The Spread of Carbapenemase Genes in *Klebsiella pneumoniae* in Iran: a Systematic Review

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Abstract

Introduction: The emergence and global spread of carbapenemases produced by *Klebsiella pneumoniae* is a serious problem to health services worldwide. *K. pneumoniae*, belonging to the Enterobacteriaceae family, is commonly found in the human gastrointestinal tract and environment, especially in the hospital environment. Carbapenem is administered as the first treatment for severe infections created by multi-drug resistant *K. pneumoniae*. Despite the fact that the carbapenemase-producing *K. pneumoniae* has become more prevalent in Iran, few investigations have probed into the prevalence of different carbapenemase genes in Iran.

Method: The aim of this study was to examine the prevalence of carbapenemase genes in *K. pneumoniae* from 2010 to 2018 in Iran. PubMed and Scopus databases were searched for the articles published between 2010 and 2018 in Iran.

Results: A total of 25 papers published between 2012 and 2018 were selected. The highest frequency of *bla*NDM, *bla*IMP, *bla*VIM, *bla*KPC and, *bla*OXA48 genes were related to cities of Shiraz in 2017 [23 (26.14%)], Hamedan in 2017 [2 (50%)], Babol in 2015 [15 (41.66%)], Isfahan in 2013 [65 (44.83%)] and, and Isfahan in 2018 [90 (76.27%)], respectively. The results showed that the frequency of *bla*NDM, *bla*OXA48, and *bla*IMP genes increased in 2017 and 2018, and there was an increase in the frequency of the *bla*VIM gene in 2014 and 2015, and the *bla*KPC gene in 2013. The highest percentage of carbapenemase genes isolated in Iran were related to *bla*KPC [145 (37.08%)], *bla*OXA48 [118 (30.18%)], and *bla*NDM [88 (22.51%)], and the lowest percentages were reported in *bla*IMP [4 (1.02%)], and *bla*VIM [36 (9.21%)], respectively.

Conclusion: The results of our review showed that *bla*NDM and *bla*OXA48 carbapenemase genes have been increasing in Iran, and it seems that traveling is one of the most important factors in the transmission of carbapenemase genes.

Keyword: *Klebsiella pneumoniae*, Carbapenemase, NDM, VIM, IMP, KPC, OXA48

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Introduction

Klebsiella pneumoniae is usually found in the human gastrointestinal tract and environment, especially in the hospital environment.^{1,2} It can cause hospital infections, including pneumonia, blood infections, wound, and meningitis.³ These bacteria rapidly acquired antibiotic resistance, especially to carbapenem.⁴ Antibiotic resistance is a global health problem caused by increased antibiotic consumption in clinical and veterinary fields.⁵ Antibiotic resistance in gram-negative bacteria, especially Enterobacteriaceae, is one of the major

causes of mortality and a serious health problem.^{6,7} Carbapenems are used as the first line of treatment for severe infections caused by multi-drug resistant *K. pneumoniae*.^{1,8} After extended-spectrum beta-lactamases, carbapenemase is another group of β -lactamases in which hydrolysis of carbapenem antibiotics, causes resistance to Gram-negative bacteria.^{9,10}

The most important carbapenemase genes include *bla*NDM, *bla*KPC, *bla*OXA48, *bla*IMP, and *bla*VIM. In 1996 for the first time, the *bla*KPC gene was reported in the United States¹¹ followed by

Table 1. Number of Articles Per Year

Year	2012	2013	2014	2015	2016	2017	2018	Total
Frequency	2	2	3	4	1	6	7	25
Percent	8	8	12	16	4	24	28	100

Table 2. Frequency Percentage of Samples

Samples	Urine	Wound	Sputum	Blood	Feces	CSF	Respiratory Secretions	Other Samples	Unknown
Number	705	214	17	154	55	15	352	297	981
Percent	25.22	7.66	0.61	5.50	1.97	0.54	12.77	10.63	35.10

and respiratory secretions [352 (12.77%)] samples, and the least frequent samples include cerebrospinal fluid (CSF) [15 (0.54%)], sputum [17 (0.61%)], feces [55 (1.97%)], blood [154 (5.50%)] and wound [214 (7.66%)] samples, respectively. Also, in these studies, the highest number of samples is related to the year 2017 [535 (23.67%)] and the lowest number of clinical specimens is in 2012 [48 (2.12%)].

Samples were collected from hospitalized patients in 20 articles [20 (80%)] and from outpatients in five articles [5 (20%)]. Furthermore, most specimens were collected from intensive care units (ICU) and burns wards.

The highest percentage of carbapenem resistance was related to ertapenem (63%), meropenem (62%), doripenem (62%), and imipenem (60%), respectively, as displayed in Table 3. In addition, the highest percentage of resistance to other antibiotics is illustrated in Figure 3, which is related to cefotaxime (48%), ceftazidime (44%), piperacillin (28%), azetronam (24%), ampicillin (16%), cefepime (16%), trimethoprim-sulfamethoxazole (12%) and ceftriaxone (12%), respectively.

According to the reviewed articles for the detection

Figure 2. The Number of Articles Used in This Study Based on The City Doing a Study. **Figure 3.** The Frequency of Antibiotics Resistance Based on the Articles Used in This Study.

of carbapenemases, only 4 used phenotypic methods [3 (12%)], 3 used genotypic methods [3 (12%)] and 19 studies used both phenotypic and genotypic methods [19 (76%)]. In the phenotypic methods, 22 studies [22 (88%)] used modified Hodge test (MHT) method, 4 studies used the method of E-test (Epsilonometer test) with MHT [4 (16%)], 1 study used CHROMagar and 1 study used the kit (Rosco Diagnostica, Denmark). In addition, the number of clinical samples based on phenotypic and genotypic methods in the articles used in this study is presented in Table 4.

The highest percentage of carbapenemases isolated in Iran was related to *bla*KPC [145 (37.08%)], *bla*OXA48 [118 (30.18%)], and *bla*NDM [88 (22.51%)], and the lowest percentages were in *bla*IMP [4 (1.02%)], and *bla*VIM [36 (9.21%)], respectively. Also, the largest number of carbapenemase genes is related to studies in Isfahan (57.43%), Tehran (11.03%), and Tabriz (10%), respectively (Table 4).

The results of the studies showed that the largest number of carbapenemases were reported from isolates of urine [101 (25.83%)], respiratory secretion [98 (25.06%)],

Table 3. The Frequency of Carbapenems Resistance Based on the Articles Used in This Study

Author Name	Number of Isolates	Percentage of Carbapenems Resistance				Reference
		Imipenem	Meropenem	Ertapenem	Doripenem	
Shoja et al	170	5.9%	6.5%	8.2%	7.6%	25
Agha-Seyed Hosseini et al	181	19.9%	20.4%	5.6%	7.2%	26
Kiaei et al	30	23.3%	26.7%	30%	N	27
Fazeli et al	112	42%	41.1%	N	N	28
Shokri et al	120	60%	62%	63%	62%	29
Khorvash et al	29	29%	29%	N	N	30
Gheitani et al	100	N	N	50%	N	31
Hosseinzadeh et al	112	13.7%	13.7%	N	N	32
Shahcheraghi et al	45	6.6%	28.8%	20%	N	33
Rastegar et al	29	54%	N	N	N	34
Japoni Nejad et al	100	8%	12%	N	N	35
Nobari et al	180	7.7%	23.3%	16.1%	N	36
Bina et al	270	13.9%	14.5%	15.5%	N	37
Rajabnia et al	50	52%	N	N	N	38
Eftekhar and Naseh	55	20%	20%	N	N	39
Shokri et al	128	55%	58%	N	N	40
Akhi et al	63	N	N	34.9%	N	41
Ghotaslou et al	57	19.9%	24%	28.6%	N	42
Tavakoly et al	118	4.9%	N	N	N	43

unknown [83 (21.23%)] and wound [43 (10.99%)], and the smallest number of carbapenemases was reported in blood [13 (3.32%)], sputum [6 (1.53%)], CSF [6 (1.53%)] and feces [39 (9.97%)], respectively.

The frequency of the carbapenemase genes based on the year of publication of the articles is shown in Figure 4. The highest prevalence of *bla*NDM, *bla*IMP, *bla*VIM, *bla*KPC and, *bla*OXA48 genes were observed in Shiraz in 2017 [23 (26.14%)], Hamedan in 2017 [2 (50%)], Babol in 2015 [15 (41.66%)], Isfahan in 2013 [65 (44.83%)] and Isfahan in 2018 [90 (76.27%)], respectively. In addition, the distribution of *K. pneumoniae* carbapenemase-produced in various geographical areas of Iran in the period 2012-2018 is displayed in Figure 5.

Discussion

Infections with multi-drug resistant bacteria as carbapenem-resistant *K. pneumoniae* are considered as a serious problem to global health.⁵⁰ The extensive dissemination of *K. pneumoniae* carbapenemases producer has led to the spread of this resistant pathogen worldwide.^{8,51,52} The present study was conducted to estimate the prevalence of carbapenemase genes in *K. pneumoniae* carbapenemase genes of *K. pneumoniae* in different cities of Iran. According to our findings, most studies have been conducted in Tehran [9 (36%)] and then in Isfahan [7 (28%)], because Tehran is the capital of Iran and enjoys more facilities, more research centers, more medical schools, and treatment centers. Isfahan is

also one of the large and densely populated provinces of Iran and is close to Tehran. There were an almost equal number of studies in other Iranian cities.

The results of this review showed that the most clinical specimens were from urine and respiratory secretions due to the easy colonization of *K. pneumoniae* in the respiratory tract system and the urinary tract system.

According to the results of this review, the rate of resistance to carbapenem antibiotics in *K. pneumoniae* varied from 5.6% to 63%, indicating a high range of resistance to these antibiotics and since they are the last line of treatment for severe infections, they should be administered with caution. Also, a recent report indicated that the rate of antibiotic resistance had increased in Portugal.⁵³ Widespread antibiotic resistance examination

Figure 4. The Frequency of Carbapenemase Genes Based on Year.

Table 4. The Frequency of Carbapenemase Genes Found in Studied Cities

Author Name	City	Date	No. of Sample	No. of MHT Positive Isolate (%)	Type of Method for Identification Carbapenemase Gene	No. of blaNDM	No. of blaNDM1	No. of blaNDM7	No. of blaIMP	No. of blaIMP1	No. of blaVIM	No. of blaVIM1	No. of blaKPC	No. of blaKPC2	No. of blaOXA48	Reference
Shoja et al	Bandar-abbas	2017	170	4 (2.35%)	Phenotypic and genotypic	-	4	-	-	-	-	-	-	-	-	25
Shahcheraghi et al	Hamadan	2017	65	29 (44.62%)	Phenotypic and genotypic	1	-	-	2	-	2	-	-	-	1	44
Agha-Seyed Hosseini et al	Kashan	2016	181	N	Genotypic	-	-	-	-	-	-	-	21	-	-	26
Kiaei et al	Kerman	2018	30	5 (16.66%)	Phenotypic and genotypic	9	-	-	-	-	-	-	-	-	-	27
Fazeli et al	Isfahan	2015	112	6 (5.36%) + E-test ^a	Phenotypic and genotypic	6	-	-	-	-	-	-	-	-	-	28
Shokri et al	Isfahan	2017	120	81 (67.5%)	Phenotypic and genotypic	18	-	-	-	-	-	-	-	-	-	29
Moghadampour et al	Isfahan	2018	80	0 (0%) + E-test ^a	Phenotypic and genotypic	-	-	-	-	-	-	-	-	-	-	45
Khorvash et al	Isfahan	2018	29	N	Genotypic	-	-	-	1	-	3	-	-	-	1	30
Solgi et al	Isfahan	2018	96	77 (80.21%)	Phenotypic and genotypic	6	-	-	-	-	-	-	-	-	90	46
Gheitani et al	Isfahan	2018	100	68 (68%)	Phenotypic and genotypic	-	-	-	-	-	-	-	-	-	-	31
Hosseinzadeh et al	Shiraz	2017	112	27 (24.11%)	Phenotypic and genotypic	23	-	-	-	-	-	-	-	-	2	32
Azimi et al	Tehran	2012	3	3 (100%) (KPC) ^b	Phenotypic	-	-	-	-	-	-	-	-	-	-	47
Shahcheraghi et al	Tehran	2012	45	0(0%)	Phenotypic and genotypic	1	-	-	-	-	-	-	-	-	-	33
Rastegar et al	Tehran	2013	29	19 (65.52%) (KPC) ^b	Phenotypic	-	-	-	-	-	-	-	-	-	-	34
Japoni Nejad et al	Tehran	2014	100	6(6%) + E-test ^a	Phenotypic and genotypic	-	-	-	-	-	10	-	-	-	-	35
Nobari et al	Tehran	2014	180	24(13.33%) + E-test ^a	Phenotypic and genotypic	3	-	-	-	-	5	1	-	-	-	36
Bina et al	Tehran	2015	270	41 (15.18%)	Phenotypic and genotypic	-	-	-	-	-	-	-	33	-	-	37

Table 4. Continues

Author Name	City	Date	No. of Sample	No. of MHT Positive Isolate (%)	Type of Method for Identification	Gene	No. of blaNDM	No. of blaNDM1	No. of blaNDM7	No. of blaIMP	No. of blaIMP1	No. of blaVIM	No. of blaVIM1	No. of blaKPC	No. of blaKPC2	No. of blaOXA48	Reference
Rajabnia et al	Babol	2015	50	10(20%)	Phenotypic and genotypic		-	-	-	-	-	-	15	-	-	-	38
Eftekhari and Naseh	Tehran	2015	55	4 (7.27%)	Phenotypic and genotypic		-	-	-	-	-	-	-	-	-	-	39
Solgi et al	Tabriz	2017	33	CHROMagar phenotypic method 29 (87.8%)	Phenotypic and genotypic		17	-	-	-	-	-	-	-	-	22	48
Shokri et al	Isfahan	2013	128	65 (50.78%) (KPC) ^b	Phenotypic		-	-	-	-	-	-	-	-	-	-	40
Akhi et al	Tabriz	2014	63	20 (31.75%)	Phenotypic and genotypic		-	-	-	-	-	-	-	-	-	-	41
Solgi et al	Tehran	2017	35	17 (48.57%)	Phenotypic and genotypic		-	-	1	-	-	-	-	-	-	-	49
Ghotaslou et al	Other	2018	57	N	Genotypic (Kit)		-	-	-	-	-	-	-	4	-	2	42
Tavakoly et al	Other	2018	118	7 (5.93%)	Phenotypic and genotypic		-	-	-	-	-	-	-	-	-	-	43

^a Studies that used the E-test in addition to the MTH test.^b Genes that identified using phenotypic tests.

-: reported gene.

Figure 5. Iran Geographic Distribution of *Klebsiella pneumoniae* CarbaPenemase-Producing During 2012-2018.

in European countries shows that the mean percentage of resistance against third-generation cephalosporins antibiotics (ceftazidime, cefotaxime) is 30.3%.⁵⁴

The highest antibiotic resistance in *K. pneumoniae* in 10 years based on the articles used in this study was related to the cephalosporins antibiotics.

The results showed that the most common carbapenemase genes were related to *blaKPC* [145 (37.08%)], *blaOXA48* [118 (30.18%)], and *blaNDM* [88 (22.51%)].

blaNDM is the most common carbapenemase in Europe, India, North America, Pakistan, Australia and other parts of Asia.³⁰

The *blaNDM* gene increased slightly in 2014 and 2015 but increased significantly in 2017 and 2018 based on the findings of the present study. *blaIMP* and *blaVIM* were reported in South America, North America, Asia, Australia, and Europe.³⁴ The results of our study also demonstrated that the frequency of the *blaIMP* gene increased only in 2017 and the *blaVIM* gene became more prevalent in 2017 but decreased gradually in 2018. *blaKPC* was reported to be the most common carbapenemase in the United States and *blaOXA* was reported in Europe, Turkey, northern Africa and the Middle East.⁵⁵

In our study, the *blaOXA48* gene increased gradually

only in 2017 and 2018 and *blaKPC* gene increased in 2013 and then decreased gradually until 2018.

The results of this review during 2010-2018 showed that the *blaNDM*, *blaOXA48* and *blaIMP* genes increased in 2017 and 2018 more than in eight years ago and the *blaVIM* gene in 2014 and 2015 and the *blaKPC* gene in 2013 increased and then declined, respectively. This increase is due to the easy dissemination of these genes by plasmids among Enterobacteriaceae bacteria, and on the other hand, the importance of studying resistance to carbapenems as a treatment for severe infections.

Nahid et al⁵⁶ collected 356 clinical isolates of the hospitals. Out of a total of 356 isolates, 160 displayed imipenem resistance and 131 showed MBLs production. In MBL positive isolates, 31 isolates reported harboring the *blaNDM-1* gene out of which 13 (41.93%) were *K. pneumoniae*. In 2016, Khan et al reported that the prevalence of the *blaNDM* gene was 78%,⁵⁷ which indicates the high prevalence of this gene in Pakistan. This high prevalence is because the primary source of the *blaNDM* genes was in India and Pakistan.⁵⁸⁻⁶⁰ Also, the high prevalence of this gene in the study in Kerman, Iran, as one of the cities close to the border with Pakistan, can be due to people coming from the bordering countries for trade or treatment.

In Turkey, the prevalence of the *bla*NDM gene was reported to be 19% in 2013 and 52.9% in 2016, respectively.^{61,62} According to the studies in Turkey, the high prevalence of the *bla*NDM gene in Tabriz may be because of the trade and treatment of people coming from the bordering countries in this city.

Limitations of the Study

In this study, Persian databases such as Scientific Information Database (SID) and Magiran were not used and only articles in English were examined.

Conclusion

Whereas information from all cities of Iran is still limited, this systematic review provides a picture of the prevalence of carbapenemase genes in *K. pneumoniae* in Iran. The findings showed that resistant genes of carbapenemases like the *bla*NDM and *bla*OXA48 genes are becoming more prevalent in Iran, and worldwide, which is worrying and alarming. Traveling is probably one of the main reasons for the transmission of carbapenemase genes. Also, physicians should be careful about the correct use of antibiotics.

Authors' Contribution

ASD designed the study, performed the searching of databases, and wrote the manuscript. NS performed the searching of databases and revised the manuscript.

Ethical Approval

Not applicable.

Competing Interests

No conflict of interest was reported by the authors.

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