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Research Article

Evaluation of Antibiotic Resistance in Pediatric Patients Suffering from Cancer

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Abstract

Introduction: The discovery of antibiotics has revolutionized the field of healthcare since many lethal infections which were previously impossible to treat are now have become much curable. However, a high reliance of the clinicians on antibiotics have led to their irrational use which has given rise to a serious problem in the form of Antimicrobial Resistance (AMR) a phenomenon where the microbes develop the capacity to neutralize the antimicrobial capacity of the antibiotics. In cancer patient AMR is not so frequent as compared to other patients who suffer from infectious diseases but still if cancer patients during their chemotherapy encounter the issue of AMR their cancer treatment becomes highly challenging.

Objective: To evaluate the prevalence of AMR in the cancer affected pediatric patients being treated with antibiotics.

Materials and Methods: In this cross-sectional study 300 pediatric patients who received prescriptions with at least one antibiotic suffering from cancer and were treated with at least one antibiotic were included. The data was collected with the consent of their guardians from the cancer ward of The Children's hospital and The Institute of Child Health, Lahore, Pakistan by utilizing non-probability sampling technique (convenient sampling) for the period of 6-months.

Results: The study findings depicted that the children aged between 4 to 7 years got affected by various cancers and lymphoblastic leukemia (47%) was the most frequently occurring cancer. Urine, blood and mucosal swabs were used for sampling but majority of the samples were the blood (29%) samples that were used to detect the occurrence of AMR. It was observed that the study population was more susceptible to gram-negative bacteria than gram-positive bacteria. The incidence of AMR was higher in gram-negative bacteria than that of gram-positive bacteria. Among the collected samples the bacteria showed sensitivity for ciprofloxacin (23%), amikacin (21%), piperacillin (24%) and ceftazidime (23%). Considering the resistance patterns among the tested antibiotics that were prescribed to the cancer patients various penicillin antibiotics and ceftazidime showed a higher incidence of the AMR.

Conclusion: The AMR is a serious problem that is encountered during the treatment of infections in the pediatric patients affected by cancer thus, the appropriate selection of antibiotics by the clinicians is a matter of serious concern so as to prevent AMR and to obtain maximum therapeutic outcomes of the chemotherapy.

Keywords: Antimicrobial Resistance; Cancer; Antibiotics; Gram-Negative Bacteria; Pediatric Patients

Introduction

The cancer which is the uncontrollable division of the body cells, "lead to a fundamental abnormality of the cell function". "The proliferation of the cancer cells is not responsive to the signals that normalize the cellular mitosis and other functions [1]". The abnormal behavior of the cancer cells alters the function of the normal body cells that results in the form of the spread of malignancy to various body organs [2]. Annually, 300,000 children and adolescents are diagnosed with cancer worldwide [3]. The carcinomas being diagnosed in pediatric patients vary from those in adult patients. Pediatric patients suffering from cancer are more responsive to chemotherapy as compared to carcinomas diagnosed in adult patients [4]. Adult carcinomas are mainly originated from epithelial cells. In contrast, childhood carcinomas are originated from Central Nervous System (CNS) neoplasms or they are leukemias, lymphomas and sarcomas which are derived from embryonic accidents [5]. About 25% of the total diagnosed cancers in children are ALL (acute lymphoblastic leukemia) and AML (acute myeloid leukemia), diagnosed through bone marrow testing and tissue imaging techniques. Astrocytoma is the most common cancer among the intraspinal and CNS tumors that account to 17% of the total childhood cancer cases. Papillary thyroid carcinoma (9%), soft tissue sarcoma (7%), malignant bone tumors (6%), renal tumors (4%) and hepatic tumors (1%) are the common tumors occurring in children [6].

Following the chemotherapeutic and radiation related neutropenia in cancer patients, bacterial infections are serious complication encountered by the cancer patients. Some infections caused by Multi-Drug Resistant (MDR) gram-negative bacilli such as *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumonia, Acinetobacter baumannii, Pseudomonas aeruginosa* and *Enterobacter spp*. are difficult to treat and broad-spectrum antibiotics used against them further impart toxicological manifestations on cancer affected children [7]. The key factors that lead to antibiotic resistance in pediatrics are namely the irrational use of antibiotics, less reliance on microbiological report before the selection of antibiotic and the presence of antibiotics in the clinical environment where the patients are admitted [8]. When antibiotics are incorrectly prescribed or are not properly followed up, they lead to poor infection control in pediatrics particularly those immunosuppressed cancer patients who are more susceptible to certain MDR nosocomial infections [9]. Most of the antibiotics that are used to treat infections in pediatric patients, such as penicillin, aminoglycosides, fluoroquinolones, glycopeptides and tetracyclines are susceptible to AMR. They need an immense care to be administered to the pediatric patients diagnosed with cancer [10]. According to the statistics published by 8th European Conference on Infections in Leukemia (ECIL) the MDR are mainly caused by β-lactamase-producing Enterobacteriaceae (15-24%), aminoglycoside-resistant gram-negative bacteria (5-14%) and carbapenem-resistant Pseudomonas aeruginosa (10%) [11].

The hypothesis of this study is that the pediatric patients suffering from cancer are more suspectable to infectious diseases which are Multi-Drug Resistant (MDR) so appropriate selection of antibiotics for such infections is of utmost importance. The main objective of this study was to evaluate the prevalence of AMR in the pediatric patients who were treated for the cancer and were prescribed at least one antibiotic for the treatment of their infections (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumonia, Acinetobacter baumannii, Pseudomonas aeruginosa* and *Enterobacter spp*) they encountered during their cancer therapy.

Materials and Methods

Study Design

This is a cross-sectional observational study being designed to study the various patterns of antibiotic resistance in pediatric patients affected by cancer.

Sample Size

The guardians of pediatric cancer patients were approached and after seeking their consent patients fulfilling the inclusion criteria were included. The Cochrane formula was used to calculate the sample size. The first part of the Cochrane formula was used to specifically define the randomly distributed pediatric cancer patient population suffering from various infections.

$$n_0 = \frac{Z^2 pq}{e^2}$$

Where:
e is the desired level of precision (i.e., the margin of error),
p is the (estimated) proportion of the population which has the attribute in question,
q is 1 - p.

The z-value is found in a Z table

$$n = \frac{n_0}{1 + \frac{(n_0 - 1)}{N}}$$

Here n0 is Cochran's sample size recommendation, N is the patient population size and n is the new, adjusted sample size which was calculated as 150 patients.

Place and Duration of Study
Data was collected from cancer ward in The Children's Hospital and The Institute of Child Health, Lahore from 15th June to 15th August (2 months).

Inclusion Criteria
Patients of different age groups (1-15) of both genders diagnosed with cancer, who were willing to participate in the study and were prescribed with at least one antibiotic during the time of study were included.

Exclusion Criteria
Patients diagnosed with cancer and were not prescribed with any antibiotic or they did not encounter any antibiotic resistance were excluded from the study.

Procedure of Research
A total of 300 cancer patients of different age groups, that were prescribed with at least one antibiotic and have encountered antibiotic resistance were contacted to be included in this study. Various wards of Children's hospital were visited and the guardians of subjects (children) fulfilling the inclusion criteria of this study were interviewed and data was collected on a specially designed data collection form. The first part of the questionnaire was emphasized on the demographic and socio-economic parameters of the included subjects. The second part of questionnaire covered the history and type of cancer, duration of chemotherapy, protocol of cancer and symptoms before the start of antibiotics.

Data Analysis
The collected data was coded and analyzed by Microsoft Excel and results were presented in form of graphs and tables.

Results
The patients diagnosed with Hodgkin's lymphoma, acute lymphoblastic leukemia, adenocarcinoma and osteosarcoma were observed for bacterial infections and those who exhibited the AMR were studied accordingly. Table 1 describes the percentage of the occurrence of each cancer among the pediatric patients included in this study.

Cancers Diagnosed in Pediatric Patients	Percentage of the Patients Diagnosed with a Particular Cancer
Acute Lymphoblastic Leukemia	47%
Osteosarcoma	13%
Metastatic Ewing Sarcoma	12%
Hodgkin's Lymphoma	11%
Adenocarcinoma	9%
Non-Hodgkin's Lymphoma	8%
Relapsed Hodgkin's disease	0%

Table 1: Percentage of pediatrics diagnosed with different carcinomas.

The Fig. 1 describes the age range (1 -15 years old) of the included pediatric patients being treated for various cancers.

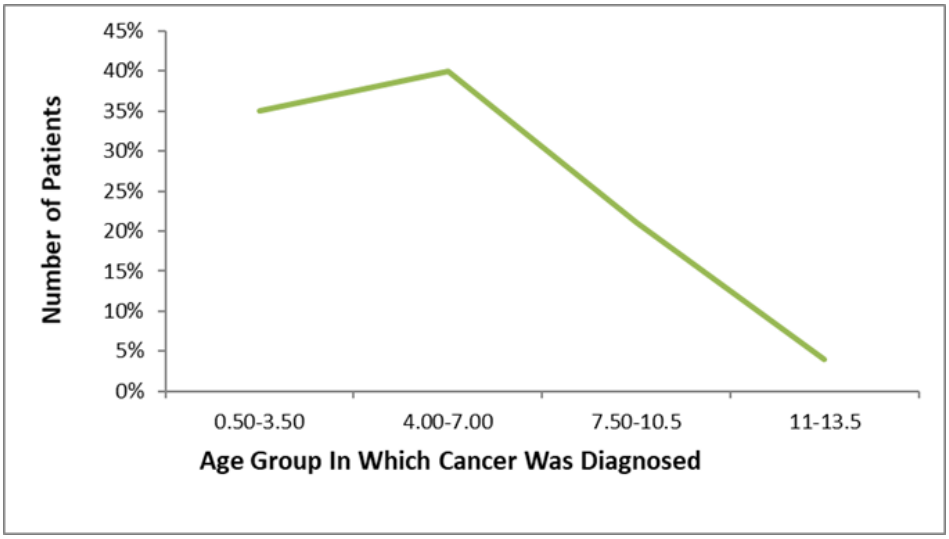

Figure 1: Images showing the age range (1 -15 years old) of the included pediatric patients being treated for various cancers.

The Table 2 describes the percentages of the patients as per the duration of chemotherapy of the pediatric cancer patients.

Duration of Chemotherapy	Percentage of Patients
1-3 months	79%
4-6 months	15%
7-9 months	4%
9-12 months	2%

Table 2: Duration of chemotherapy of the treated pediatric cancer patients.

The Table 3 describes the clinical aspects of the included pediatric patients being observed during the data collection process of the included pediatric patients.

Febrile Status of Patients		Causative Agents of Infections		Patients with Neutropenia	
Patients	Percentage	Gram +ve	Gram	Neutropenic	Non-Neutropenic
Febrile Patients	97%	51%	49%	95%	5%
Afebrile Patients	3%	--	--		

Table 3: Clinical observations pertaining to the included patients.

The Fig. 2 presents the percentage of different types of gram-positive bacteria that were spotted in the samples collected from the included pediatrics patients. *Staphylococcus aureus* was the most frequent gram-positive specie found in the patients' samples.

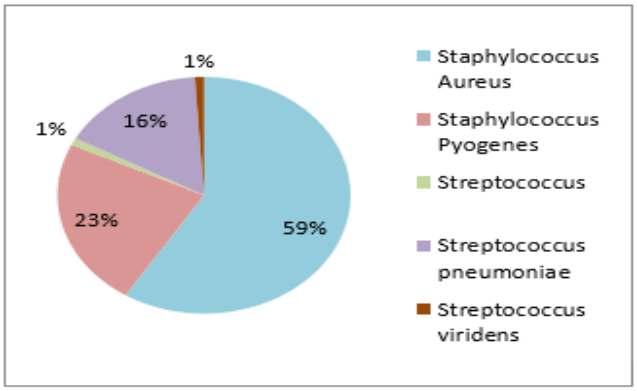

Figure 2: Different percentages of gram-positive bacteria found in patients' samples.

The Fig. 3 presents the percentage of different types of gram-negative bacteria being spotted in the samples collected from the included pediatric patients among which *Escherichia coli* was the most frequent gram-negative specie found in 36% of the patients' samples.

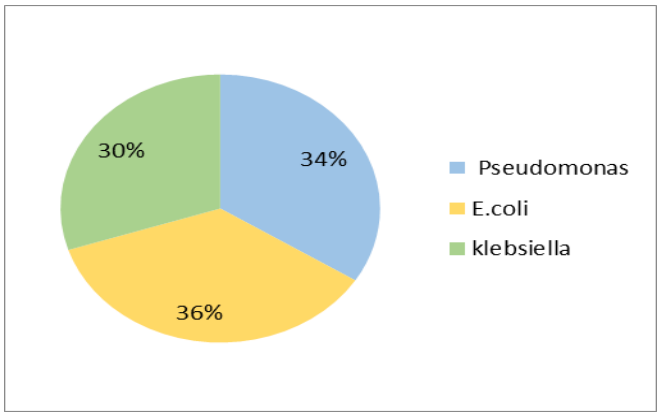

Figure 3: Different percentages of gram-positive bacteria found in patients' samples.

In Fig. 4 different percentages of antibiotics showing the incidence of AMR in pediatric patients. The antibiotics that were found most susceptible to AMR were mainly penicillin (24%) and ceftazidime (23%). Other important antibiotics displaying the occurrence of resistance were meropenem (19%) and amoxicillin (16%).

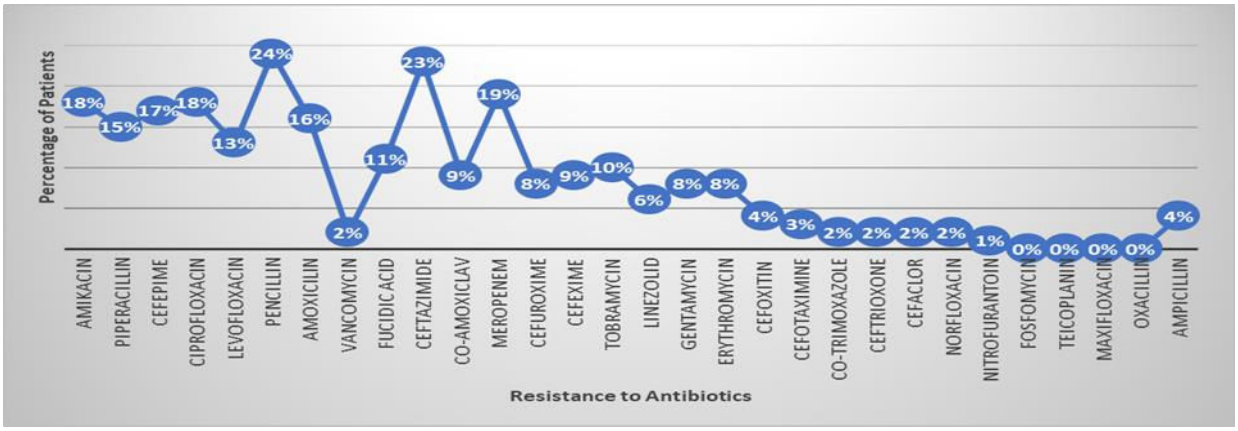

Figure 4: Percentages of antibiotics that show resistance in patients.

The Fig. 5 presents the percentages of the antibiotics showing the highest and least effectiveness in curing the infections among the study population. Ciprofloxacin (23%) appeared to be the most effective for the patients along with Amikacin (21%), Piperacillin (16%) and Cefepime (16%).

The Fig. 5 presents the percentages of the antibiotics showing the highest and least effectiveness in curing the infections among the study population. Ciprofloxacin (23%) appeared to be the most effective for the patients along with Amikacin (21%), Piperacillin (16%) and Cefepime (16%).

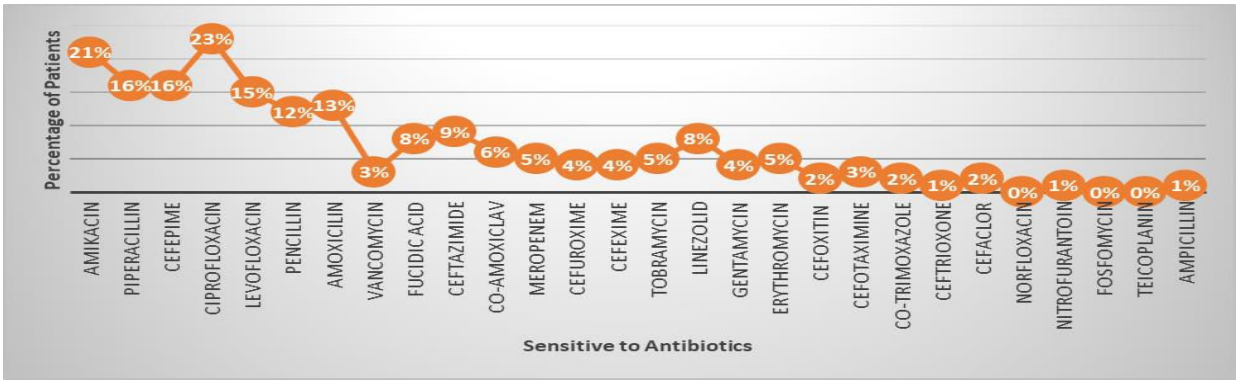

Figure 5: Percentages of antibiotics that showed sensitivity in patients.

The antibiotic sensitivity and resistance patterns in included pediatric cancer patients is presented in Table 4.

Antibiotics	Resistant n (%)	Sensitive n (%)	No. of Patients
Amikacin	55 (18%)	62 (21%)	117
Piperacillin	44 (15%)	47 (16%)	91
Cefepime	51 (17%)	47 (16%)	98
Ciprofloxacin	53 (18%)	69 (23%)	122
Levofloxacin	40 (13%)	45 (15%)	85
Pencillin	71 (24%)	35 (12%)	106
Amoxicilin	49 (16%)	40 (13%)	89
Vancomycin	5 (2%)	8 (3%)	13
Fucidic acid	32 (11%)	24 (8%)	56
Ceftazimide	68 (23%)	26 (9%)	94
Co-amoxiclav	28 (9%)	18 (6%)	46
Meropenem	56 (19%)	15 (5%)	71
Cefuroxime	25 (8%)	12 (4%)	37
Cefexime	28 (9%)	13 (4%)	41
Tobramycin	31 (10%)	14 (5%)	45
Linezolid	17 (6%)	25 (8%)	42
Gentamycin	25 (8%)	11 (4%)	36
Erythromycin	24 (8%)	15 (5%)	39
Cefoxitin	11 (4%)	7 (2%)	28
Cefotaximine	9 (3%)	8 (3%)	17
Co-trimoxazole	7 (2%)	7 (2%)	14
Ceftrioxone	5 (2%)	4 (1%)	9
Cefaclor	5 (2%)	5 (2%)	10

Norfloxacin	5 (2%)	1 (0%)	6
Nitrofurantoin	3 (1%)	3 (0%)	6
Fosfomycin	1 (0%)	2 (1%)	3
Teicoplanin	1 (0%)	1 (0%)	2
Moxifloxacin	2 (0%)	0 (NA)	2
Oxacillin	1 (0%)	0 (NA)	1
Ampicillin	12 (4%)	3 (1%)	15

Table 4: Pattern of antibiotics use with appropriate resistance and sensitivity among pediatric patients.

According to the Table 4, it could be seen that ciprofloxacin was the most frequently used antibiotic among the included cancer patients i.e., 122 out of total 300 patients used the said antibiotic followed by amikacin used in 117 patients whereas oxacillin was the least prescribed antibiotic.

Discussion

According to research findings, antibiotics have the capacity to promote cancer apoptosis, inhibit cancer growth and prevent cancer metastasis. For these reasons, antibiotics are increasingly being used to assist in the treatment of cancers [12]. But using antibiotics can increase the risk of resistance in patients. Antibiotic Resistance (AR) in previously susceptible microorganisms is a complicated and multifaceted process. AMR supports the establishment and selection of resistant bacteria and inadequate infection prevention and control methods contribute to their spread [13,14]. Overall mortality due to infections is commonly cited as less than 1% due to advancements in supportive treatment, particularly the early introduction of broad-spectrum antibiotics. However, as antibacterial resistance spreads over the world and new antibiotics become scarce, the influence of infection on overall survival is likely to be shifted [15].

Infections caused by MDR gram-negative bacteria are of special concern. According to a study conducted in 2018, gram-negative bacteria cause half of all Blood Stream Infections (BSI) in children with cancer, with Enterobacteriaceae being the most common [16]. Single-center reports on the susceptibility of bacteria that cause BSI in this population are common and are highly region-specific [17]. Extended-Spectrum-Beta-lactamase (ESBL) producing Enterobacteriaceae, fluoroquinolone-resistant gram-negative bacteria and carbapenem-resistant Pseudomonas aeruginosa were the top three clinical concerns highlighted in a survey of 37 European hematology-oncology centers (including 15 that treated pediatric patients). The survey also discovered that gram-negative bacteria resistance rates were much greater in South-East European cities than in Northwest European cities [17]. As the neutropenic and non-neutropenic patients were also determined, 5% of the patients were neutropenic and 95% of patients were non-neutropenic. As far as febrility is concerned, 97% were febrile and 3% were afebrile. According to a study, febrile neutropenia is one of the most common acute side effects of pediatric cancer treatment, necessitating the use of empirical broad-spectrum antibiotics right away. According to some risk criteria, patients might be classed as low or high risk (duration of neutropenia, depth of neutropenia, type of cancer, stage of disease, bone marrow involvement, type of treatment, additional health problems). The initial evaluation should include the history of the febrile neutropenic child, a comprehensive physical examination, blood cultures (peripheral and catheter), urine and culture and cultures of lesions. So, the recommended course of action for treating febrile neutropenic youngsters is to admit them to the hospital, especially if they are at high risk and administer broad-spectrum intravenous antibiotics [18]. "The identified organisms among patients were 49% gram-positive bacteria and 51% gram-negative bacteria". Several studies involving cancer patients have recently revealed a clear trend in the epidemiology of bacterial infections, showing a shift in the prevalence of gram-positive to gram-negative bacteria as well as the widespread emergence of antimicrobial-resistant strains among gram-negatives isolated from the blood [19]. Among the patients identified with gram-positive bacteria, *Staphylococcus aureus* affected 59% of patients, *Staphylococcus pyogenes* affected 23% of patients, Streptococcus affected 1% of patients and Streptococcus pneumonia affected 16% of patients *Escherichia coli* and *Streptococcus viridans* affected 1% of patients. Among the patients identified with gram-negative bacteria, *E. coli* affected 36% of the patients, pseudomonas affected 34% of patients and Klebsiella affected 30% of patients. According to a study, the rate of gram-negative bacteria in cancer patients' recovery has ranged from 24.7 to 75.8% (mean 51.3%) since 2007. Among gram-negative bacteria, *E. coli* was the most prevalent (mean frequency of isolation was 32.1%), followed by *Pseudomonas aeruginosa* (mean frequency of isolation was 20.1% [20].

When studied the pattern of antibiotic resistance in patients, the analysis depicted that about 1 to 5% of patients were resistant to cefaclor, ceftriaxone, oxacillin, norfloxacin, vancomycin and cefotaxime. Less than 10% of patients were resistant to cefixime, co-amoxiclav and cefuroxime. 16% of patients were resistant to piperacillin. Less than 20% were resistant to ciprofloxacin, amikacin and cefepime and 24% of the patients were resistant to penicillin. While studying the sensitivity patterns, we observed that less than 5% of the population was sensitive to gentamycin, co-trimoxazole, cefotaxime and ceftriaxone. Less than 10% of the population was sensitive to erythromycin, ceftazidime, co-amoxiclav and fucidic acid. Less than 20% of the population was sensitive to levofloxacin, piperacillin and amoxicillin. 21% of the population was sensitive to amikacin while 23% of the population was sensitive to ciprofloxacin. The highest rate of sensitivity is associated with ciprofloxacin which is around 23% and which suggested that most of the patients receiving ciprofloxacin showed satisfactory response to it. A retrospective study was conducted in which oral ciprofloxacin plus penicillin V (group A) was compared to amikacin plus carbenicillin or ceftazidime (group B). Among the patients with febrile solid tumor or nonlymphocytic lymphoma a total of 108 neutropenic febrile episodes (5 exclusions) were randomized into two groups: 55 episodes in group A and 48 episodes in group B. The cause of the majority of febrile episodes was unknown. With two occurrences of bacteremia, there were ten microbiologically recorded events. Both treatments went over well. The oral regimen was significantly less expensive than the parenteral regimen. Treatment success was 94.5% for group A and 93.8% for group B without any changes to the regimen proving ciprofloxacin more effective than other antibiotics like amikacin plus carbenicillin or ceftazidime [21]. A study based on tests conducted from 2010 to 2012 in patients aging less than 18 years having Acute Lymphoblastic Leukemia (ALL) and Acute Myeloid Leukemia (AML) receiving chemotherapy described that a total of 149 patients were included in this study. Patients showed a visible response to ciprofloxacin and the rate of infection was decreased. Thus, making it useful for prophylactic as well as treatment purposes [22]. According to a study published in 2013, children having age less than 18 years with Acute Lymphoblastic Leukemia (ALL) or lymphoma were given oral ciprofloxacin 20 mg/kg/day or placebo from the starting of their chemotherapy. Rectal swab cultures were taken before and after the intervention. After comparing the results, it was found that by using ciprofloxacin, the occurrence of febrile episodes in patients with acute lymphoblastic leukemia was decreased during the induction phase of chemotherapy. Thus, it was concluded that ciprofloxacin showed good tolerance and had less side effects in neutropenic patients with acute lymphoblastic leukemia. The long-lasting effects of ciprofloxacin still requires further investigation [23].

The use of broad-spectrum antibiotics mitigates their action not only on the pathogenic bacteria but also such antibiotics disrupt the normal microbiome that further complexes the treatment of the infectious diseases particularly in the pediatric cancer patients [24]. A remarkable approach has been introduced in the form of using narrow spectrum antibiotics which minimize the antimicrobial impact on non-targeted antibiotics. The most imminent example of narrow spectrum antibiotics are bacteriophages, mono-clonal antibodies, bacteriocins and antisense molecules such as peptide-conjugated phosphonodiamidite morpholino oligomers [25]. The application of narrow spectrum antibiotics' concept is only feasible for the treatment of ESKAPE pathogens if the treatment plan includes rapid diagnostic techniques especially the culture sensitivity test report availability as soon as possible before the onset of the antimicrobial therapy [26]. Further steps towards the prevention of AMR in immune compromised cancer patients having infections as well could be a rapid switch onto definitive antimicrobial therapy by efficient diagnosis through matrix-assisted laser desorption ionization-time-of-flight mass spectrometry and rapid antigen testing [27]. Moreover, according to the new guidelines of the Infectious Diseases Society of America (IDSA) the most preferred and their alternative antibiotics for treating Extended Spectrum Beta Lactamase (ESBL) producing bacterial infections are suggested in order to avoid irrational use of antibiotics particularly in the pediatric cancer patients [28].

Conclusion

The antibiotic resistance has the potential of affecting people at any stage of chemotherapy that puts the patients' life in danger. Therefore, the problem of AMR needs an urgent attention of healthcare scientists and healthcare governing bodies. In the current study, it was observed that the most of the study population was susceptible to gram-negative bacteria i.e., *E. coli* and *S. aureus*. Though, different antibiotics have been discovered against various infectious or pathogenic microbes, yet, some of these micro-organisms are smart enough to resist against the antibiotics. Majority of the patients were found sensitive to ciprofloxacin whereas the resistance was seen against penicillin and ceftazidime thus depicting ciprofloxacin a reliable antibiotic for treating infections. High resistance in cancer pediatric patients resulted in a decreased antibiotics' ability to treat infections which sequentially caused higher mortality rate amongst such patients. It is inferred from the findings of this study that there should be a defined policy or guideline at government level regarding the appropriate selection of antibiotics which will be highly

helpful to control AMR in cancer pediatric patients and will also enhance the chances of their survival. Since the antibiotic resistance in pediatric cancer patients has retarded much of the gains pertaining to their cancer treatment the cancer advocates should imply much of their political and social powers to resolve this healthcare challenge. There is an immense need of collective efforts of both oncological and infectious disease experts to derive a central policy to combat infectious disease challenge in cancer patients with a special focus on pediatric cancer patients in order to safeguard the effectiveness of newly discovered advancements regarding oncological therapy.

Conflict of Interest

The authors have no conflict of interest to declare.

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