4,200 cancer patients revealed that inadequate empirical antimicrobial therapy in the first twenty-four hours of chemotherapy may lead to an increased morbidity and mortality.<sup>18</sup> It was concluded that the wrong antibacterial management in the critical 24 hours' time was linked with a higher number of deaths.

In a local 2013 study by Fayyaz *et al.*, it was found that the majority of the isolates were gram positive (47.3%)

and out of the *staphylococcus spp.* 67 percent were methicillin resistant.<sup>19</sup> In our study however, 52 percent were methicillin resistant. The difference between the rate of resistance could be because of the study population. The current study only included patients who had undergone chemotherapy whereas, the former study included all patients with bone marrow transplant, kidney transplant in addition to malignancy.

Unnecessary and rampant use of antimicrobial drugs like methicillin and vancomycin have led to resistant strains of bacteria including MRSA (methicillin resistant *Staphylococcus aureus*) and VRSA (vancomycin-resistant *Staphylococcus aureus*), respectively.<sup>20</sup> A study by Jaksic *et al.*, reported Linezolid to be effective against all MRSA organisms.<sup>21</sup> Similarly in our study 100% MRSA were sensitive to Linezolid.

Failure to identify the causative organism and irrational use of antibiotics is a global challenge. Over fifty percent of all antibiotics which are prescribed or administered are unnecessary or inappropriate. Whereas the other fifty percent of patients are either non-compliant or are not adhering to correct use of antibiotics.<sup>22</sup> Some of the factors affecting this irrational and inappropriate use of antimicrobials include socio-economic status, doctors' knowledge and educational training, patient burden, misdiagnosis, unavailability of adequate antimicrobial guidelines, and unrestricted pharmaceutical marketing.<sup>23</sup> In Pakistan, it is unfortunately a very common practice to administer and prescribe antibiotic therapy without a culture sensitivity report hence, patients are given unnecessary doses of antibiotics which eventually lead to bacterial resistance.<sup>24</sup> In a local qualitative study by Saleem *et al.*, it was found that the majority of the practicing physicians did not have adequate knowledge on the current spectrum of infection, appropriate use of antimicrobials and were unaware about the ongoing antimicrobial resistance patterns in their local settings.<sup>24</sup> The current data indicate that the initial empiric coverage, even in low risk, febrile neutropenic patients, needs to be broad spectrum until the blood cultures become available. Potent gram-negative coverage is essential particularly the coverage against *P. aeruginosa*



considering the latest trend towards these gram-negative organisms.

It is important to realize the challenging situation that we are currently dealing with before we run out of options. With the changing infection spectrum and multidrug resistant organisms on the verge, it is time to formulate strict regulations, promote awareness campaigns, arrange training sessions for practitioners and develop a proper local guide on antimicrobial use.

## CONCLUSION

The study highlights the most common bacterial strains isolated from neutropenic cancer patients undergoing chemotherapy. Gram negative bacteria were more frequently isolated as compared to the gram positives bacteria. Resistance to the majority of the commonly used antimicrobial drugs was noted. The emergence of CRE isolates and increase in MRSA is very concerning. Therefore, continuous antimicrobial resistance surveillance of the ever-changing spectrum of causative organisms and their characterization is very important to treat the bloodstream infections (BSI) in cancer patients with chemotherapy induced neutropenia.

## CONFLICT OF INTEREST

None

## AUTHOR CONTRIBUTION:

**Maliha Ashfaq:** Conceptualized, drafted the article,

**Ghulam Haider:** Provided supervision, developed study design, conducted critical appraisal

**Tooba Ather and Mahnoor Ahsan:** Contributed in data acquisition and drafting of manuscript

**Mohammad Ejaz Khan and Sana Seher:** Contributed in drafting of manuscript and proofreading

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