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ORIGINAL RESEARCH

Prevalence of Extended-Spectrum Beta-Lactamase-Producing *Enterobacteriaceae* Causing Bloodstream Infections in Cancer Patients from Southwest of Iran

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Introduction: This study aimed to evaluate the frequency rate of extended-spectrum beta-lactamase-producing *Enterobacteriaceae* (ESBL-PE) causing bloodstream infections (BSIs) in cancer patients referred to one of the major referral hospitals in Ahvaz city, southwest Iran.
Materials and Methods: In this study, 1700 blood cultures were collected from 610 cancer patients suspected to have BSI from October 2016 to August 2017 referred to the Shafa cancer hospital, Ahvaz, southwest of Iran. The blood culture bottles were incubated aerobically at 35–37ºC for 24 hours and then sub-cultured on routine microbiology culture media. The bacterial colonies were identified using standard tests. The antibiotic susceptibility testing was achieved by the disc-diffusion method. The phenotypic detection of ESBLs was carried out by the combination disc-diffusion test (CDDT). Finally, the polymerase chain reaction (PCR) was performed to investigate the presence of bla_{TEM}, bla_{CTX}, bla_{SHV}, and bla_{PER} genes.
Results: The prevalence of BSI in cancer patients was 16.4% (100/610). Gram-negative rods with rate of 74% (74/100) were the most prevalent bacteria. The frequency of *Enterobacteriaceae* family was 21% including *Escherichia coli* (n: 8), *Klebsiella pneumoniae* (n: 6), *Enterobacter* spp. (n: 5), *Citrobacter freundii* (n: 1), and *Serratia marcescens* (n: 1). All isolates were multidrug-resistant (resistance to three or more antibiotics). The results of CDDT showed that 42.8% (9/21) of *Enterobacteriaceae* isolates had a positive ESBL test of which 100% (9/9) indicated positive band for at least one of the ESBL genes by PCR method. The $bla_{CTX\text{-}M}$ and bla_{TEM} genes were detected in 38% (8/21) and 23.8% (5/21) of isolates, respectively, while the bla_{SHV} and bla_{PER} were not detected in any isolates.
Conclusion: Based on the results, surveillance, and antibiotic stewardship programs should be implemented for cancer patients to prevent the spread of more ESBL-PE that have limited therapeutically choices.

Keywords: extended-spectrum beta-lactamase, ESBL, cancer patients, *Enterobacteriaceae*, hematological malignancies, Iran

Introduction

Bloodstream infection (BSI) is a significant complication in cancer patients receiving cytotoxic chemotherapy due to their immunocompromised condition, which accompanies with a high rate of morbidity and mortality.[1] The most common outcome of chemotherapeutic agents is neutropenia that could lead to the severity of bacterial infections in patients suffering from cancer.[2]

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The incidence of BSIs among cancer patients has been reported to range from 11.8 to 33.3%, and among these the greater proportion have caused by Gram-negative bacteria.[3] In recent years, the spread of BSI caused by extended-spectrum beta-lactamase-producing *Enterobacteriaceae* (ESBL-PE) has been reported increasingly in patients with cancer in different regions of the world.[4,5] Moreover, emerging of multidrug-resistant *Enterobacteriaceae* has become a major public health problem.[5]

The ESBLs are carried on bacterial plasmids that can be transferred to other bacteria.[6] Several ESBL classes have been detected in *Enterobacteriaceae* strains of which the CTX-M, TEM, and SHV beta-lactamases are the most common types.[7] ESBL-PE are usually resistant to most beta-lactam antibiotics, however, carbapenems are considered the drugs of choice for treatment of infections caused by these bacteria.[7,8]

Since there is no adequate epidemiological information of ESBL-PE in cancer patients in Iran, this study aimed to evaluate the frequency of BSI causing ESBL-PE in patients suffering from different cancers in the southwest of Iran to provide a guide for suitable empiric antibiotic therapy.

Materials and Methods

Ethical Consideration

The current study was approved by the ethics committee of Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran (No: IR.AJUMS.REC.1395.323). Written informed consent was obtained from all patients.

Sampling

This cross-sectional study was carried out on blood cultures obtained from cancer patients suspected to BSI during 10 months period from October 2016 to August 2017 referred to the Shafa cancer hospital, Ahvaz, Iran. The Shafa hospital is one of the major referral hospitals for cancer patients in the southwest of Iran which located in Khuzestan province. The demographic data collected from every patient including age, sex, duration of hospitalization, and cancer type. During the febrile period, a volume of 5–10 mL or 1–3 mL of the peripheral blood sample was collected from adults and pediatric patients, respectively. For each patient, 3 separate blood samples from 3 different sites were collected. The blood samples were inoculated in blood culture bottles containing trypticase soy broth (TSB) (Baharafshan Co., Tehran, Iran) and incubated aerobically at 35–37ºC for 24 hours.

Microbial Identification

Bacterial identification carried out by sub-culture of the sample of bottles on blood agar, chocolate agar, MacConkey agar, and mannitol salt agar. All media were prepared from Merck Co., Darmstadt, Germany. The bacterial colonies were identified using standard biochemical tests including coagulase, catalase, triple sugar iron agar, Simmons citrate, urease, indole production, Methyl red/Voges-Proskauer, and oxidase.[9] When the same bacterium was isolated from three samples of one patient, only one isolate was considered for further investigation.

Antimicrobial Susceptibility Testing

Antimicrobial susceptibility test was carried out for *Enterobacteriaceae* isolates by the disc-diffusion method according to guidelines of the Clinical and Laboratory Standards Institute (CLSI).[10] The isolates with turbidity equal to 0.5 McFarland standards were lawn cultured on Mueller-Hinton agar (MHA) plates. Then the antimicrobial discs were placed on the MHA plates. Finally, the plates were incubated at 35ºC for 24h. The antibiotics used were as follows: piperacillin (100 µg), tetracycline (75 µg), piperacillin-tazobactam (100/10 µg), ceftazidime (30 µg), cefotaxime (30 µg), cefepime (30 µg), imipenem (10 µg), meropenem (10 µg), gentamicin (10 µg), ciprofloxacin (5 µg), and aztreonam (5 µg). *Escherichia coli* ATCC 25922, and *Pseudomonas aeruginosa* ATCC 27853 were used as quality control strains. Methicillin-resistant *S. aureus* (MRSA) and methicillin-resistant coagulase-negative staphylococci (MRCONS) isolates were identified using the cefoxitin disc according to guidelines of CLSI.[10] The bacterial suspensions equal to 0.5 McFarland standards were inoculated on MHA and a cefoxitin (30 µg) disc placed on the medium. The plates incubated at 33–35ºC for 18–24 h. The isolate was considered methicillin-resistant when the inhibition zone was equal to ≤ 21 mm or ≤ 24 mm for MRSA and MRCoNS, respectively. *S. aureus* ATCC 29213 and ATCC 33591 were used as methicillin-sensitive and resistant control strains, respectively.

Phenotypic Detection of ESBLs

The *Enterobacteriaceae* isolates that were resistant to one or more of third-generation cephalosporins were screened for ESBL production by combination disc-diffusion test (CDDT) included ceftazidime and cefotaxime alone and with ceftazidime + clavulanic acid and cefotaxime +

clavulanic acid (Mast group, Merseyside, UK). An ESBL positive isolate was identified by the increase of inhibition zone size of ≥ 5 mm in the presence of clavulanic acid.[11] *Escherichia coli* ATCC 25922, and *Klebsiella pneumoniae* ATCC700603 were used as the ESBL negative and positive controls, respectively.

Polymerase Chain Reaction (PCR) for Detection of ESBL Genes

DNA Extraction

The total DNA was extracted from fresh colonies of *Enterobacteriaceae* isolates by the boiling method as described previously.[12] Briefly, 2 or 3 colonies of an overnight growth of each isolate on nutrient agar (Merck Co., Darmstadt, Germany) were suspended in 500 mL of DNase- and RNase-free water. The suspension was boiled at 100 °C for 10 min in a dry block incubator (Polystat 5; Bioblock Scientific, France), then centrifuged at 14,000 g for 10 min. Finally, 0.5 mL of the supernatant was used as DNA template for PCR. The extracted DNA was stored at −20°C until analysis.

PCR Protocol

The phenotypic ESBL positive isolates in this study were investigated for the presence of bla_{CTX-M}, bla_{TEM}, bla_{SHV}, and bla_{PER} by PCR using specific primer mentioned in Table 1. The PCR was performed in the BIO-RAD C1000 thermal cycler (Applied Biosystems, USA) in a final volume of 25 µL containing 12.5 µL of PCR master mix, 1 µL of each primer (10 pmol), 1 µL of sample DNA, and 9.5 µL of nuclease-free water. The PCR conditions were as follows: initial denaturation at 94°C for 5 minutes, followed by 35 cycles of denaturation at 95°C for 35 seconds, different annealing temperatures (Table 1) for 35 seconds, and extension at 72°C for 30 seconds, with a final extension period of 72°C for 5 minutes. The amplicons were analyzed by agarose gel electrophoresis stained with safe stain (Sinaclon Co., Tehran, Iran) and visualized using an ultraviolet gel documentation device (Protein Simple, San Jose, CA, USA). The control positive genes were prepared from the Pasteur Institute of Iran.

Statistical Analysis

The statistical analysis was performed using SSPS version 22.0 (IBM Corporation, Armonk, NY, USA). The comparison of variables was carried out by the chi-square test and Fischer's exact test where appropriate. A p-value < 0.05 was considered statistically significant.

Results

In this study, 610 cancer patients aged 1 to 76 years (mean 42 years) referred to Shafa hospital in Ahvaz city, southwest of Iran were evaluated. Hematological malignancies were seen in 400 (65.5%) patients while the remaining had solid organ cancer. During the study period, 1700 peripheral blood cultures were collected from 610 patients. Overall, 450 blood cultures of three hundred patients were positive for bacterial growth, of which 100 non-duplicate isolates were identified. In other words, the prevalence of BSI in cancer patients was 16.4% (100/610) of which 75% was seen in patients with hematological malignancies and 25% in solid tumors cases (Table 2). Of these patients, 53 (53%) were females while 47 (47%) were males. The neutropenia (neutrophil count below <1000/mm3) was seen in 79.4% and 14.3% of hematological cancer and solid tumor patients, respectively.

Gram-negative rods with the rate of 74% (74/100) were the most prevalent bacteria. The *Pseudomonas aeruginosa* was the most frequent isolate (41%), followed by Coagulase-negative staphylococci (16%), and *Acinetobacter baumannii* (12%). Moreover, 10 (10%) *S. aureus* strains were isolated of which 5 isolates were methicillin-resistant. Of the 16 coagulase-negative staphylococci, 8 isolates were methicillin-resistant. The

Table 1 The Primer Sequences Used for Extended-Spectrum Beta-Lactamase Genes Detection

Primer	Oligonucleotide Sequence (5′ to 3′)	Gene	Product Size (bp)	Annealing Temperature (°C)
TEM-F TEM-R	GTATCCGCTCATGAGACAATAACCCTG CCAATGCTTAATCAGTGAGGCACC	bla_{TEM}	919	60
SHV-F SHV-R	CGCCTGTGTATTATCTCCCTGTTAGCC TTGCCAGTGCTCGATCAGCG	bla_{SHV}	843	62
CTX-M-F CTX-M-R	ATGGCGGCCGCGGCGGTGCTTAA AGCGCGGCCGCGCTACAGTACAGC	bla_{CTX-M}	158	59
PER-F PER-R	AATTTGGGCTTAGGGCAGAA ATGAATGTCATTATAAAAGC	bla_{PER}	925	57

Table 2 Demographic Features of Cancer Patients with Bloodstream Infections

Patients Characteristics		Patients with Bloodstream Infections (n=100) n (%)
Age (years)		42±18
Male/Female		47 (47%)/53 (53%)
Duration of hospitalization (days)		42±28
Hematological malignancies		75 (75%)
	Acute lymphoblastic leukemia	30 (30%)
	Acute myeloid leukemia	16 (16%)
	Hodgkin lymphoma	10 (10%)
	Non-Hodgkin lymphoma	8 (8%)
	Multiple myeloma	11(11%)
Solid organ malignancies		25 (25%)
	Bone tumor	4 (4%)
	Breast cancer	5 (5%)
	Lung cancer	2 (2%)
	Rectum tumor	1 (1%)
	Thyroid tumor	1 (1%)
	Brain tumor	1 (1%)
	Ewing sarcoma	1 (1%)
	Colorectal carcinoma	5 (5%)
	Adenocarcinoma	5 (5%)

frequency of the *Enterobacteriaceae* family was 21% including *Escherichia coli* (n: 8), *Klebsiella pneumoniae* (n: 6), *Enterobacter* spp. (n: 5), *Citrobacter freundii* (n: 1), and *Serratia marcescens* (n: 1) (Table 3). The resistance rate in *Enterobacteriaceae* isolates was as follows: cefotaxime 76.1%, ceftazidime 85.7%, cefepime 47.6%, imipenem 28.6%, meropenem 90.4%, piperacillin 76.1%, piperacillin-tazobactam 28.6%, tetracycline 38.1%, gentamycin 28.6%, ciprofloxacin 28.6%, and aztreonam 52.3%. The most effective antibiotics against *E. coli* were imipenem and gentamycin with a 62.5% susceptibility rate, while the less effective antibiotics were ceftazidime and cefotaxime with an 87.5% resistance rate. The detailed results of antibiotic susceptibility test for *E. coli, K. pneumonia*, and *Enterobacter* spp. are presented in Table 4. The *Citrobacter freundii*, and *Serratia marcescens* isolates were resistant to all tested antibiotics except for piperacillin-tazobactam, gentamycin, and ciprofloxacin. All *Enterobacteriaceae* isolates were resistant to three or more antibiotics and considered as multidrug-resistant (MDR) strains. The MDR patterns of *Enterobacteriaceae* isolates are shown in Table 5.

The results of CDDT showed that 42.8% (9/21) of *Enterobacteriaceae* isolates had a positive ESBL test of which 100% (9/9) indicated positive band for at least one of the ESBL genes by PCR method. The $bla_{\text{CTX-M}}$ and bla_{TEM} genes were detected in 38% (8/21) and 23.8% (5/21) of isolates, respectively, while the bla_{SHV} and bla_{PER} were not detected in any isolates. Also, 4 (19%) isolates co-harbored $bla_{\text{CTX-M}}$ and bla_{TEM} genes. The phenotype and genotype results of ESBL-PE are summarized in Table 6. The statistical analysis revealed that the production of ESBLs in *Enterobacteriaceae* was not significantly associated with resistance to a particular type of antibiotic (p-value > 0.05) and there was no difference between the two groups of ESBL producers and non-producers. The data were not shown.

Discussion

Infection is a significant problem in immunosuppressed patients with cancer due to chemotherapy treatment. Patients

Table 3 Bacterial Isolates Causing Bloodstream Infection in Cancer Patients

Species	Number of Isolates	Sex (Male/Female)	Hematologic Malignancies	Solid Organ Tumors
Pseudomonas aeruginosa	41	14/27	30	11
Escherichia coli	8	3/5	5	3
Klebsiella pneumonia	6	4/2	5	1
Enterobacter species	5	3/2	5	–
Citrobacter freundii	1	1/-	1	–
Serratia marcescens	1	1/-	1	–
Acinetobacter baumannii	12	7/5	11	1
Coagulase-negative staphylococci	16	9/7	12	4
Staphylococcus aureus	5	2/3	3	2
Methicillin-resistant *S. aureus*	5	1/4	2	3

Table 4 Antibiotic Resistance Patterns of *Enterobacteriaceae* Isolates

Antibiotics	*Escherichia coli* (n:8)			*Klebsiella pneumoniae* (n:6)			*Enterobacter* species (n:5)		
	S*	I*	R*	S	I	R	S	I	R
Aztreonam	1 (12.5%)	2 (25%)	5 (62.5%)	2 (33.3%)	0	4 (66.6%)	5 (100%)	0	0
Cefepime	3 (37.5%)	0	5 (62.5%)	3 (50%)	0	3 (50%)	5 (100%)	0	0
Cefotaxime	0	1 (12.5%)	7 (87.5%)	1 (16.7%)	1 (16.7%)	4 (66.6%)	1 (20%)	1 (20%)	3 (60%)
Ceftazidime	0	1 (12.5%)	7 (87.5%)	0	1 (16.7%)	5 (83.3%)	0	1 (20%)	4 (80%)
Ciprofloxacin	3 (37.5%)	0	5 (62.5%)	4 (66.6%)	1 (16.7%)	1 (16.7%)	3 (60%)	2 (40%)	0
Gentamycin	5 (62.5%)	0	3 (37.5%)	4 (66.6%)	1 (16.7%)	1 (16.7%)	5 (100%)	0	0
Imipenem	5 (62.5%)	2 (25%)	1 (12.5%)	2 (33.3%)	1 (16.7%)	3 (50%)	2 (40%)	3 (60%)	0
Meropenem	0	1 (12.5%)	7 (87.5%)	0	0	6 (100%)	1 (20%)	0	4 (80%)
Piperacillin	1 (12.5%)	1 (12.5%)	6 (75%)	0	1 (16.7%)	5 (83.3%)	1 (20%)	1 (20%)	3 (60%)
Piperacillin-Tazobactam	4 (50%)	2 (25%)	2 (25%)	2 (33.3%)	2 (33.3%)	2 (33.3%)	2 (40%)	1 (20%)	2 (40%)
Tetracycline	2 (25%)	1 (12.5%)	5 (62.5%)	3 (50%)	1 (16.7%)	2 (33.3%)	3 (60%)	1 (20%)	1 (20%)

Notes: *S, susceptible; I, intermediate; R, resistant.

Table 5 The Multidrug Resistance Patterns of *Enterobacteriaceae* Isolates

Isolates	Resistance Pattern	Number (%)
Escherichia coli(n: 8)	PIP-TET-CAZ-CTX-CFP-MEM-CIP-ATM	4 (50%)
	PIP-PTZ-CAZ-CTX-MEM-GEN	2 (25%)
	TET-CAZ-CTX-CFP	1 (12.5%)
	IMI-MEM-GEN-CIP-ATM	1 (12.5%)
Klebsiella pneumoniae (n: 6)	PIP-PTZ-TET-CAZ-CTX-CFP-IMI-MEM-ATM	2 (33.3%)
	PIP-CAZ-CTX-MEM-ATM	2 (33.3%)
	PIP-CAZ-CFP-MEM	1 (16.7%)
	IMI-MEM-GEN-CIP	1 (16.7%)
Enterobacter species (n:5)	PTZ-CAZ-MEM	2 (40%)
	PIP-TET-CTX	1 (20%)
	PIP-CAZ-CTX-MEM	2 (40%)

Abbreviations: PIP, piperacillin; TET, tetracycline; PTZ, piperacillin-tazobactam; CAZ, ceftazidime; CTX, cefotaxime; CFP, cefepime; IMI, imipenem; MEM, meropenem; GEN, gentamicin; CIP, ciprofloxacin; ATM, azteronam.

suffering from BSI during neutropenia episodes caused by chemotherapy should use an adequate antibiotics as soon as possible. The BSI caused by Gram-negative bacteria has poor prognoses in these patients. Rapid initiation of treatment by adequate antibiotic for neutropenic patients result in reduce the mortality rate.[13,14] Thus, the evaluation of the microbial spectrum of BSI in the cancer patients is an important aspect that should be considered in every country for rapid empirical therapy.

In this study, 16.4% of patients suffering from hematological and solid organ malignancies had BSI which was lower than the previous study by Obeng-Nkrumah et al[3] from Ghana who reported the BSI in 22% of cancer patients and higher than the report by Lubwama et al[15] from Uganda who showed the BSI in 14.1% of cancer patients.

In the current research, The Gram-negative bacteria cause 74% of all BSI cases that was consistent with previous reports.[16,17] However, previous studies from Iran and Australia indicated the Gram-positive cocci isolates as a leading cause of BSIs in cancer patients.[18–20] These dissimilarities in the bacterial spectrum of different regions and countries indicate that recognizing infection-related pathogens in each area is very important for better control of these microorganisms in the cancer patients. In recent years, various countries have reported that the spectrum of bacteria causing BSIs in the cancer patients has shifted from Gram-positive isolates to Gram-negative strains and Gram-negative bacteria appear to occupy the place of Gram-positive isolates, which may be due to the relatively lower use of indwelling medical devices, as well as lower prescribing of prophylactic antibiotic treatments in cancer patients.[3,21,22] Among Gram-positive bacteria the coagulase-negative staphylococci with 16% were the most frequent strains followed by *S. aureus* with a 10% frequency rate that was comparable to findings of Rosa et al[23] from Brazil. Furthermore, half of *S. aureus* isolates were methicillin-resistant. In the current study, the *P. aeruginosa* was the most frequent isolate (41%) in BSI that was in line with findings of Marin et al[24] from Spain while in contrast with our results a report by Islas-Munoz et al[25] from Mexico showed the *E. coli* as the most predominant isolate causing BSI in cancer patients. Besides, the *Enterobacteriaceae* isolates that were detected in 21% of

Table 6 The Frequency of Extended-Spectrum Beta-Lactamase Genes in *Enterobacteriaceae* Isolates

Bacterial Isolates	No.	Gender	Age	ESBL (CDDT)	Extended-Spectrum Beta-Lactamase Gene			
					bla_{CTX-M}	bla_{TEM}	bla_{SHV}	bla_{PER}
Escherichia coli (n=8)	EC1	M	72	+	+	+	-	-
	EC2	M	50	+	-	+	-	-
	EC3	F	63	+	+	+	-	-
	EC4	M	52	–	–	–	–	-
	EC5	M	8	+	+	–	–	-
	EC6	M	1	+	+	–	–	-
	EC7	M	2	+	+	+	-	-
	EC8	F	76	+	+	-	-	-
Klebsiella pneumoniae (n=6)	KP1	M	44	-	-	-	-	-
	KP2	M	64	-	-	-	-	-
	KP3	M	1	+	+	+	-	-
	KP4	M	54	+	+	-	-	-
	KP5	F	20	-	-	-	-	-
	KP6	F	1.5	-	-	-	-	-
Enterobacter species (n=5)	ES1	M	3	-	-	-	-	-
	ES2	F	56	-	-	-	-	-
	ES3	M	51	-	-	-	-	-
	ES4	M	5	-	-	-	-	-
	ES5	F	62	-	-	-	-	-
Citrobacter freundii (n=1)	CF1	M	35	-	-	-	-	-
Serratia marcescens (n=1)	SM1	F	6	-	-	-	-	-

Abbreviations: EC, *Escherichia coli*; KP, *Klebsiella pneumonia*; ES, *Enterobacter* species; CF, *Citrobacter freundii*; SM, *Serratia marcescens*; M, male; F, female.

BSI cases in this study included *E. coli* (8%), *K. pneumoniae* (6%), *Enterobacter* spp. (5%), *C. freundii* (1%), and *S. marcescens* (1%). The frequency of the *Enterobacteriaceae* family was in agreement with a report from European countries that claimed these bacteria account for approximately 30% (range 8–56%) of the BSIs in hematology centers.[26] Also, in this study, the *E. coli* isolates occupy the first place among the *Enterobacteriaceae* family in BSIs cases. Likewise, in a prospective study conducted from September 2012 to September 2014 by Babu et al[27] from India, the *E. coli* was the most frequent isolate followed by *Acinetobacter baumannii* and *K. pneumonia*.

Importantly, the results of antibiotic susceptibility testing revealed that all *Enterobacteriaceae* isolates were MDR, of which 42.8% were ESBL producers. In recent decades, the spread of ESBL-PE has become one of the major health concerns because these bacteria have the ability to transfer the antibiotic resistance genes to other bacteria that lead to severe infection with limited therapeutic options. To our knowledge, this is the first research that investigated the prevalence of ESBL-PE in BSIs among cancer patients in Iran. The high frequency of MDR ESBL-producing Gram-negative rods among cancer patients was in line with reports from Uganda,[15,28] and India.[29] In our study, ESBLs were identified in 9 (42.8%) of 21 *Enterobacteriaceae* isolates and similar to what has been described in previous reports the *E. coli* strains were the main ESBL producers.[30] Also, there was no significant association between age (p-value: 0.88), sex (p-value: 0.25), and type of cancer (p-value: 0.91) with ESBL-PE in this study. Another noteworthy finding of this study was the higher prevalence rate of ESBL-PE compared to other Eastern Mediterranean countries in which the pooled prevalence of ESBL-PE was reported 7%.[31]

Carbapenems, such as imipenem, ertapenem, and meropenem are recommended antibiotics for treatment of infection cases caused by ESBL-PE.[8] However, the meropenem with a resistance rate of 90.4% did not seem to be an appropriate antibiotic to treat infections caused by *Enterobacteriaceae* in cancer patients in our region. Another very harmful challenge for the health system of all countries is the increasing trend of

carbapenem-resistant *Enterobacteriaceae* that have also emerged in Iran.[32] Meanwhile, another carbapenem, imipenem with 71.4% susceptibility rate showed a more efficiency against MDR *Enterobacteriaceae* in this study. Likewise, the piperacillin-tazobactam, gentamycin, and ciprofloxacin with 71.4% susceptibility rate showed good effects against *Enterobacteriaceae* and could be considered for BSIs treatment. Given the good efficacy of ciprofloxacin as a fluoroquinolone, it seems that these antibiotic categories could be prescribed for BSI treatment in cancer patients in our region. This recommendation relies on the high susceptibility rate of the blood culture isolates to fluoroquinolone in clinical trials performed in Western countries as the American Society of Clinical Oncology policy recommends immediate quinolone-based oral empiric antibiotic therapy in cancer patients.[33] In the current cross-sectional study the high resistance rate against third-generation cephalosporins which may due to ESBLs production highlights the need of our institution to make an urgent policy to restrict the use of this antibiotic category. In the current study, $bla_{\text{CTX-M}}$ with 38% frequency rate was the most prevalent gene followed by bla_{TEM} gene with a prevalence of 23.8% that was in parallel with previous reports that showed the predominance of $bla_{\text{CTX-M}}$ in various countries.[34–36] Also 19% of ESBL-PE co-harbored $bla_{\text{CTX-M}}$ and bla_{TEM} genes. So far, similar to our findings, several studies have reported the co-existence of ESBL genes in *Enterobacteriaceae*.[34,36,37]

Conclusion

This study showed the predominance of MDR Gram-negative bacteria caused BSIs in cancer patients that harboring ESBL genes. Thus, surveillance and antibiotic stewardship programs should be implemented for cancer patients to prevent the spread of more ESBL-PE that have limited therapeutically choices. Also, we found that the piperacillin-tazobactam, gentamycin, and ciprofloxacin could be considered in the treatment of BSIs caused by *Enterobacteriaceae* in our region. Further studies involving healthcare centers of different regions of Iran is needed to warrant the selection of appropriate empirical antibiotics, particularly in cancer patients.

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Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare that they have no conflicts of interest.

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