Prevalence of Drug-resistant *Klebsiella pneumoniae* in Iran: A Review Article

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**Abstract**

**Background:** The infections caused by drug resistant strains of *Klebsiella pneumoniae* are becoming an important health problem worldwide. There are several reports on antimicrobial resistant status of *K. pneumoniae* in Iran. However, a comprehensive analysis on drug-resistant *K. pneumoniae* from different parts of Iran has not yet been performed.

**Methods:** The searches were done according to several English and Persian databases including PubMed, Scopus, Iranmedex, and SID to identify studies addressing antibiotic resistant *K. pneumoniae* in Iran from Jan 1998 to Nov 2014. Comprehensive Meta-Analysis (V2.2, Biostat) software was used to analyze the data.

**Results:** The incidence rate of imipenem and ceftazidime resistance in *K. pneumoniae* isolates was 3.2% (95% confidence interval [CI], 1.5-6.5) and 55.7% (95% CI, 46.9-64.1), respectively. The highest rate of resistance in isolates of *K. pneumoniae* was seen against ampicillin (82.2%), aztreonam (55.4%) and nitrofurantoin (54.5%).

**Conclusion:** There is a relatively high prevalence of drug resistant *K. pneumoniae* isolates in Iran. Thus, a high degree of awareness among physicians and microbiologists, active infection control committee, appropriate antimicrobial therapy, improvement of hygiene condition and monitoring of drug resistant isolates are urgently needed in order to better control the emergence and spread of drug-resistant *K. pneumoniae* isolates in hospital settings.

**Keywords:** *Klebsiella pneumoniae*, Drug resistance, Iran

**Introduction**

*Klebsiella pneumoniae* is an important causative agent of hospital-acquired infections, including severe pneumonia, urinary tract infection as well as sepsis and wound infections (1, 2). This bacterium can survive in hospitals, persist on environmental surface and colonize different parts of human body. Therefore, transmission of this opportunistic pathogen can easily occur among patients via the hands of healthcare personnel. Furthermore, the increased use of antibiotics and persistent exposure of *K. pneumoniae* to a number of antimicrobial agents, facilitating the emergence of multidrug-resistant strains, which has further intensified the infection control strategies in many health care settings (3).

The most important resistant isolates of *K. pneumoniae* are carbapenem and cephalosporin resistant strains (4). These strains can cause seri-
ous infections in immunocompromised patients, in association with prolonged hospital, stays, limited therapeutic options and increased mortality rates, ranging from 12% to as high as 72%, depending on the study population (5-9). In these regards, a reliable estimate of the extent of drug resistant isolates of \textit{K. pneumoniae} is needed for the programmatic management of drug resistant strains within the context of national infection control programs. This study was designed to determine the prevalence of drug resistant strains of \textit{K. pneumoniae} in Iran according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (10, 11).

**Methods**

**Search strategies**

We conducted the search using PubMed, Web of Science, Cochrane library and Scopus for all studies addressing the prevalence of drug resistant strains of \textit{K. pneumoniae} in Iran, from Jan 1998 to Nov 2014. The applied keywords include \textit{Klebsiella}, \textit{Klebsiella pneumoniae}, antibiotic resistance, antibiotic susceptibility, and Iran. Iranian databases including Iranmedex and Scientific Information Database (SID) were also searched (with Persian keywords).

**Inclusion and exclusion criteria**

We considered all the original articles about the incidence rate of drug resistant strains of \textit{K. pneumoniae} from hospital-acquired infections in Iran. These articles should reference to the standard method, which recommended by clinical and laboratory standards Institute (CLSI) for drug susceptibility testing of \textit{K. pneumoniae} against; carbapenems, cephalosporins and the other most used antimicrobial agents. Due to the following reasons, some studies were excluded from our analysis. Articles have focused only on community acquired \textit{K. pneumoniae} or focused only on non-\textit{K. pneumoniae} stains, and studies not used CLSI recommended drug susceptibility testing methods. Furthermore, case reports, meta-analyses or systematic reviews, letters to editor, review articles, non-English or Persian studies, and duplicate publication, were also excluded.

**Data extraction and definitions**

The extracted data in current study include the first author’s name, the publication time, year of study, number of samples, and prevalence of drug resistant strains of \textit{K. pneumoniae}. Two authors extracted data from all of the included studies independently and a third investigator reviewed results.

**Statistical analysis**

The comprehensive meta-analysis software (ver. 2.0) was used to analyse the data. Because of the heterogeneity between studies, random effects models were used and tested with the Cochrane Q test. Moreover, Egger weighted regression and Begg rank correlation tests were performed to assess possible publication bias.

**Results**

Initially, 1353 articles were collected (Fig. 1). However, in a secondary screening, 1308 of them were excluded according to duplication, title, and abstract evaluation, and full-text of 45 papers was evaluated. Finally, 27 articles describing the prevalence of the ceftazidime- and/or imipenem-resistant strains of \textit{K. pneumoniae} were selected for meta-analysis (Table 1). In all included studies, antimicrobial susceptibility testing had been performed using disc diffusion method as recommended by CLSI guidelines. Most of the studies were done in Tehran (n=11) compared with Isfahan (n=4), Fars (n=3), East Azerbaijan (n=2), Semnan (n=2), Hamadan (n=2), K. Boyer Ahmadi (n=1), West Azerbaijan (n=1) and Kerman (n=1). Fig. 2 shows the distribution of drug-resistant strains of \textit{K. pneumoniae} in different regions of Iran. The prevalence of imipenem and ceftazidime resistance was found to be 3.2% (95% CI, 1.5-6.5) and 55.7% (95% CI, 46.9-64.1), respectively (Table 2). Fig. 3 and 4 show the forest plot of the Meta-analysis of imipenem and ceftazidime resistant \textit{K. pneumoniae}.  

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Table 1: Included studies after full-text evaluation

| References | Published time | Enrollment time | Province | Total number of samples | Isolates of Klebsiella pneumoniae | Number of Ceftazidime (%) | Resistance to Imipenem (%) |
|------------|----------------|-----------------|----------|-------------------------|----------------------------------|---------------------------|---------------------------|
| 12         | 2007           | 2002-2005       | Tehran   | 200                     | 33                               | 24(73)                    | -                         |
| 13         | 2005           | 2003-2004       | Tehran   | 115                     | 100                              | 28(28)                    | 0(0)                      |
| 14         | 2011           | 2006-2009       | Tehran   | 250                     | 250                              | 95(38)                    | 3(1)                      |
| 15         | 2010           | 2007-2008       | Tehran   | 101                     | 25                               | 23(92)                    | 2(8)                      |
| 16         | 2008           | 2007-2008       | Tehran   | 164                     | 40                               | 20(50)                    | -                         |
| 17         | 2009           | 2007-2008       | Tehran   | 65                      | 30                               | 23(77)                    | 0(0%)                     |
| 18         | 2010           | 2008-2009       | Tehran   | 81                      | 62                               | 53(85)                    | 0(0%)                     |
| 19         | 2014           | 2009-2010       | Tehran   | 50                      | 30                               | 26(87)                    | -                         |
| 20         | 2013           | 2009-2011       | Tehran   | 360                     | 45                               | 34(76)                    | 3(7)                      |
| 21         | 2014           | 2011-2012       | Tehran   | 83                      | 83                               | 46(35)                    | 20(24)                    |
| 22         | 2012           | 2011-2012       | Tehran   | 120                     | 45                               | 21(47)                    | -                         |
| 23         | 2011           | 2009-2010       | Isfahan   | 211                     | 30                               | 7(23)                     | -                         |
| 24         | 2014           | 2013-2014       | Isfahan   | 123                     | 15                               | -                         | 0(0)                      |
| 25         | 2011           | 2009-2010       | Isfahan   | 167                     | 36                               | 23(64)                    | 0(0)                      |
| 26         | 2013           | 2010-2011       | Isfahan   | 61                      | 61                               | 30(49)                    | -                         |
| 27         | 2013           | 2009-2010       | Fars      | 571                     | 60                               | 28(47)                    | 1(2)                      |
| 28         | 2012           | 2009-2010       | Fars      | 328                     | 144                              | -                         | 12(8)                     |
| 29         | 2013           | 2009-2010       | Fars      | 60                      | 60                               | 28(47)                    | 1(2)                      |
| 30         | 2008           | 2007-2008       | East      | 88                      | 47                               | 43(91)                    | 0(0)                      |
| 31         | 2010           | 2008-2009       | East      | 72                      | 72                               | 58(81)                    | -                         |
| 32         | 2010           | 2007-2008       | Semnan    | 310                     | 76                               | 18(24)                    | -                         |
| 33         | 2009           | 2007-2008       | Semnan    | 382                     | 107                              | 21(20)                    | -                         |
| 34         | 2014           | 2007-2008       | Kerman    | 413                     | 75                               | 52(69)                    | 2(3)                      |
| 35         | 2005           | 1999-2001       | West      | 251                     | 19                               | 3(16)                     | -                         |
| 36         | 2013           | 2010-2012       | Kohgiluyeh and Boyer Ahmad | 202 | 180 | 93(52) | - |
| 37         | 2013           | 2011-2012       | Hamedan   | 120                     | 120                              | 44(37)                    | 0(0)                      |
| 38         | 2009           | 2004-2006       | Hamedan   | 209                     | 30                               | -                         | 2(7)                      |

Table 2: The prevalence of imipenem and ceftazidime resistance among Klebsiella pneumoniae

| Subgroups | No. of study | Prevalence of drug resistance (95% CI) | n/N* | Heterogeneity Test | Egger’s test for publication bias |
|-----------|--------------|----------------------------------------|------|--------------------|---------------------------------|
|           |              | overall effects of resistant to imipenem | 16   | 3.2 (1.5-6.5)      | 46/1182                         |
|           |              | overall effects of resistant to ceftazidime | 24   | 55.7 (46.9-64.1)   | 841/1686                        |

CI, confidence interval; n, number of events (drug resistance); N, total number of Klebsiella pneumoniae from the included studies

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Some evidence for publication bias for imipenem and ceftazidime was observed ($P<0.05$ for Begg rank correlation analysis; $P<0.05$ for Egger weighted regression analysis) (Fig. 5, 6). The resistance of *K. pneumoniae* to other important antimicrobial agents is shown in Table 3.

Fig. 1: Summary of the literature search and study selection

Fig. 2: Distribution of drug-resistant *Klebsiella pneumoniae* in different regions of Iran
### Table 3: Drug resistance status in *Klebsiella pneumoniae*

| References | Enrollment time | Case number | Carbapenem | Cephalosporins | Aminoglycosides | Fluoroquinolones | Monobactam | Penicillins | Macrolid | Cotrimoxazole |
|------------|----------------|-------------|-------------|----------------|-----------------|-----------------|-------------|-------------|----------|---------------|
|            |                |             | IM          | P | ME          | Z | CT          | X | CR          | O | CP          | M | AM | K | G | CIP | AZT | AMP | NF | T |                |
| 12         | 2002-2005      | 33          | 24          | 19 | 19          | - | 14          | 21 | 15          | - | 26          | - | 14 | - | - | - | - | - | - | - |                |
| 13         | 2003-2004      | 100         | 0           | 28 | -           | 20 | 9           | 30 | 20          | - | -           | - | 31 | - | - | - | - | - | - | - |                |
| 14         | 2006-2009      | 250         | 3           | 95 | 91          | 86 | 100         | 53 | 82          | 85 | -           | - | - | - | - | - | - | - | - | - |                |
| 15         | 2007-2008      | 25          | 2           | 23 | 22          | 23 | 22          | 24 | -           | 17 | -           | 24 | 13 | 18 | - | - | - | - | - | - |                |
| 16         | 2007-2008      | 40          | -           | -  | 20           | - | 19          | 8  | 14          | 12 | -           | 40 | 16 | 20 | - | - | - | - | - | - |                |
| 17         | 2007-2008      | 30          | 0           | -  | 23           | 6 | 20          | 25 | 20          | 16 | -           | 30 | 18 | 18 | - | - | - | - | - | - |                |
| 18         | 2008-2009      | 62          | 0           | -  | 53           | 56 | 47          | 44 | 14          | 30 | 32          | 59 | -  | 16 | 47 | - | - | - | - | - | - |                |
| 19         | 2009-2010      | 30          | -           | 26 | 25          | - | -           | 16 | 17          | 26 | -           | 30 | -  | - | - | - | - | - | - | - |                |
| 20         | 2009-2011      | 45          | 3           | 13 | 34          | 37 | -           | 33 | 11          | - | 32          | 32 | -  | - | - | - | - | - | - | - |                |
| 21         | 2011-2012      | 83          | 20          | 20 | 46          | 50 | 49          | 30 | 12          | 29 | 46          | 49 | 65 | - | - | - | - | - | - | - |                |
| 22         | 2011-2012      | 45          | -           | 21 | -           | - | -           | -  | -           | - | 43          | - | 23 | 31 | - | - | - | - | - | - |                |
| 23         | 2009-2010      | 30          | -           | 7  | 5           | - | -           | 0  | 7           | 6 | -           | 21 | 10 | 8  | - | - | - | - | - | - |                |
| 24         | 2013-2014      | 15          | 0           | 0  | 21           | - | -           | 15 | 8           | 12 | -           | 15 | 10 | - | - | - | - | - | - | - |                |
| 25         | 2009-2010      | 36          | 0           | 23 | 21          | 22 | 12          | 13 | -           | - | 33          | 7 | 28 | - | - | - | - | - | - | - |                |
| 26         | 2010-2011      | 61          | -           | 30 | 49          | 37 | -           | -  | -           | - | -           | - | - | - | - | - | - | - | - | - |                |
| 27         | 2009-2010      | 60          | 1           | 28 | 34          | 29 | 5           | 13 | 19          | 60 | -           | 26 | - | - | - | - | - | - | - | - |                |
| 28         | 2009-2010      | 144         | 12          | -  | -           | - | 61          | 65 | 42          | - | 23          | - | 43 | - | - | - | - | - | - | - |                |
| 29         | 2009-2010      | 60          | 1           | 28 | 34          | 29 | 5           | 13 | 19          | 60 | -           | 26 | - | - | - | - | - | - | - | - |                |
| 30         | 2007-2008      | 47          | 0           | 43 | 42          | 44 | 39          | 5  | -           | 41 | -           | - | - | - | - | - | - | - | - | - |                |
| 31         | 2008-2009      | 72          | -           | 58 | -           | - | 31          | 53 | 31          | - | 68          | 53 | -  | - | - | - | - | - | - | - |                |
| 32         | 2007-2008      | 76          | -           | 18 | 19          | - | -           | 19 | 35          | - | 73          | - | 41 | - | - | - | - | - | - | - |                |
| 33         | 2007-2008      | 107         | -           | 21 | 24          | - | -           | 19 | 21          | - | 97          | - | 27 | - | - | - | - | - | - | - |                |
| 34         | 2007-2008      | 75          | 2           | 52 | 25          | 27 | -           | 48 | 21          | - | 35          | - | - | - | - | - | - | - | - | - |                |
| 35         | 1999-2001      | 19          | -           | 3  | -           | 0 | 5           | 3   | 14          | - | -           | 3 | - | - | - | - | - | - | - | - |                |
| 36         | 2010-2012      | 180         | 41          | 93 | 87          | 81 | -           | 40 | 65          | 31 | 83          | - | 138 | 108 | - | - | - | - | - | - | - | - |                |
| 37         | 2011-2012      | 120         | 0           | 44 | 50          | 52 | 30          | - | -           | 32 | -           | 20 | 52 | - | - | - | - | - | - | - |                |
| 38         | 2004-2006      | 30          | 2           | 46 | 74          | 81 | 711         | 509 | 448         | 359 | 581         | 613 | 399 | 645 | 364 | 635 | - | - | - |                |
| Mean Rate  |                |             | 1.63        | 1.97 | 1.41        | 1.37 | 1.11        | 1.09 | 2.05        | 1.96 | 1.87        | 1.87 | 1.87 | 1.63 | 1.54 | 1.54 | 1.63 | 1.63 | - | - | - |                |

**Abbreviations:** 1. IMP, imipenem; 2. MEM, meropenem; 3. CAZ, ceftazidime; 4. CTX, cefotaxime; 5. CRO, ceftiraxone; 6. CPM, cefepime; 7. AMK, amikacin; 8. GM, gentamycin; 9. CIP, ciprofloxacin; 10. AZT, aztreonam; 11. AMP, ampicillin; 12. NF, nitrofurantoin; 13. SXT/TMP, trimethoprim/sulfamethoxazole

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**Fig. 3:** Forest plot of the meta-analysis on imipenem resistance. CI, confidence interval
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Fig. 4: Forest plot of the meta-analysis on ceftazidime resistance. CI, confidence interval

Fig. 5: Funnel plot of the meta-analysis on imipenem resistance

Fig. 6: Funnel plot of the meta-analysis on ceftazidime resistance

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Discussion

The emergence and spread of carbapenem and cephalosporin resistant strains of *K. pneumoniae* are a considerable threat to public health (2). The major goal of this systematic review was to evaluate the current situation and distribution of drug-resistant *K. pneumoniae* in Iran. This analysis showed that 3.2% *K. pneumoniae* isolates from Iran was resistant to imipenem and 55.7% to ceftazidime. Thereby despite ceftazidime, the imipenem remains as a powerful weapon against *K. pneumoniae* isolates in Iran. In the current study more than half of *K. pneumoniae* isolates were resistant to other important antimicrobial agents such as aztreonam (55.4 %), nitrofurantoin (54.5%) and co-trimoxazole (51.8%), we highly recommend that antimicrobial test should be performed prior to any antibiotic prescription in *K. pneumonia* infections. Very low number of *K. pneumonia* population (17.8%) were sensitive to ampicillin suggesting ampicillin is not effective drug for empiric treatment of *K. pneumonia* infections unless we use it in combination with other relevant drugs.

The relatively high rates of drug resistant isolates of *K. pneumoniae* observed in this study may have several negative effects on public health issues (39). For example, this could cause difficulty in treating *K. pneumoniae* associated infections since fewer effective drugs are available for treating those highly drug-resistant strains. Unfortunately, these microorganisms are even showing rising rates of resistance to new expensive antibiotics subsequently considered the treatment of choice (40). This is due to the widespread use of broad-spectrum antibiotics in health care settings for empiric treatment of infections. Furthermore, patients infected with these pathogens require prolonged antimicrobial therapy that has considerable implications for the individual patient and for the health care settings. Finally, infections due to these highly resistant strains are reported to be associated with higher morbidity and mortality rates (41). In Iran, 50000 people die each year because of multidrug-resistant bacterial infections and that this costs Iranian economy 2.5 million dollars annually (4).

Some important reasons for the increasing rates of drug resistant isolates in Iran include limited infection surveillance programs, the lack of communication between physicians and microbiologists, lack of standardized or accepted criteria to determine drug resistant isolates, limited laboratory facilities, and poor sanitation. Therefore, active infection control committee, appropriate antimicrobial therapy, and improvement of hygiene condition will prevent or lower the emergence of antimicrobial-resistant pathogens (42). Current review was carried out according to provinces of Iran and the published time. Because of many hospitals and health care centers in Tehran Province, Iran, patients from other provinces come to Tehran for better treatment. Therefore, most of the studies in this analysis belonged to Tehran, where the ceftazidime- and/or imipenem-resistant strains of *K. pneumoniae* mostly reported by researchers.

Conclusion

There is a relatively high prevalence of drug resistant *K. pneumoniae* isolates in Iran. Thus, a high degree of awareness among physicians and microbiologists, active infection control committee, appropriate antimicrobial therapy, improvement of hygiene condition and monitoring of drug resistant isolates are urgently needed in order to better control the emergence and spread of drug-resistant *K. pneumoniae* isolates in hospital settings.

Ethical considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

Conflict of Interests

The authors declare that there is no conflict of interests.
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