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(Review Paper)

Antibiotics Resistance Patterns &Carbapenemase Genes Distribution of *Klebsiella pneumoniea* in Iran:A Review Article

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Abstract

Resistant *Klebsiella pneumoniae* to the latest solution (carbapenem antibiotics) distributed worldwide. The proliferation of carbapenemase genes among *Klebsiella pneumoniae* strains has led to their resistance to the carbapenem group. The aim of this study is to estimate antibiotic resistancepatterns and distribution of carbapenemase genes of *Klebsiella pneumoniea* in Iran. PubMed, Scholar ,SID, and Iran civilica databases were searched for the related articles that were published between 1999 and 2019. A total of 225 articles were found, out of which 70 relevant articles were selected for complete evaluation. According to the results, the highest rates of drug resistance in Klebsiella pneumoniae were observed against aztreonam (58%), cephalosporins family (54%), and then SXT (52%). The incidence rate of resistance was 19% for carbapenems family (IMP, MER), 37% for aminoglycosides family (GM, AN) and 41% for quinolones family (FM, CIP). Among the genes encoding CRE during 2014–2019, OXA, KPC, NDM, VIM, IMP, and GES were found with a prevalence of 39%, 35%, 18%, 13%, 11%, and 3%, respectively. Conclusion: Carbapenem resistance and the production of the metallo-beta-lactamase enzyme in K. pneumoniae are increasing. Due to the presence of carbapenemase-producing genes and the possibility of horizontal transfer of these genes to other bacteria, combined with changing the patterns of antibiotic use, more attention should be paid to the predisposing criteria for controlling nosocomial infections.

Key words: *Klebsiella pneumoniae*, Drug resistance, Carbapenemase, Iran

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Introduction

Klebsiella pneumonia is an opportunistic bacterium that causes about 10% of all infections in hospitals and is one of the most important causes of urinary tract, respiratory and bloodstream infections, especially in patients with weakened immune systems [1].

Mortality, between 30%and 75%, has been reported for patients with carbapenem-resistant infections. [2]. Death has been shown in patients with carbapenem-resistant blood infections above 50%, More than27% deaths have been reported in patients with pneumonia or carbapenem-resistant *K. pneumoniae*. [2].

Multidrug-resistant (MDR) *Klebsiella pneumoniae* is one of the leading causes of infections in hospitals. Recently, with the proliferation of beta-lactam-resistant strains, the proliferation of carbapenem-resistant and colistin-resistant isolates has significantly reduced treatment options and made it more difficult to control infections [3]. One of the main mechanisms of resistance among *klebsiella pneumonia* isolates is the production of the enzyme carbapenemase. Carbapenems are a family of broad-spectrum beta-lactamases that can hydrolyze penicillins, cephalosporins, monobactam, and carbapenems[3].

Molecular Classification of Carbapenemase Enzymes

There are four classes in this group: Molecular classes A, C, and D that there is serine at active sites of these β-lactamases, Meanwhile molecular class B β-lactamases are metalloenzymes with zinc in their active-site [3].

Class A Carbapenemases

Enzymes identified in this category. Some have chromosomal coding - including: NmcA (carbapenemase A metalloenzyme A), SME (Serratia marcescens enzyme), IMI-1 to IMI-3 (Imipenem-hydrolyzing _-lactamase), SFC-1 (Serratia fonticola carbapenemase-1), and Some have plasmid coding, such as: KPC-2 to KPC-13 (Klebsiella pneumoniea carbapenemase), derivatives (GES-1 to GES-20) of GES (Guyana broad spectrum), but all of them are inhibited by clavunic acid Actively hydrolyze [4]. Among these, KPCs spread rapidly around the world and spread to many countries in Asia, North America and Europe, as well as in Africa. Bacteria containing KPC are resistant to lactam, making it difficult to treat KPC-related infections in patients [4].

Studies have found a single genetic element (transposon Tn4401) in blaKPC genes [5].

Class B Carbapenemases

These enzymes can also hydrolyze carbapenems. They are also inhibited by ethylene diamine tetraacetic acid(EDTA), Zn2+ , and other divalent cations. The action of lactam drugs with zinc ions in the active site of the enzyme causes hydrolysis. The most important members of the Metallo beta-lactamase family include New Delhi Metallo-beta Lactamase 1 (NDM-1), Imipenem-resistant *Pseudomonas* (IMP), VIM(Verona integron-encoded metallo-lactamase), GIM (German Imipenemase), and SIM (Seoul imipenemase). The genes that encode these enzymes are usually located in integrons and in gene cassettes[5].

In 2010, the NDM-1 gene is spread by travelers all over the world, like Europe and America, and similar species have been reported in India[6].

More than 8 types of NDM-genes have been identified. NDM genes have been found abundantly in *Klebsiella pneumoniae* and Escherichia coli isolates, but have also been reported in *Acinetobacter baumannii* and *Pseudomonas aeruginosa* [6].

So far, 18 types of carbapenemas of IMP type have been identified. This enzyme was first studied in Japan in the 1990s. Most enzymes have been studied in *Acinetobacter* and *Pseudomonas* species as well as in Enterobacteriaceae family. IMP genes were also reported in Brazil and Canada in 1997. These genes are spreading around the world [7].

The VIM was first reported in Verona, Italy, in 1997.These metallo-bata lactamases are associated with integrons. 14 types of VIM genes have been identified. The VIM and IMP genes are cohesive and are carried by the plasmid. VIM genes are rarely found in *Enterobacteriaceae* and have been reported in *Pseudomonas aeruginosa* and *Pseudomonas putida*[7].

Class D Carbapenemases

The enzymes in this group are serine-lactamase and are inhibited by EDTA or clavulanic acid. The enzyme OXA is a well-known type of this group and it has little activity against carbapenems. This enzyme is mostly found in non-fermenting bacteria such as *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and sometimes in isolates of the family *Enterobacteriaceae* [8] .The OXA carbapenemase was first reported by Paton et al. [8].

The function of OXA carbaponemases is controlled by upstream elements [8]. The worry about OXA carbapenemses is that they can mutate very quickly and perform a wide range of activities [7].

OXA-48 is the most abundant type of this enzyme and has been found in *Klebsiella pneumoniae* inTurkey, the Middle East, North

Africa and Europe. Due to point mutations in OXA-48-producing organisms, it is difficult to determine their true extent. [7].

OXA-24 carbamates are found in *Acinetobacter* species in the environment, and the OXA-23 type is more common in the United States and Europe. OXA-58 carbs have been reported in large numbers around the world [7].

The update findings about *Klebsiella* antibiotic resistance is very important for optimum treatment approach and prevention of new resistance development. Therefore, in this article, the published findings about antibiotic resistance pattern and distribution of carbapenemase genes of *Klebsiella pneumoniea* in Iran are evaluated.

Methods

Databases

Numerous searches were conducted to find published studies between November 1999 and March 2019. The studies that were performed and published were identified using searches in the MEDLINE / Index Medicus Database, PubMed, Google Scholar, and Science Direct. The keywords below are used to find related studies in databases and search engines:

"carbapenem-resistant, resistant *Klebsiell pneumoniae*, Drug resistance, and Iran".

Study setting

Different studies reported from different parts of Iran had evaluated and classified.

These studies have been categorized into two distinct groups:

Studies that considered Drug-resistant *Klebsiella pneumonia* according to the disk diffusion method and Studies that used genotypic method.

Criteria for selecting articles

The selected articles have the following features:

1-Studies that considered the resistance pattern of *Klebsiella pneumoniae.*

2-Clinical strains obtained from Iranian hospitals.

3-Clinical strains that were taken only from hospitalized patients.

4- Studies that checked out the standards and guidelines of the clinical and laboratory standards institute (CLSI) for the preparation and interpretation of the tests.

5-Articles that examined the prevalence of metallo-beta-lactamase genes in IRAN.

The studies that examined strains other than *Klebsiella pneumoniae*, articles that were not performed in accordance with the principles CLSI, unclear report of the results and duplicate publications have been removed.

RESULTS

A total of 225 articles were found. After primary screening,308 remained after duplicates were removed. In the next stage70 relevant articles were selected to be evaluated completely. In all studies used, the disk diffusion method was used to perform antimicrobial susceptibility testing according to CLSI guidelines. 20 studies were the most of the studies from Tehran and number of other provinces were included: 14 in Isfahan, 3 in north of Iran, 2 in Chahar mahal and bakhtiari , Fars and East Azarbaijan, and 1 each in Lorestan, Korasan ,Qaznvin , Hamedan , Kermanshah, Markazi, Sistan and bluchestan ,west Azarbaijan ,Semnan, Qom ,Kurdestan, Kerman, Khuzestan ,Yazd and Ilam .

The highest resistance to carbapenems family(IMP, MER), in Sistan and Baluchestan is 42% and the lowest in Ilam is 0%. 10% of cases in Tehran 30% in Isfahan,50% in Hamedan and Kurdestan,5% in Fars,40% in East.Azarbijan and Mazandaran and 100% in Ilam were sensitive to carbapenems family. The highest resistance to cephalosporins family (CAZ,CTX.CPM.CRO)in East.Azarbijan is 92% and the lowest in Qazvin is 19%.The highest resistance to Azteronam, in Sistan and Baluchestan is 88% and the lowest in Kermanshah is 33%.The highest resistance to amino glycosides family(GM,AN) in Kermanshah is 65% and the lowest in Qom is 6%.The highest resistance to quinolones family(FM,CIP) in lorestan is 90% and the lowest in Ilam is 12%.The highest resistance to SXT in East.azarbijan is 74% and the lowest in Semnan is 25%. Based on the study of genes containing carbapenemase in Tehran ,Isfahan ,Mazandaran ,Markazi ,Khorasan, Chahar mahal&bakhtiari, Kermansha ,Hormozgan, Qom ,Kerman, Fars ,Est.Azarbijan and yazd during 2013–2019 ,OXA,KPC,NDM,VIM ,IMP and GES genes were found .The most isolated genes NDM and the least isolated gene is GES. The NDM1 and KPC genes were first identified in 2013 and OXA48 gene for the first time in 2014 in Tehran

According to studies, NDM1, OXA48 genes in Tehran and KPC gene in Isfahan have been further studied and identified. After the mentioned genes, VIM, GES, IMP genes have been identified to a lesser extent.

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Table.1 Antibiotic resistance pattern of *Klebsiella pneumoniea* in Iran

Refer	Years of study	Province	Carbapenems (IMP, MEM)	Aminoglycosides (GM, AMK)	Cephalosporins (CAZ,CRO,CTX ,CPM)	Monobactam (AZT)	Quinolones (FM, CIP)	Sulfunamides (SXT)
[9-17, 43-47]	1999-2016	Tehran	14.4	43.7	58.9	71	44.2	56.8
[5, 18-22, 51-55]	2006-2017	Isfahan	32	46.1	71.7	71.3	48.3	58.7
[23-25]	2010-2015	Fars	27.6	36.1	47	37.5	54.5	56.5
[26-28]	2011-2018	Mazandaran	16.6	50.6	62.7	37	45.7	58.9
[29,49]	2012-2015	Chahar mahal &bakhtiari	19.2	35.1	41.8	40.1	32.5	53
[30-31]	2007-2018	E.azarbyjan	39.2	56	92.5	87.2	67.5	74.3
[32]	2011-2015	W.azarbyjan	23.8	40.8	56.1	60	38.3	-
[45]	2014	Markazi	8.5	42.6	65.7	62	47.1	60.5
[33]	2013	Hamedan	15	38.5	41.1	43.3	47.8	62
[35]	2015	Kermanshah	27.5	65.5	80.4	33	37.8	55
[60]	2017	Kerman	5.8	25	45	-	33	38
[34]	2013	Qazvin	-	20	19.5	-	17.1	43
[35]	2016	Semnan	-	39.7	23	-	40	25.2
[59]	2018	Qom	10.4	6.1	37.2	-	38.2	60.3
[36]	2016	Gilan	16.2	23.1	63.1	68	46.7	46
[37]	2014	Kurdestan	13.4	38.6	71.7	80	34.2	53.7
[38]	2015	Sistan and bluchestan	24.5	45.8	55.6	80.4	23.1	86.3
[68]	2017	Yazd	18.3	22.4	36.3	-	23.8	-
[39]	2014	Lorestan	5.8	28.4	71.8	54	90.2	-
[42]	2015	Khorasan	24.5	36.4	31.5	-	33.4	46.2
[40]	2013	Khuzestan	17.2	54.9	56.4	45.6	45.4	-
[41]	2010	Ilam	-	18	67.6	-	12	41

Note: Numbers indicate the percentage of average resistance of *Klebsiella pneumoniae* to antibiotics. Abbreviations: IMP, imipenem; MEM, meropenem; CAZ, ceftazidime; CTX, cefotaxime; CRO, ceftrixone; CPM, cefepime; AMK , amikacin; GM, gentamycin; CIP, ciprofloxacin;. AZT, aztreonam; FM, Nitrofurantoin;.SXT, trimethoprim/sulfamethoxazole

Table.2 The emergence of carbapenemase genes in *Klebsiella pneumoniea* in Iran

Province	Year	Study/ team	Found carbapenemase Genes	Reference
Tehran	2013	Lari	KPC(FIRST)	[43]
Tehran	2013	Shah cheraqi	NDM(FIRST)	[44]
Markazi	2014	Japoni-Nejad	VIM,GES	[45]
Tehran	2014	Nobari	KPC,VIM,NDM	[46]
Tehran	2014	Azimi	OXA-48(FIRST),VIM-4	[47]
Mazandaran	2014	Shahande	IMP	[48]
Isfahan	2014	Moayednia	KPC	[5]
Tehran	2014	Nobari	KPC,VIM,OXA,GES	[46]
Chahar mahal&bakhtiari	2014	Hashemi zadeh	KPC	[49]
Isfahan	2015	Fazeli	NDM1	[23]
Khorasan	2015	Qazvini	KPC	[42]
Tehran	2015	Zeiqami	IMP,VIM	[50]
Kermanshah	2015	Zare	VIM	[35]
Isfahan	2015	Aqaseyedhosseni	KPC	[51]
Mazandaran	2015	Rajabnia	VIM	[52]
Isfahan	2016	Firooze	KPC,GES	[53]
Isfahan	2017	Khorvash	VIM,IMP,OXA	[54]
Isfahan	2017	Firooze	NDM1	[55]
Tehran	2017	Solgi	NDM-7(FIRST),OXA-48	[56]
Isfahan	2017	Shokri	NDM-1	[57]
Hormozgan	2017	Shoja	NDM-1	[58]
Qom	2018	Khodadadian	VIM-1,IMP-1	[59]
Kerman	2017	Keiaei	NDM-1-ST268(FIRST),OXA	[60]
Fars	2018	Hossein zadeh	NDM-1,OXA-48	[61]
Tehran	2018	Solgi	NDM-1,OXA-48	[62]
Isfahan	2016	Shokri	KPC	[63]
Tehran	2018	Jafari	NDM-1,OXA-48	[64]
Tehran	2018	Tabrizi	VIM-2	[65]
Isfahan	2018	Moqadampour	NDM,OXA-48,IMP	[66]
East Azarbijan	2018	Armin	NDM1	[67]
Tehran	2019	Yaghoubi	OXA-48,NDM-1	[68]

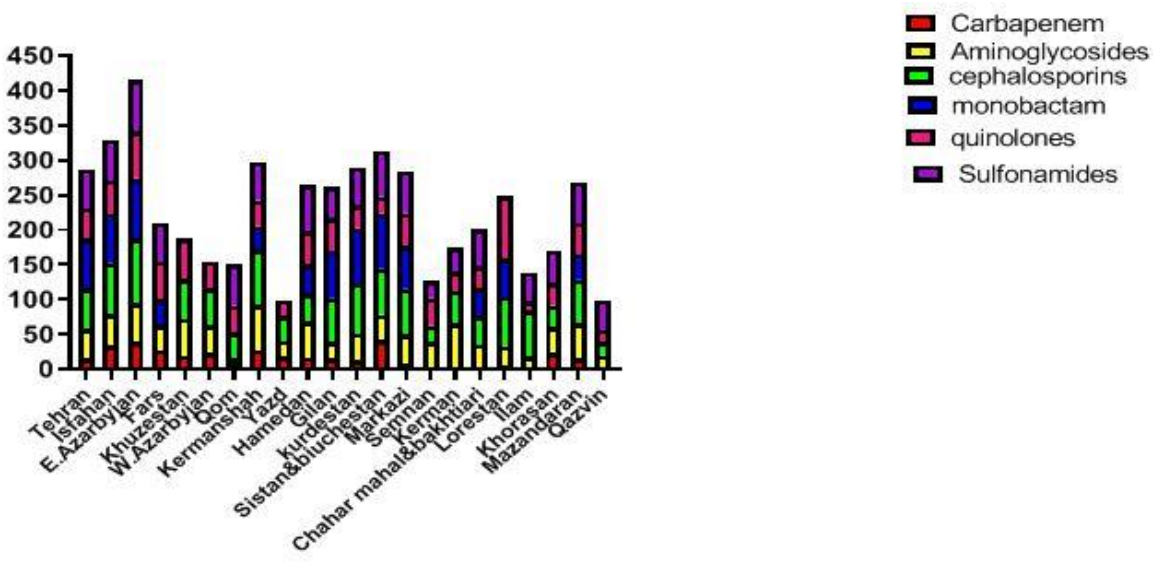

Figure.1 Antibiotic resistance pattern in *Klebsiella pneumoniea* among provinces of Iran

Discussion

The growing threat to public health includes the rapid spread of CRE (Carbapenem-resistant Enterobacteriaceae) into the community. These organisms can resist bacterial isolates and spread them in the bacterial community. Although many attempts have been made to control carbapenem resistance, there is still no useful solution to this problem. [8].

At present, the carbapenemase-encoding genes are more abundant in certain regions of the world especially, Europe, Asia and South America and places like South Africa are not doing well while the situation in other places. In order to control such resistances, the carbapenemase-encoding genes must be closely monitored.

Faster detection of carbapenemase-producing bacteria in the microbiology laboratory is the most important step and provides key solutions for controlling CRE infections. Therefore, timely identification of carbapenemase-producing isolates, both in clinical and carrier infections, must be done to prevent incurable infections [69].

Based on the studies collected in this article in Iran, the resistance *of Klebsiella pneumoniae* to the carbapenems (IMP,MER) family has increased by 50%,betweem 2010-2018 compared to 2000-2009.

The resistance *of Klebsiella pneumoniae* to quinolones family (FM,CIP) has increased by 25% whereas the family of cephalosporins (CAZ,CTX.CPM.CRO) and aminoglycosides(GM,AN) and monobactam(AZT) did not change much in 2010-2018 compared to 2000-2010.

European Antimicrobial Resistance Monitoring Network (EARS-Net) shows very diverse data between 0% to 64.7% for 2017 on *Klebsiella pneumoniae* carbapenem resistance to invasive infections, The average population percentage for the European Union / EEA, regardless of the statistically significant trend between 2014 and 2017, is 7.3% in 2014 and 7.2% in 2017. Observation and reporting of carbapenem-resistant *Klebsiella pneumoniae* increased in Slovakia, Poland and Portugal between 2014-2017, while resistance decreased in Croatia, Slovenia and Italy [69].

In Southeast Asian countries, such as Vietnam, the Philippines, Indonesia, and Thailand, less than 5% of *Klebsiella pneumoniae* resistant to carbapenem was identified between 2014-2017 [69].

Although there is little data on access to microbial resistance in Africa, much effort has been made, with in two countries Uganda and Madagascar estimating carbapenem resistance in *Klebsiella pneumoniae* at more than 5% [69].

Hypervirulent K. pneumoniae strains with a hypermucoviscous appearance expand in the environment and cause severe infections even in healthy, disease-free youth [70]. Despite of anti microbial resistance is low in strains with high virulence factors *Klebsiella pneumoniae* , but carbapenem-resistant *Klebsiella pneumoniae* strains have been reported to have high pathogenicity with high transmission potential in Asia [70]. The highest number of deaths due to microbial resistance has been reported in India, in which 84% of bacteremia-related deaths were reported, which 86 *Klebsiella pneumoniae* strains isolated with the

highest pathogenicity factors (performed by positive strand test) and carbapenem resistance (Marked by a minimum concentration of meropenem inhibitor (MIC) ≥16µg / ml) . Enterobacteriaceae with diverse carbapenem genes and resistance to carbapenem have spread throughout the world [70].

Conclusion:

There is a relatively high prevalence of antibiotic resistance in the families of cephalosporins, monobactam and sulfonamide. Carbapenem resistance and production of the metallo-beta-lactamase enzyme in *K. pneumoniae* are increasing,too.

Due to the presence of carbapenemase-producing and the possibility of horizontal transfer of these genes to other bacteria, while changing the pattern of antibiotic use, more attention should be paid to the criteria for controlling nosocomial infections.

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