Abstract

**Background:** Multidrug-resistant *Pseudomonas aeruginosa* (MDR *P. aeruginosa*) is known as a serious threat to human health worldwide. Limited information is available concerning the prevalence of MDR *P. aeruginosa* in Iran. The aim of the present study was to investigate the relative frequency of MDR *P. aeruginosa* in different parts of Iran. **Materials and Methods:** Using appropriate keywords and well-known English and Persian database, available data about MDR *P. aeruginosa* in Iran were retrieved. After applying predefined criteria, relevant studies were selected. **Results:** By using random-effect models, the pooled incidence of MDR *P. aeruginosa* was estimated 58% (95% confidence interval [CI]; 0.54–0.61). The highest and lowest prevalence of MDR *P. aeruginosa* were observed in Tehran (100%) (95% CI; 0.94–1.00) and Zahedan (16%) (95% CI; 0.10–0.24), respectively. The highest resistance rate was against cefazidime (50%) (95% CI; 0.46–0.54) and amikacin (50%) (95% CI; 0.46–0.54). **Conclusion:** Our findings are of concern since they demonstrate the high prevalence rate of MDR *P. aeruginosa* in the majority of Iranian hospitals.

**Keywords:** *Pseudomonas aeruginosa*, antibiotic resistance, multidrug-resistant *Pseudomonas aeruginosa*

Introduction

Multidrug-resistant *Pseudomonas aeruginosa* (MDR *P. aeruginosa*) due to simultaneous resistance against different class of antibiotics is of paramount importance to health-care settings worldwide. Treatment outcomes of patients infected with MDR *P. aeruginosa* owing to limited available antibiotics are considered to be a serious threat to health-care providers. In fact, infection caused by MDR *P. aeruginosa* has several negative impacts on patient outcomes, including higher mortality, an increase in the length of hospital stay, and considerable increase in hospital costs.

Although different definition of MDR isolates is applied in literatures, MDR *P. aeruginosa* is known as an isolates resistant against antibiotics belonged to at least three different classes, especially aminoglycosides, carbapenems, and fluoroquinolones.

Antibiotic-resistant determinants are often spread through mobile genetic elements such as plasmid and integron. Integrons are genetic structures capable of capturing genes, consisting of conserved segments and a variable region between the conserved segments.

Effective antibiotic treatment is dependent on antibiotic resistance pattern; therefore, in this study, we investigated the prevalence of MDR *P. aeruginosa* in different parts of Iran. As a secondary aim, we estimate the prevalence of resistance against other antibiotics which are widely used to treat *P. aeruginosa* infections.

Materials and Methods

We searched international databases (ISI web of science, Scopus, PubMed, and Google Scholar) as well as two national scientific search engines including Magiran (www.magiran.com) and Iranian Scientific Information
In this study, a total of 4854 articles were found through database search [Figure 1]. In first step, 2359 articles were excluded due to duplication. In the secondary screening and after abstract evaluation, 2145 of publications were excluded. Finally, 350 articles were retained for detailed full-text evaluation. According to quality assessment criteria and inclusion/exclusion criteria, a total of 23 articles with full text reporting the prevalence of MDR P. aeruginosa were recruited for the systematic review and meta-analysis[11-33] [Table 1]. In total, 10 studies from Tehran, 3 studies from Isfahan, 3 studies from Ahvaz, 2 studies from Orumieh, 1 study from Zahedan, 1 study from Zanjan, 1 study from Tabriz, 1 study from Guilan, and 1 study from Hamedan were involved.[11-33] Figure 2 shows the distribution of MDR P. aeruginosa in different parts of Iran. By using random-effect models, the pooled prevalence of MDR P. aeruginosa was estimated to be 58% (95% confidence interval [CI]: 0.54–0.61). However, an evident heterogeneity of MDR P. aeruginosa-relative frequency was seen (Cochrane Q test, Q statistic = 463.38, P < 0.001, the extent to which the overall calculations might depend on a specific study, sensitivity of study was performed. Publication bias was checked by Egger’s regression asymmetry test and Begg’s adjusted rank correlation test.[8-10] Statistical analyses were done using the STATA software package version 11.2 (STATA Corp, College Station, TX, USA).

Results

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The highest and lowest prevalence of MDR \( P. \) aeruginosa were observed in Tehran (100%) (95% CI; 0.94–1.00) and Zahedan (16%) (95% CI; 0.10–0.24), respectively.

We also checked the prevalence rate of resistance against ceftazidime, imipenem, meropenem, aztreonam, amikacin, gentamycin, ciprofloxacin, and piperacillin/tazobactam [Table 2]. The highest resistance rate was against ceftazidime (50%) (95% CI; 0.46–0.54) and amikacin (50%) (95% CI; 0.46–0.54) followed by piperacillin/tazobactam (49%) (95% CI; 0.44–0.54) and the lowest rate was against imipenem (31%) (95% CI; 0.27–0.35) [Table 2]. There was an asymmetry in Begg’s funnel plot when depicting the effect sizes (logit event rate for MDR resistance) against their standard error [Figure 4]. The Begg’s and Egger’s test also confirmed an asymmetry (Begg’s test, \( P = 0.008, \) Egger’s test, \( P = 0.002 \)). We explored the magnitude of the bias using trim and fill analysis. Two studies could be added using trim and fill analysis; however, the overall prevalence was not changed notably after filling the two studies (event rate = 58%, 95% CI: 56–60). The funnel plot showing the observed studies as well as studies filled after the trim and fill analysis is provided in Figure 4.

**DISCUSSION**

Appropriate selection of antibiotics is dependent on antibiotic resistance profile and active surveillance of changing trends in resistance patterns; therefore, we conducted this study to estimate the prevalence and distribution of MDR \( P. \) aeruginosa in different parts of Iran, using data provided by published papers.

The prevalence of \( P. \) aeruginosa infection in different parts of Iran is high.\(^{13}\) Our findings revealed that the prevalence of MDR \( P. \) aeruginosa was 58% and is varied in different provinces of Iran, with highest and lowest rates observed in Tehran (100%) (95% CI: 0.94–1.00) and Zahedan (16%) (95% CI; 0.10–0.24), respectively [Table 1].

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**Table 1: Characteristics of studies involved in the systematic review and meta-analysis**

| First author                          | Publication year | Location | Enrollment period | Total sample | MDR prevalence (%) | Reference |
|---------------------------------------|-----------------|----------|-------------------|--------------|-------------------|-----------|
| Farshadzadeh et al.                   | 2014            | Ahvaz    | 2010-2011         | 185          | 95.1              | [15]      |
| Khosravi                              | 2017            | Ahvaz    | 2016              | 93           | 100               | [23]      |
| Farajzadeh Sheikh et al.              | 2014            | Ahvaz    | 2011-2012         | 223          | 44.4              | [14]      |
| Tavajihoi et al.                      | 2011            | Isfahan  | 2010-2011         | 86           | 32.5              | [32]      |
| Safaei et al.                         | 2017            | Isfahan  | 2015              | 96           | 95.8              | [29]      |
| Radan et al.                          | 2016            | Isfahan  | 2013-2014         | 150          | 38                | [27]      |
| Mirsalehian et al.                    | 2010            | Tehran   | 2007              | 170          | 87.1              | [24]      |
| Ghanbarzadeh Corehsh et al.           | 2015            | Tehran   | 2013              | 144          | 93.1              | [16]      |
| Salimi et al.                         | 2010            | Tehran   | 2008              | 129          | 32.6              | [30]      |
| Goudarzi and Eftekhar                 | 2013            | Tehran   | 2011              | 133          | 100               | [18]      |
| Talebi-Taheer et al.                  | 2016            | Tehran   | 2014              | 91           | 89                | [31]      |
| Kashfi et al.                         | 2017            | Tehran   | 2014-2015         | 60           | 93.3              | [22]      |
| Jafari et al.                         | 2013            | Tehran   | 2011              | 100          | 100               | [20]      |
| Azami et al.                          | 2013            | Tehran   | 2003-2004         | 130          | 53.8              | [12]      |
| Mozami Goudarzi and Eftekhar          | 2015            | Tehran   | 2011              | 112          | 74.1              | [25]      |
| Saderiand Owlia                       | 2015            | Tehran   | 2013              | 88           | 54.5              | [28]      |
| Yousefi et al.                        | 2010            | Orumieh  | 2007-2008         | 160          | 56.3              | [33]      |
| Jazani et al.                         | 2012            | Orumieh  | 2010              | 100          | 58                | [21]      |
| Bokacian et al.                       | 2015            | Zahedan  | 2012-2013         | 116          | 16.4              | [13]      |
| Hemmati et al.                        | 2014            | Zanjan   | 2013-2014         | 120          | 65                | [19]      |
| Nikokar et al.                        | 2013            | Guilan   | 2010-2011         | 86           | 45.3              | [26]      |
| Goli et al.                           | 2016            | Tabriz   | 2014              | 100          | 68                | [17]      |
| Alkhani et al.                        | 2014            | Hamedan  | 2009              | 106          | 88.7              | [11]      |

MDR: Multidrug resistant

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**Figure 2: Distribution of multidrug-resistant \( Pseudomonas \) aeruginosa in different parts of Iran**

\( I^2 = 95.25 \) [Figure 3]. The highest and lowest prevalence of MDR \( P. \) aeruginosa were observed in Tehran (100%) (95% CI; 0.94–1.00) and Zahedan (16%) (95% CI; 0.10–0.24), respectively.

We also checked the prevalence rate of resistance against ceftazidime, imipenem, meropenem, aztreonam, amikacin, gentamycin, ciprofloxacin, and piperacillin/tazobactam [Table 2]. The highest resistance rate was against ceftazidime (50%) (95% CI; 0.46–0.54) and amikacin (50%) (95% CI; 0.46–0.54) followed by piperacillin/tazobactam (49%) (95% CI; 0.44–0.54) and the lowest rate was against imipenem (31%) (95% CI; 0.27–0.35) [Table 2]. There was an asymmetry in Begg’s funnel plot when depicting the effect sizes (logit event rate for MDR resistance) against their standard error [Figure 4]. The Begg’s and Egger’s test also confirmed an asymmetry (Begg’s test, \( P = 0.008, \) Egger’s test, \( P = 0.002 \)). We explored the magnitude of the bias using trim and fill analysis. Two studies could be added using trim and fill analysis; however, the overall prevalence was not changed notably after filling the two studies (event rate = 58%, 95% CI: 56–60). The funnel plot showing the observed studies as well as studies filled after the trim and fill analysis is provided in Figure 4.
The study by Gill et al. between 2014 and 2015 on MDR P. aeruginosa rates of patients admitted to Intensive Care Unit showed similar percentage of resistance, with 50% of all isolates being MDR.\textsuperscript{35} In addition, the finding of Khan et al. demonstrated that the prevalence of MDR P. aeruginosa in different hospitals of Karachi, Pakistan, is lower than our findings, with 30% of isolates being MDR.\textsuperscript{36} A comprehensive study conducted at 28 hospitals in Thailand from 2000 to 2005 revealed that the prevalence of MDR P. aeruginosa was 20\%–30\%,\textsuperscript{37} which is lower than our findings.

Comprehensive antibiotic resistance surveillance in European countries demonstrated that the percentages of MDR P. aeruginosa isolates in thirty participated countries ranged from 0\% (Estonia and Iceland) to 49.4\% (Romania).\textsuperscript{38} Sixteen countries (Germany, Bulgaria, Austria, Lithuania, Malta,}
Ireland, Luxembourg, Finland, Cyprus, Sweden, Norway, United Kingdom, Netherlands, Denmark, Iceland, and Estonia) reported resistance percentages below 10%, 11 reported 10%–25% (including Belgium, Slovenia, Portugal, Spain, France, Poland, Croatia, Hungary, Czech Republic, Latvia, and Italy), and the remaining three (Slovakia, Greece, and Romania) reported MDR percentages above 25%.[38]

Unfortunately, despite the existence of several reports on antibiotic resistance patterns on *P. aeruginosa* isolated from clinical samples in Iran, there is not a comprehensive study on the prevalence of MDR *P. aeruginosa* in Iranian hospitals; hence, we tried to do a comprehensive study across Iran.

Based on our data, resistance to ceftazidime (50%) is higher than the percentage reported from Iceland (0%), United Kingdom (3.7%), and Sweden (6.8%).[38] Furthermore, our study revealed that compared with most European countries, resistance to other antibiotics such as imipenem, meropenem, ciprofloxacin, piperaclillin/tazobactam, amikacin, gentamycin, and aztreonam is high [Table 2]. For example, Europe antimicrobial resistance surveillance in 2013 reported the percentage of fluoroquinolones-resistant isolates ranged from 0% (Iceland) to 53.1% (Slovakia). At the same time, the percentage of aminoglycosides-resistant isolates ranged from 0% (Iceland and Malta) to 51.2% (Romania). Carbapenem-resistant isolates of *P. aeruginosa* in Denmark was 2.9%, which is significantly lower than our results.[39]

The emergence and dissemination of MDR *P. aeruginosa* is of paramount concern because these isolates are simultaneously resistant against multiple antibiotics; therefore, limited choices such as colistin and polymyxin B remain available to treat patients infected by these isolates.

This study faces some limitations that should be considered; first, due to restricted access to some data provided by theses, in-press articles, or nonopen access articles, some data might have been missed; second, for some parts of the country, the relevant data were unavailable; hence, this study could not completely represent the status of prevalence rate for Iran.

**Conclusion**

*P. aeruginosa* is one of the most important pathogens in Iranian hospitals. Our findings are of concern since they demonstrate the high prevalence rate of MDR *P. aeruginosa* in the majority of Iranian hospitals. Indiscriminate use of antibiotics has resulted in the development of multidrug-resistant *P. aeruginosa* infections, which is a serious threat to health of patients. To prevent further dissemination of these isolates, appropriate infection control practices must be implemented.

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**Conflicts of interest**

There are no conflicts of interest.

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