Original Article

Antimicrobial Resistance Pattern and Spectrum of Multiple-drug-resistant Enterobacteriaceae in Iranian Hospitalized Patients with Cancer

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Abstract

Background: Nosocomial infections are one of the most leading causes of morbidity and mortality in patients with cancer. The emergence of multiple-drug-resistant (MDR) strains of Gram-negative bacteria causing nosocomial infection has become a serious concern in cancer patients. Therefore, the present study aimed to determine the spectrum and antibiotic resistance pattern of Gram-negative bacteria related nosocomial infections among Iranian cancer patients. **Materials and Methods:** This descriptive cross-sectional study was conducted during the 6 months from December 2015 to May 2016 in two tertiary care centers located in Isfahan and Arak Province. Gram-negative bacteria obtained from different clinical specimens from hospitalized patients with cancer and were identified using standard microbiological methods. Antibiotic susceptibility pattern was determined by the disk diffusion method according to the Clinical and Laboratory Standards Institute (CLSI) recommendation. **Results:** Of totally 259 culture positive cases, *Escherichia coli* showed the highest isolation rate (60.6%) followed by *Klebsiella pneumoniae* (26.6%) and *Proteus* spp (11.2%). The rate of MDR isolates were 91.5% (237/259). Overall, the most frequent source of bacterial isolation was urinary tract infection (65.6%) followed by skin and soft-tissue infection (23.6%). The antibiotic susceptibility results showed meropenem (MEN) and ceftazidime as the most effective antibiotics for *E. coli*, *K. pneumoniae,* and *Proteus* spp. isolates. Moreover, MEN was the most effective antibiotic against MDR isolates. **Conclusion:** The study findings showed a significant distribution of MDR Gram-negative bacteria which may increase the burden of healthcare-associated infections in cancer patients. Although, carbapenem can be considered as effective agents toward MDR strains for empirical antibiotic therapy in our region.

Keywords: *Antibiotic resistance, cancer, enterobacteriaceae, nosocomial infection*

Introduction

Cancer is a significant cause of death worldwide, and more than half of them occur in developing countries.[1] The most common causes of cancer death are lung, liver, colorectal, stomach, breast cancer, and leukemia.[1] The new advances in treatment options increased survival rates of cancer patients in the past decades.[2] However, severe immunosuppression as an adverse consequence of these treatment strategies increases the risk of opportunistic infections.[3]

Nosocomial infections are one of the most serious complications and the leading cause of morbidity and mortality in patients with cancer.[4] There are several risk factors for acquisition of nosocomial infections such as neutropenia, stem cell transplantation, long-term catheterization, and the extensive use of medical devices such as stents, shunts, and central venous catheters.[4,5] The most common sites of infections are bloodstream infections (BSIs), respiratory tract infections, urinary tract infections (UTIs), and surgical site infections.[4,5] A wide range of bacteria has been reported as a cause of nosocomial infections that among them, Gram-negative bacteria, particularly *Pseudomonas aeruginosa, Acinetobacter baumannii*, and Enterobacteriaceae are the most prevalent.[5] The reported prevalence of these organisms estimated more than 30% of hospital-acquired infections and 70% of infections in the intensive care unit.[5]

The emergence of multiple-drug-resistant (MDR) strains of Gram-negative bacteria causing nosocomial infection has become a serious concern, especially in cancer patients.[6] In recent years, the majority of conducted studies in cancer patients have

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only focused on BSIs, and there is no study looking at the overall prevalence of Gram-negative bacteria related infections among Iranian cancer patients. Therefore, the present study aimed to determine the spectrum and antibiotic resistance pattern of Gram-negative bacteria related nosocomial infections among Iranian cancer patients. This information can help clinicians to choose effective empirical therapies and provide good epidemiological profiles to compare our situation with others.

Materials and Methods

Study design

This descriptive cross-sectional study was conducted during the 6 months from December 2015 to May 2016 in two tertiary care centers located in Isfahan and Arak Province (located in the central part of Iran). These centers providing treatment for cancer patients with radiotherapy, chemotherapy, and hormonal therapy. All hospitalized cancer patients undergoing anti-cancer therapy. Demographic characteristics consisted of demographic data including age, sex, admission date, hospitalization duration, ward, type of cancer, and sites of infections were collected from the patients. This study was in accordance with the declaration of Helsinki and approved by the regional Ethics Committee. We only used medical records, and the details were kept strictly confidential.

Sampling and isolation

Nonduplicate clinical specimens were collected from urine, wound, blood, sputum, and stool samples from cancer patients. All clinical specimens were cultured on blood agar and MacConkey agar and incubated aerobically at 37°C for 24 h. Standard microbiological methods consist of reaction with Triple Sugar Iron agar, Simmons' citrate agar, Christensen's urea agar, Indole test, Methyl red, and Voges–Proskauer tests were followed for the isolation and identification of Gram-negative bacteria.

Antimicrobial susceptibility testing

Antibiotic susceptibility pattern was determined by the disk diffusion method on Mueller– Hinton agar (Himedia, India) according to the CLSI recommendation.[7] The used antibiotic disks were imipenem (10 µg), meropenem (MEN) (10 µg), cefepime (FEP) (30 µg), ceftazidime (CAZ) (30 µg), cefotaxime (CTX) (30 µg), co-trimoxazole (SXT) (75 µg), gentamicin (GM) (10 µg), amikacin (AN) (30 µg), ciprofloxacin (CIP) (5 µg) ofloxacin (OFX) (5 µg), and nitrofurantoin (FM) (300 µg) disks (Padtan Teb, Iran). Antimicrobial susceptibility of *Salmonella* and *Shigella* isolates was determined toward ampicillin (10 µg), CTX (30 µg), FEP (30 µg), SXT (75 µ), CIP (5 µg), and nalidixic acid (30 µg). *Escherichia coli* ATCC 25922 was used as a control strain for susceptibility testing. MDR was defined by nonsusceptible to ≥1 agent in ≥3 antimicrobial categories as previously described.[8]

Statistical analysis

Analyses were performed using SPSS™ software, version 21.0 (IBM Corp., New York, USA). The results are presented as descriptive statistics in terms of relative frequency. Values were expressed as the mean ± standard deviation (SD) (continuous variables) or percentages of the group (categorical variables).

Results

Totally 259 nonduplicates Gram-negative bacteria collected from clinical specimens at two studied hospitals in Isfahan and Arak, Iran. Out of the 259 positive cultures, 142 (54.8%) belonged to females and 117 (45.2%) were from males. The mean age of the patients was 48.5 ± 18.9 (mean ± SD) years, and the age range was from 8 to 89 years. The most prevalent cancer type among patient was blood cancer (35.1%) followed by prostate cancer (11.6%). Of culture-positive cases, *E. coli* showed the highest isolation rate (60.6%) followed by *Klebsiella pneumoniae* (26.6%) and *Proteus* spp.(11.2%). Overall, the rate of MDR isolates were 91.5% (237/259). The full results of bacterial isolation and MDR rates according to the type of cancer are presented in Table 1. Overall, the most frequent source of bacterial isolation was from UTIs (65.6%) followed by skin and soft tissue infections (SSTIs) (23.6%) [Table 2]. The majority of patients were hospitalized in ICUs (64.5%) followed by internal wards (33.6%), and surgery wards (1.9%).

The antibiotic susceptibility results showed MEN and CAZ as the most effective antibiotics toward *E. coli, K. pneumoniae* and *Proteus spp.* isolates. The results of antibiotic susceptibility pattern of pathogens obtained from cancer patients are shown in Table 3. All the recovered *Salmonella* isolates were susceptible to ampicillin, CTX, FEP, CIP, and trimethoprim/sulfamethoxazole and only resistant to nalidixic acid. Moreover, *Shigella* isolates were susceptible to FEP, CIP, and nalidixic acid. For 237 MDR isolates in this study, the highest antibiotic sensitivity was toward MEN and CAZ with 67.9% and 59.5%, respectively.

Discussion

The management of nosocomial infections in patients with cancer is a priority of public health due to its rapid onset and high level of morbidity and mortality.[4] Due to diverse nature of nosocomial infections etiology and antibiotic resistance patterns in periodic intervals, routine surveillance is needed to prevent the occurrence and transmission of nosocomial pathogens.[4,9] In the present study, we have analyzed the distribution and antibiotic resistance of nosocomial pathogens isolated from Iranian cancer patients.

In the present study, 65.6% of cancer patients developed UTIs and 23.6% SSTIs. This is consistent with other studies

Table 1: Distribution of isolated bacteria in according to type of cancer[a]

Cancer type	*Escherichia coli* (*n*=157)		*Klebsiella pneumonia* (*n*=69)		*Proteus* spp. (*n*=29)		*Salmonella* spp. (*n*=2)		*Shigella* spp. total (*n*=2)		Total (*n*=259)	
	Total	MDR	Total	MDR	Total	MDR	Total	MDR	Total	MDR	Total	MDR
Blood cancer	52 (57.1)	50 (96.2)	26 (28.6)	25 (96.2)	12 (13.2)	12 (100)	0	0	1 (1.1)	0	91	87 (95.6)
Prostate cancer	20 (69)	17 (85)	7 (24.1)	7 (100)	1 (3.4)	1 (100)	1 (3.4)	0	0	0	29	25 (86.2)
Uterus cancer	13 (54.2)	12 (92.3)	10 (41.7)	9 (90)	1 (4.2)	1 (100)	0	0	0	0	24	22 (91.7)
Skin cancer	13 (59.1)	13 (100)	5 (22.7)	4 (80)	3 (13.6)	2 (66.7)	0	0	1 (4.5)	0	22	19 (86.4)
Breast cancer	14 (66.7)	13 (92.9)	5 (23.8)	5 (100)	2 (9.5)	2 (100)	0	0	0	0	21	20 (95.2)
Bladder cancer	9 (56.3)	8 (88.9)	2 (12.5)	2 (100)	5 (31.3)	2 (40)	0	0	0	0	16	12 (75)
Lung cancer	10 (66.7)	10 (100)	4 (26.7)	4 (100)	1 (6.7)	1 (100)	0	0	0	0	15	15 (100)
Ovary cancer	9 (64.3)	9 (100)	3 (21.4)	3 (100)	2 (14.3)	2 (100)	0	0	0	0	14	14 (100)
Thyroid cancer	6 (60)	6 (100)	3 (30)	2 (66.7)	1 (10)	1 (100)	0	0	0	0	10	9 (90)
Stomach cancer	5 (62.5)	5 (100)	1 (12.5)	1 (100)	1 (12.5)	0	1 (12.5)	0	0	0	8	6 (75)
Bone cancer	2 (66.7)	2 (100)	1 (33.3)	1 (100)	0	0	0	0	0	0	3	3 (100)
Colon cancer	1 (50)	1 (100)	1 (50)	1 (100)	0	0	0	0	0	0	2	2 (100)
Esophageal cancer	1 (50)	0	1 (50)	1 (100)	0	0	0	0	0	0	2	1 (50)
Lymphoma cancer	2 (100)	2 (100)	0	0	0	0	0	0	0	0	2	2 (100)

[a]All data presented as *n* (%).MDR: Multiple-drug-resistant

Table 2: Distribution of Gram-negative isolates in according to sources of infections[a]

Sources of infection[b]	*Escherichia coli*		*Klebsiella pneumoniae*		*Proteus* spp.		*Salmonella* spp. (*n*)		*Shigella* spp.		Total	
	Total	MDR	Total	MDR	Total	MDR	Total	MDR	Total	MDR	Total	MDR
UTI	94 (59.9)	89 (94.7)	47 (68.1)	45 (95.7)	29 (100)	24 (82.8)	0	0	0	0	170 (65.6)	158 (92.9)
SSTI	51 (32.5)	48 (94.1)	10 (14.5)	9 (90)	0	0	0	0	0	0	61 (23.6)	57 (93.4)
RTI	6 (3.8)	5 (83.3)	10 (14.5)	9 (90)	0	0	0	0	0	0	16 (6.2)	14 (87.5)
BSI	6 (3.8)	6 (100)	2 (2.9)	2 (100)	0	0	0	0	0	0	8 (3.1)	8 (100)
GI	0	0	0	0	0	0	2 (100)	0	2 (100)	0	4 (1.5)	0

[a]All data presented as *n* (%), [b]UTI: Urinary tract infection, SSTI: Skin and soft tissue infection, RTI: Respiratory tract infection, BSI: Bloodstream infection, GI: Gastrointestinal infection, MDR: Multiple-drug-resistant

Table 3: The antibiotic susceptibility pattern of pathogens isolated from cancer patients

Class	Antibiotic	*Escherichia coli*, total (*n*=157)		*Klebsiella pneumonia*, total (*n*=69)		*Proteus* spp. total (*n*=29)	
		Resistant, *n* (%)	Susceptible, *n* (%)	Resistant, *n* (%)	Susceptible, *n* (%)	Resistant, *n* (%)	Susceptible, *n* (%)
β-lactams	CAZ	64 (40.8)	93 (59.2)	27 (39.1)	42 (60.9)	6 (20.7)	23 (79.3)
	CTX	99 (63.1)	58 (36.9)	33 (47.8)	36 (52.2)	13 (44.8)	16 (55.2)
	FEP	77 (49)	80 (51)	34 (49.3)	35 (50.7)	15 (51.7)	14 (48.3)
Aminoglycosides	GM	105 (66.9)	52 (33.1)	30 (43.5)	39 (56.5)	16 (55.2)	13 (44.8)
	AN	78 (49.7)	79 (50.3)	33 (47.8)	36 (52.2)	10 (34.5)	19 (65.5)
Fluoroquinolones	CIP	85 (54.1)	72 (45.9)	38 (55.1)	31 (44.9)	13 (44.8)	16 (55.2)
	OFX	92 (58.6)	65 (41.4)	38 (55.1)	31 (44.9)	16 (55.2)	13 (44.8)
Carbapenems	MEN	49 (31.2)	108 (68.8)	20 (29)	49 (71)	9 (31)	20 (69)
	IPM	81 (51.6)	76 (48.4)	41 (59.4)	28 (40.6)	9 (31)	20 (69)
Anti-metabolites	SXT	91 (58)	66 (42)	41 (59.4)	28 (40.6)	18 (62.1)	11 (37.9)
Nitrofurans	FM	64 (40.8)	93 (59.2)	28 (40.6)	41 (59.4)	13 (44.8)	16 (55.2)

CAZ: Ceftazidime, CTX: Cefotaxime, FEP: Cefepime, GM: Gentamicin, AN: Amikacin, CIP: Ciprofloxacin, OFX: Ofloxacin, MEN: Meropenem, IPM: Imipenem, SXT: Co-trimoxazole, FM: Nitrofurantoin

which reported UTIs and SSTIs as the common sites of infections in cancer patients.[10-12] We found that *E. coli* and *K. pneumoniae* were the most frequent Gram-negative bacteria isolated from cancer patients. Despite some reports inconsistent with our findings,[11,13-15] still, there is controversy about the prevalence of common etiology of nosocomial infections in patients with cancer. However, some reasons may explain the observed discrepancies in etiology of nosocomial infections. The variation in the prevalence of Gram-negative bacteria may arise from the differences in sample size, the source of infections, type of cancer, and geographical distribution.

Regarding antimicrobial susceptibility among Gram-negative bacteria, with some variation closest to our findings Eslami Nejad *et al*. from Kerman and Abdollahi *et al*. from Tehran introduced carbapenem and third-generation cephalosporins as the most effective antibiotics against pathogens recovered from Iranian cancer patients.[10,16] Moreover, despite the comparable antibiotic resistance results of our study with other foreign studies, antibiotic susceptibility patterns have a variable nature according to the geographical area.[11,12,17,18]

In our results, the estimated rate of MDR isolates was remarkable (91.5%). Our estimated MDR rates were significantly higher compared to those that were previously reported for *E. coli* (37%), and *K. pneumoniae* (33%) by Eslami Nejad *et al*. from Kerman (Southeast Iran, 2010) among cancer patients who developed BSIs.[16] Besides the study of Eslami Nejad *et al*. as the only specific report on MDR rate among Iranian cancer patients,[16] there are several recent studies that showed high rates of MDR pathogens in Iranian hospitals.[19-21] In recent years, the emergence of MDR strains is growing problem in Iranian health-care centers, especially extended-spectrum beta-lactamases and carbapenem producing strains of enterobacteriaceae.[22,23] The study findings showed the promising effect of carbapenem for MDR isolates and can be recommended for treatment of related infections in patients with cancer. Despite reports that are indicating to increasing trend of carbapenem resistance among enterobacteriaceae our findings emphasize the effectiveness of these agents.

As the main limitation of the present study, we did not explore the microbial spectrum of Gram-positive bacteria as one of the main causes of nosocomial infections in cancer patients.[13,24]

The continuous evolution of pathogens in hospital environments necessitates continuous updating of local data on bacterial etiology and antimicrobial susceptibility to improve the outcome of nosocomial infections.

Conclusion

The study findings showed a significant distribution of MDR Gram-negative bacteria which may increase the burden of healthcare-associated infections in cancer patients. Although, carbapenem can be considered as effective agents toward MDR strains for empirical antibiotic therapy in our region. Moreover, mechanisms of resistance should also be investigated for better characterization of antibiotic-resistant Gram-negative isolates.

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Conflicts of interest

There are no conflicts of interest.

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