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# Prevalence of Antibiotic Resistance in Pediatric Malignancy Patients: A Two-Year Retrospective Study in Basra City

**Hanan AlAulddin Abdul Jabbar, Ali Mohammed Hadi**
Department of Clinical Pharmacy, College of Pharmacy, University of Basra, Basra, Iraq
**Corresponding author:** Hanan AlAulddin Abdul Jabbar, **Email:**pgph.hanan.alaa@uobasrah.edu.iq, **Tel:** +9647705757223

## ABSTRACT

**Background:** The most frequent side effects of chemotherapy are infections, which have substantial morbidity and mortality rates in immunocompromised patients.

**Aim:** To screen the prevalence of resistance between antibiotics administered to infected patients in hematological malignancy wards.

**Subjects and Methods:** A retrospective cross-sectional study of pediatric oncology patients was conducted from January 2021 to June 2022 at Basra children hospital. The study included 500 patients with hematological malignancies.

**Results:** This study involved 57.8% male and 42.2% female patients. Leukemia was the most common diagnosis 59% while other solid tumors was 41%. Febrile neutropenia was only 5.8%, bacterial infection was predominant at 49.8% while the fungal infection was 9.4%, and 4.8% suspected viral infection. We found that the high percentage of antibiotics used were Cephalosporin (41.4%) and the lower percentage of antibiotics were Quinolone 0.4%.

**Conclusion:** The most frequent form of infection was a bacterial infection, and the most frequently prescribed antibiotic for oncology patients was cephalosporin. The chest represented the most severely infected place.

**Keywords:** Neutropenia, Pediatric oncology, Bloodstream infections, Antibiotic, Basrah.

## INTRODUCTION

For chemotherapy-treated cancer patients, bloodstream infections (BSIs) continue to be a major source of morbidity and mortality. A significant risk factor for acquiring numerous mild to severe infections including sepsis and septic shock, is chemotherapy brought on by bone marrow suppression. Other risk factors include the use of indwelling central venous catheters (CVC) for the diagnosis of leukemia, undernutrition, and recently administered chemotherapy [(1)].

Additionally, because numerous immune pathways are impaired during treatment, bacterial infections can coexist occasionally with both invasive and non-invasive fungal and viral infections.

Over the past few years, significant alterations in the range of bacteria identified from blood cultures in cancer patients have been recorded [(1)]. Antibiotics may be used to reduce the adverse effects of pathogenic bacteria. Unfortunately, improper use of antibiotics is hastening the creation of antibiotic strains that are resistant to bacteria, which has alarming clinical implications for the treatment of illnesses. Today, a lot of diseases happen because germs resist traditional medicine. In actuality, bacteria are genetically capable of developing resistance to a wide range of antibiotics [(2)].

About half of patients with respiratory tract infections in children receiving chemotherapy now frequently have respiratory viruses as the source of their infection, a finding that is similar to Khan ***et al.*** [(3)] study, which showed that 44% of cases of children and adolescents with leukemia and fever had respiratory infections. **Sheng *et al.*** [(4)] observed that rates were 75% in their study.

Invasive fungal infections, especially in those with hematological abnormalities treated with high-dose chemotherapy or bone marrow transplants, are a significant contributor to the death of children with cancer [(3)]. Invasive aspergillus infections are among the most common infections, but there are also more and more cases of other fungi besides aspergillus that are being documented [(5)].

It appears that during the past few decades, there has been a rise in the prevalence of invasive fungal infections in children, mostly as a result of the prolonged survival of infants with immune deficiency disorders [(6)].

The morbidity and even death linked to the care of severe bacterial infections in children with cancer can be decreased by using a preventative strategy. Standard treatment for febrile neutropenia involves giving antibiotics to patients until their fever breaks and their neutrophil count improves [(7)].

Between 40% and 90% of febrile neutropenia cases respond to empirical antibiotics. A careful understanding of the local positive blood cultures and their sensitivity and resistance profile is thus required for the development of effective treatment and doable techniques to treat bloodstream infections. Serious infections are frequently treated with beta-lactams as the first line of defense, then carbapenems frequently seen as the final resort [(8)].

## AIMED OF THE STUDY

Screening the prevalence of resistance between antibiotics administered to infected patients in hematological malignancy wards. Also, to correlate the severity of infection with many patient characteristics (gender, kind of cancer, chemotherapy, side effects of



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chemotherapy, febrile neutropenia, causes of infection, type of infection, length of hospital stay, place of infection, number of infection sites).

## PATIENTS AND METHODS OF THE STUDY

### Study design

This study included 500 pediatric patients with hematologic malignancies who had a positive culture from January 2021 to June 2022 at Basra children's hospital as a single group to highlight the incidence of antibiotic resistance in hematology malignancies wards and its relationship to patient characteristics.

All patients' characteristics were recorded regarding age, gender, disease malignancy, hematological status, disease stage and type, and other social and medical histories and findings. Data were retrospectively collected from the medical laboratory department and the hematology department at Basra children's hospital. The hospital has a bed capacity of 100.

### Data collection:

The hospital information system was used to acquire demographic and medical information. The microbiology lab provided information on specimen sources, types of bacteria, and antibiotic susceptibility.

### Inclusion criteria:

All patients from aged 18 years or younger who received chemotherapy at Basra children's hospital presented with fever during the study period.

**Exclusion criteria:** Non-cancerous diseases requiring chemotherapy including aplastic anemia, congenital and autoimmune neutropenia, etc.

### Ethical considerations:

**Ethical approval was obtained for this study by the Ethics Committee in the College of Pharmacy, University of Basra.**

### *Statistical analysis*

Data were gathered and processed into Microsoft Excel for descriptive statistical analysis. The chi-square test and odds ratio were used to establish the link. Frequency tables and graphs are used to illustrate the findings.

## RESULTS

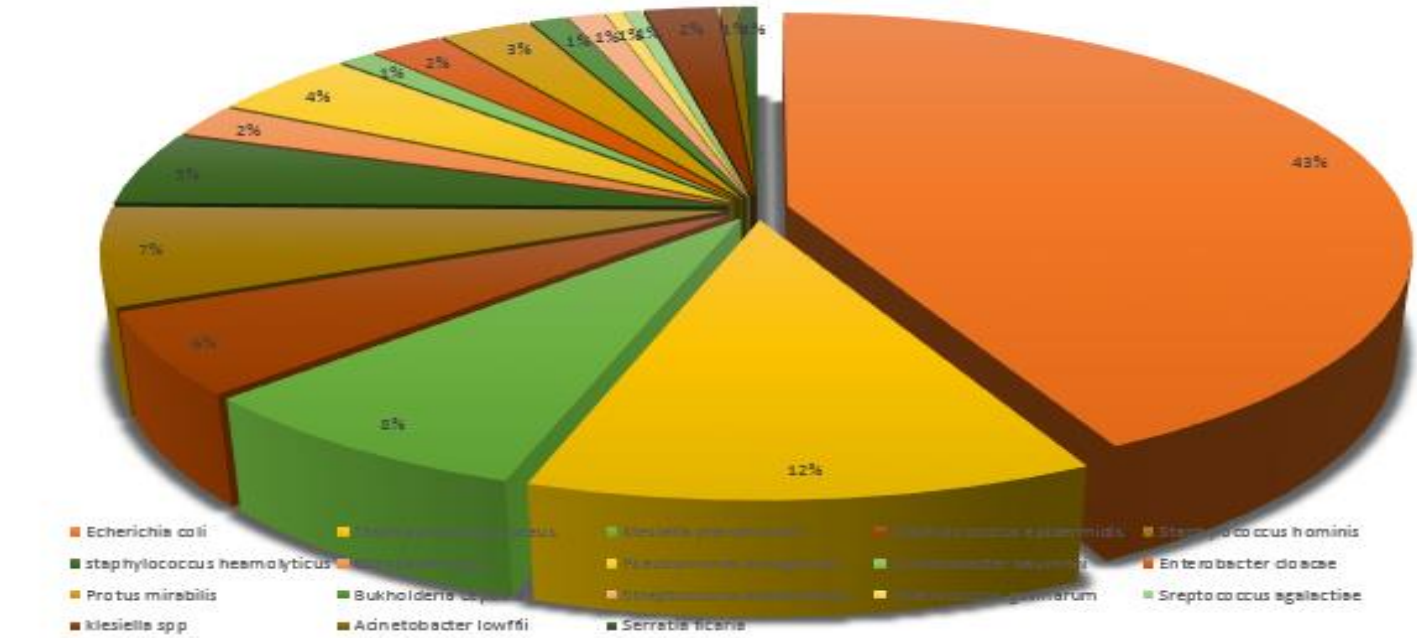
### Patients characteristics:

Table (1) showed that the highest percentage of the patients were males 289 (57.8%), and 211 (42.2%) were females. Significantly ($p<0.05$) a greater percentage of patients had Leukemia 295 (59%%) and other Solid tumors 205(41%). Frequency and percentage of isolated microorganisms were shown in figure (1).

There was a significant ($p<0.05$) difference in the percentage among patients where the percentage of patients who took chemotherapy was 228 (45.6%) and 272 (54.4%) of the patient did not take chemotherapy. Other questions about the side effect of chemotherapy, causes of infection, site of infection, and severity of the infection are reported in table (1).

**Table (1):** patients characteristics on anti-cancer therapy. Data expressed as N (%), Total N=500**.**

| | N (%) | P value |
|---|---|---|
| **Gender** | | |
| **Males** | 289 (57.8) | 0.0005 |
| **Females** | 211 (42.2) | |
| **Type of malignancy** | | |
| **Solid tumor** | 205 (41) | 0.0001 |
| **Leukemia** | 295 (59) | |
| **Did the patient take chemotherapy?** | | |
| **Yes** | 228 (45.6) | 0.0491 |
| **No** | 272 (54.4) | |
| **Are side effects of chemotherapy noted?** | | |
| **Yes** | 228 (45.6) | 0.0491 |
| **No** | 272 (54.4) | |
| **Febrile neutropenia** | | |
| **Yes** | 29 (5.8) | 0.00001 |
| **No** | 471 (94.2) | |
| **Did the patient develop an infection?** | | |
| **Yes** | 306 (61.2) | 0.00001 |
| **No** | 194 (38.8) | |
| **Severity of infection** | | |
| **Sever** | 264 (52.8) | |
| **Moderate** | 42 (8.4) | 0.00001 |
| **No infection** | 194 (38.8) | |
| **Causes of infection** | | |
| **No infection** | 196 (39.2) | |
| **Bacterial** | 291 (58.2) | 0.00001 |
| **Fungal** | 52 (10.4) | |
| **Suspected viral** | 24 (4.8) | |
| **Type of infection** | | |
| **No** | 196 (38.8) | |
| **Single causes(Almost Bacterial)** | 249 (49.8) | 0.00001 |
| **Combined (Bacterial with Fungal or Viral)** | 52 (10.4) | |
| **Complicated (Bacterial+Viral+Fungal)** | 3 (0.6) | |
| **Duration of hospital stay (days)** | | |
| **No** | 4 (0.8) | |
| **1-7 days** | 370 (74) | |
| **8-14 days** | 55 (11) | |
| **15-21 days** | 31 (6.2) | 0.00001 |
| **22-28 days** | 20 (4) | |
| **>28 days** | 20 (4) | |
| **Site of infection** | | |
| **No** | 194 (38.8) | |
| **Chest** | 257 (51.4) | |
| **Mouth** | 14 (2.8) | |
| **Mucositis** | 14 (2.8) | |
| **Skin** | 1 (0.2) | 0.00001 |
| **Eye** | 2 (0.4) | |
| **Urinary tract infection** | 10 (2) | |
| **Pancytopenia** | 18(3.6) | |
| **No. site of infection** | | |
| **N** | 194 (38.8) | |
| **Single site** | 296 (59.2) | 0.00001 |
| **Multiple sites of infection** | 10 (2) | |




P<0.05 consider significant.

**Figure (1):** Frequency and percentage of isolated microorganisms

**Antimicrobials used before culture:**

Table (2) represents the information on patients who need antibiotics treatment. Data expressed as N (%), Total N=500. There was (303) patients who received antibiotics, there was a significant ($p<0.05$) difference in the percentage of answers among patients where the percentage of correct answer was ( 60.6%).

Question number 2 about the type of antibiotic , there was a significant ($p<0.05$) difference in the percentage among patients where the percentage of patients who took cephalosporin was 41.4%, it was the highest percentage and the lowest percentage of the antibiotic taken was Quinolone (0.4%). Other questions about, NO. of antibiotics used, duration of treatment by the antibiotics and course of antibiotic, all were reported in table (2).

**Table (2)** patients on antibiotic treatment. Data expressed as N (%), Total N=500.

| | N (%) | P value |
|---|---|---|
| **Patient take antibiotic** | | |
| **Yes** | 303(60.6) | 0.00001 |
| **No** | 197(39.4) | |
| **Type of antibiotic** | | |
| **Aminoglycoside** | 57(11.4) | |
| **Antiviral** | 32(6.4) | |
| **Carbapenem** | 17(3.4) | |
| **Cephalosporin** | 207(41.4) | |
| **Glycopeptide** | 52(10.4) | 0.00001 |
| **Macrolide** | 32(6.4) | |
| **Triazol** | 44(8.8) | |
| **Echinocandin** | 4(0.8) | |
| **Pencillin** | 63(12.6) | |
| **Penicillin extended spectrum** | 29(5.8) | |
| **Antifungal** | 6(1.2) | |
| **Quinolone** | 2(0.4) | |
| **No. of antibiotics used** | | |
| **0** | 197(39.4) | |
| **1** | 134(26.8) | |
| **2** | 115(23) | |
| **3** | 38(7.6) | 0.00001 |
| **4** | 13(2.6) | |
| **5** | 3(0.6) | |
| **Duration of treatment by the antibiotics(days)** | | |
| **0** | 197(39.4) | |
| **<=7** | 227(45.4) | 0.00001 |
| **>7** | 76(15.2) | |
| **Did the patient complete the course of antibiotics?** | | |
| **Did Not receive antibiotics** | 197(39.4) | |
| **Yes** | 132(26.4) | 0.0016 |
| **No** | 171(34.2) | |

P<0.05 consider significant

**Association of the severity of infection with patients data.**

Table (3) represented the association of severity of infection with data of patients, Table (3) question number 1 about did the patient take chemotherapy? its correct answer was (228), there was a significant ($p<0.05$) difference in the percentage among patients where the percentage of correct answer was (45.6%).

Question number 2 about side effects of chemotherapy noted, there was a significant ($p<0.05$) difference in the percentage among patients where the percentage of side effects of chemotherapy noted was (45.6%) and (54.4%) of chemotherapy side effect not noted, while there was no a significant ($p=0.609$) association between the severity of infection with the causes of infection where the percentage of no infection was (39.2%). Bacterial infection percentage was (58.2%), fungal infection percentage was (10.4%) and the percentage of suspected viral was (4.8%). Other association between the severity of infection and patients data were reported in table (3).

**Table (3):** Association of the severity of infection with data of the patients. Data expressed as N(%), Total N=500

| | N(%) | P value |
|---|---|---|
| **Gender** | | |
| **Male** | 289(57.8) | 0.9078 |
| **Female** | 211(42.2) | |
| **Type of malignancy** | | |
| **Solid tumor** | 205(41) | 0.7704 |
| **Leukemia** | 295(59) | |
| **Did the patient take chemotherapy?** | | |
| **Yes** | 228(45.6) | <0.0001 |
| **No** | 272(54.4) | |
| **Are side effects of chemotherapy noted?** | | |
| **Yes** | 228(45.6) | <0.0001 |
| **No** | 272(54.4) | |
| **Febrile neutropenia** | | |
| **Yes** | 29(5.8) | <0.0001 |
| **No** | 471(94.2) | |
| **Causes of infection** | | |
| **No infection** | 196(39.2) | |
| **Bacterial** | 291(58.2) | 0.609 |
| **Fungal** | 52(10.4) | |
| **Suspected viral** | 24(4.8) | |
| **Type of infection** | | |
| **No** | 196(38.8) | |
| **Single causes(Almost Bacterial)** | 249(49.8) | 0.0172 |
| **Combined (Bacterial with Fungal or Viral)** | 52(10.4) | |
| **Complicated (Bacterial+Viral+Fungal)** | 3(0.6) | |
| **Duration of hospital stay(days)** | | |
| **No** | 4(0.8) | |
| **1-7 days** | 370(74) | |
| **8-14 days** | 55(11) | |
| **15-21 days** | 31(6.2) | 0.0001 |
| **22-28 days** | 20(4) | |
| **>28 days** | 20(4) | |
| **Site of infection** | | |
| **No** | 194(38.8) | |
| **Chest** | 257(51.4) | |
| **Mouth** | 14(2.8) | |
| **Mucositis** | 14(2.8) | |
| **Skin** | 1(0.2) | 0.9858 |
| **Eye** | 2(0.4) | |
| **Urinary tract infection** | 10(2) | |
| **Pancytopenia** | 18(3.6) | |
| **No. site of infection** | | |
| **N** | 194(38.8) | |
| **Single site** | 296(59.2) | 0.2004 |
| **Multiple sites of infection** | 10(2) | |

P<0.05 consider significant

**Frequency and percentage of incidence of Resistance for antimicrobial agents tested by susceptibility test:**

Among antimicrobial agents tested by susceptibility test Amoxicillin/Clavulanic acid (AMC) and Cefotaxime (CTX), which showed highly resistance rate of 100%(n=2), followed by Oxacillin (OX) resistant rate was 93.5%(n=43), Benzylpenicillin resistant rate was 92.2% (n=47) and Ampicillin (AM) resistant rate was 91.9% (n=34) while the lower resistant rate was 2.9% (n=1) for Doxycycline (DO), 6.1% (n=2) for Linezolid(LNZ), and 6.8% (n=8) for Imipenem (IMP) (Table 4). Each antimicrobial agent's resistance rate is displayed (Figure 2).

**Table 4:** Frequency and percentage of incidence Resistance for antimicrobial agents tested by susceptibility test

| | | | | | |
|---|---|---|---|---|---|
| **Benzylpenicillin** | **51** | **47** | **92.2** | | |
| **Piperacillin(PR)** | 81 | 66 | 81.5 | | |
| **Penicillin(P)** | 0 | 0 | | | |
| **Ampicillin(AM)** | 37 | 34 | 91.9 | | |
| **Cloxacillin** | 0 | 0 | | | |
| **Oxacillin(OX)** | 46 | 43 | 93.5 | | |
| **Amoxicillin** | 0 | 0 | | | |
| **Amoxicillin/clavulonic acid(AMC)** | 2 | 2 | 100 | | |
| **Piperacillin/Tazobactam(TPZ)** | 118 | 35 | 29.7 | | |
| **Ticarcillin/Clavulonic acid(TIM)** | 74 | 29 | 39.2 | | |
| **Ampicillin/Salbactam(SAM)** | 0 | 0 | | | |
| **Amoxicillin/Salbactam** | 0 | 0 | | | |
| **Ticarcillin(TIC)** | 79 | 61 | 77.2 | | |
| **Meropenem(MEN)** | 81 | 11 | 13.6 | | |
| **Imipenem(IMP)** | 118 | 8 | 6.8 | | |
| **Ertapenem** | 34 | 1 | 2.9 | | |
| **Aztreonam(ATM)** | 74 | 59 | 79.7 | | |
| **Cefazolin** | 38 | 30 | 78.9 | | |
| **Cefoxitin** | 35 | 12 | 34.3 | | |
| **Cefuroxime(CXM)** | 0 | 0 | | | |
| **Cefixime(CFM)** | 0 | 0 | | | |
| **Ceftriaxone(CRO)** | 26 | 66.7 | | | |
| **Cefotaxim(CTX)** | 2 | 100 | | | |
| **Ceftazidime(CAZ)** | 93 | 79.5 | | | |
| **Cefepime(FEP)** | 51 | 62.2 | | | |
| **Nalidixic acid(NA)** | 0 | | | | |
| **Ofloxacin(OFX)** | 14 | 35.9 | | | |
| **Norfloxacin(ROR)** | 0 | | | | |
| **Ciprofloxacin(CIP)** | 38 | 30.6 | | | |
| **Levofloxacin(LEV)** | 27 | 31 | | | |
| **Moxifloxacin** | 15 | 30.6 | | | |
| **Trimethoprim/Sulfamethoxazole(TXS)** | 63 | 49.6 | | | |
| **Trimethoprim(TIM)** | 10 | 40 | | | |
| **Tetracycline(TE)** | 13 | 28.3 | | | |
| **Doxycycline(DO)** | 1 | 2.9 | | | |
| **Tigecycline** | 7 | 8.8 | | | |
| **Vancomycin(VA)** | 22 | 42.3 | | | |
| **Teicoplanin** | 48 | 18 | 37.5 | | |
| **Erythromycin(E)** | 54 | 38 | 70.4 | | |
| **Clarithromycin(CLR)** | 45 | 31 | 68.9 | | |
| **Azithromycin(AZM)** | 43 | 31 | 72.1 | | |
| **Gentamicin(CN)** | 133 | 35 | 26.3 | | |
| **Amikacin(AK)** | 107 | 12 | 11.2 | | |
| **Tobramycin(TOB)** | 106 | 22 | 20.8 | | |
| **Netlimicin(NET)** | 23 | 5 | 21.7 | | |
| **Clindamycin(DA)** | 47 | 19 | 40.4 | | |
| **Rifampicin(RA)** | 49 | 22 | 44.9 | | |
| **Linezolid(LNZ)** | 33 | 2 | 6.1 | | |
| **Fucidin** | 44 | 31 | 70.5 | | |
| **Colistin** | 9 | 4 | 44.4 | | |
| **Nitrofurantoin(F)** | 76 | 8 | 10.5 | | |
| **Fosfomycin(FOS)** | 5 | 0 | 0 | | |
| **Daptomycin** | 0 | 0 | | | |
| **Mupirocin** | 0 | 0 | | | |
| **Inducible clindamycin Resistance** | 0 | 0 | | | |
| **Minocycline** | | | 60 | 16 | 26.7 |

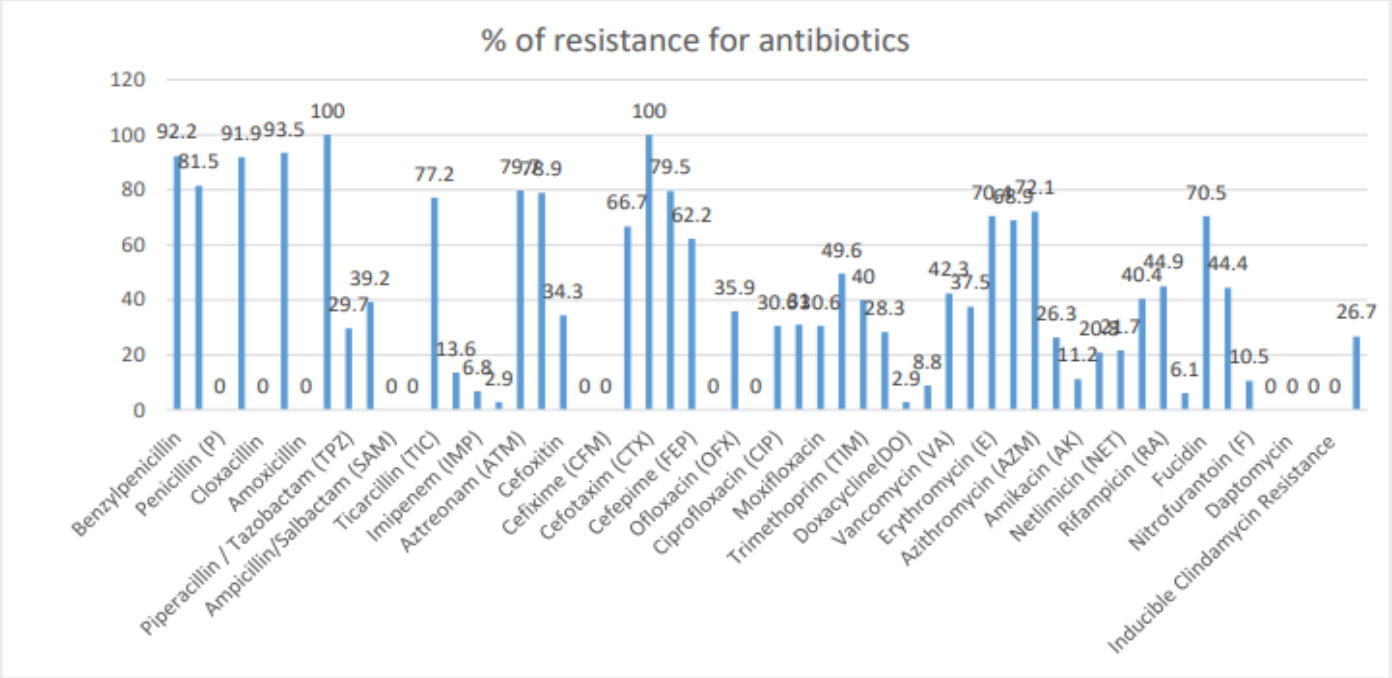



**Figure (2):** % of resistance for antibiotics.

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## DISCUSSION

Cancer patients have long faced a serious risk of infection due to the neutropenia brought on by chemotherapy. Resistance developing in bacteria and fungus has grown to be a significant issue in the treatment of high-risk cases who require extensive multiagent chemotherapy and those undergoing transplants [(3)]. Cancer patients experience high morbidity and mortality from bloodstream infections.

Due to alterations in the immune system, which regulates the body's defense systems, our study discovered that patients with illness exhibit the largest percentage (306 61.2%). [(9)], Febrile neutropenia only 29 (5.8%) because our retrospective study and the data of patients taken from the hospital information department and laboratory department, not all data were written in the patient's medical reports. In contrast with a study conducted [(10)] where 172 episodes of FN in 77 patients were evaluated 54.7% of the FN episodes were in male patients and 45.3% of the FN were female.

The current generation of chemotherapies is frequently aggressive and can cause extended periods of neutropenia, which increases the risk of infection and significantly raises morbidity and mortality for patients [(11)]. Bacterial infections accounted for the majority of infections (249, 39.2%), while secondary fungal infections (47, 9.4%) and probable viral infections (24, 4.8%) also played a significant role. The weakening of mucosal barriers (such as those caused by mucositis or typhlitis), myelosuppression, and recently placed central venous catheters are just a few of the risk factors linked to the development of bacterial infections in pediatric oncology patients (CVCs) [(12)]. The underlying diagnosis is crucial because hematologic malignancies in children carry a higher risk than solid tumors do. Risk factors for fungus infection included length and severity of neutropenia, exposure to high doses of steroids, underlying leukemia diagnosis, and advancing age. [(13)]. On viral prophylaxis in the pediatric oncology population, there is a dearth of information. This is partly owing to a lack of knowledge regarding the incidence, seriousness, and effects of viral infections in this population. [(11)].

In our study, we discovered that the most common type of antibiotic used was Cephalosporin 207 (41.4%), whereas Quinolone was used less frequently. Cephalosporins are frequently used in pediatric patients as the first-line of treatment for neutropenic fever. The majority of studies found that after their treatment, Enterobacteriaceae decreased while Enterococcus increased. Enterococcus has been linked to poor clinical results in HSCT and leukemia patients. It's interesting to note that the antibiotic's production affects how cephalosporin affects Clostridiales. Third, fourth, and

fifth-generation cephalosporins have been linked to an increase of Clostridiales and Quinolones, while first and second-generation cephalosporins have been linked to a decrease. They are mostly employed as preventative medications during chemotherapy and HSCT. Additionally, they are employed as step-down therapy after episodes of febrile neutropenia. [14], There were 227 (45.5%) antibiotic treatments lasting less than 7 days, and 76 (15.2%) lasting more than 7. Recent research indicates that switching from intravenous to oral antibiotics early may not be necessary for many illnesses, particularly when clinical recovery occurs quickly. There is little evidence for more frequent longer courses in the majority of other illnesses. The frequent use of customarily longer courses points to the dearth of evidence and the absence of widely accepted guidelines, as well as to the natural clinical tendencies to provide patients with conservative care in the face of this gap. However, prolonged use of antibiotics is linked to a rise in antimicrobial resistance, thus the possible advantages must be evaluated against the cost, particularly if they are unproven. [15].

Our study found that 171 (34.2%) of patients did not complete the course of antibiotics and 132 (26.4%) of patients finished their antibiotic courses, which contributed to increased antibiotic resistance. As a result, we can control the usage of antibiotics to lower bacterial resistance. If an infection develops, the type of bacteria that is causing it should be recognized as soon as feasible, and the number of drug combinations should be as few as possible. Patients should also be strongly encouraged to take their medications according to the recommended dosage and period of treatment [16].

In this study, we discovered a statistically significant relationship between the length of the hospital stay and febrile neutropenia, chemotherapy side effects, and infection severity (p-value 0.0001). These findings concur with this research [17], however, there was no significant association between severity of infection and gender and type of malignancy respectively P value ( 0.9078, 0.7704). These results are different from this study [18]. There was a significant association between severity of infection and gender and type of malignancy. The risk for BSI increased significantly for boys (P value=0.025) Additionally, the risk for BSIs was significantly lower for patients with solid tumors than with hematologic malignancies (P<0.001).

Our study found that there was no significant association between the severity of infection and causes of infection, type of infection, site of infection, and No. of infection sites, respectively (P value = 0.609, 0.0172, 0.9858, and 0.2004), while this study [19] showed that there was a significant correlation between them.

Among the frequency and percentage of incidence of resistance for the antimicrobial agent in our study, the high percentage of resistance was Amoxicillin/Clavulanic acid at 100%, followed by Oxacillin the percentage of resistance was 93.5%, while the lower percentage of resistance was Doxycicllin, Linezolid, and Tigecycline their percentage of resistance were respectively 2.9%, 6.1%, and 8.8%. Relatively, higher numbers of bacterial isolates were resistant to ampicillin and erythromycin. These findings are consistent with a study carried out in Basra [20, 21] that reported the rising prevalence of erythromycin resistance. A successful empirical antibiotic-treatment strategy depends heavily on an understanding of the relevant bacterial pathogens producing illnesses and an investigation of their susceptibility to antibiotics. Additionally, the regional variations in the pattern of antibiotic resistance should be investigated in order to select antimicrobials for the treatment of infection based on the local resistance profile of these uropathogens [22].

## CONCLUSION

Cancer patients receiving chemotherapy still frequently contract infections, therefore we need to find new strategies for enhancing antimicrobial coverage as well as identify high-risk patients and administer preventive antibiotics to them during neutropenic episodes. To better understand the dangers that our patients face, we need prospective data on them. We need to better inform patients and their families about the need of getting their children to the hospital as soon as possible and getting them treated right to avoid the development of a severe infection.

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