Original Article

Multidrug Resistant *Pseudomonas aeruginosa* in Iran: A Systematic Review and Metaanalysis

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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 ceftazidime (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.[1,2] 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.[1,2] 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.[3]

Although different definition of MDR isolates is applied in literatures, MDR *P. aeruginosa* is known as an isolate resistant against antibiotics belonged to at least three different classes, especially aminoglycosides, carbapenems, and fluoroquinolones.[4]

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.[5,6]

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

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database (www.sid.ir), without limitation, by using English and Persian keywords. To find relevant articles, following keywords were used, "*Pseudomonas aeruginosa,*" "multidrug-resistant *P. aeruginosa,*" "imipenem-resistant *P. aeruginosa,*" "metallo-beta-lactamase-producing *P. aeruginosa,*" and "Iran". Finally, to find additional data, reference lists of obtained papers were manually searched. The search was restricted to original research or brief reports with full text available, describing the prevalence of MDR *P. aeruginosa*. All steps were performed by two authors, independently.

Inclusion and exclusion criteria

After evaluation of abstract and full text, the study was included if first, the clinical specimens were taken from patients referring to Iranian hospitals; second, standard antibiotic susceptibility testing methods according to Clinical Laboratory Standard Institute guidelines were applied; third, MDR-*P. aeruginosa* was defined as isolate resistant against antibiotics belonged to at least three different classes, especially aminoglycosides, carbapenems, and fluoroquinolones. Papers were also excluded if first, investigation published in language other than Persian or English; second, study designed other than cross-sectional; third, duplicate studies or duplicate specimens; fourth, poor materials and methods, especially regarding antibiotic concentration and producer company; fifth, *P. aeruginosa* isolated from environmental and non-clinical samples; and sixth, based on applied criteria, the quality of study was recognized as ineligible.

Quality assessment

The quality of papers was evaluated using checklist provided by Joanna Briggs Institute.[7] In this checklist in order to assess the quality of the study, following items are checked: sample size, research objectives, statistical analysis, sample collection, and appropriate materials and methods. One score was assigned to each parameter and study was included if at least seven scores achieved.

Data extraction

According to inclusion and exclusion criteria, all collected data from the selected studies were tabulated as follows: (1) First author, (2) publication date, (3) enrollment time, (4) province of study, (5) prevalence of MDR *P. aeruginosa*, and (6) prevalence of resistance against antibiotics. Two authors extracted data from involved studies independently. Inconsistency between the reviewers was resolved through discussion.

Statistical analysis

The numbers of total participants and the numbers of participants with MDR *P. aeruginosa* were used to estimate the logit event rate and its corresponding standard as effect size for meta-analysis.[8] The logit event rates were turned back to event rate for illustrating the meta-analysis results. The random-effect model which takes the between-study heterogeneity into account was used to derive the summary effects. Between-study heterogeneities were assessed using Cochran's Q-test and *I*-squared (I^2) test.[9] In order to explore 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

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, $P < 0.001$,

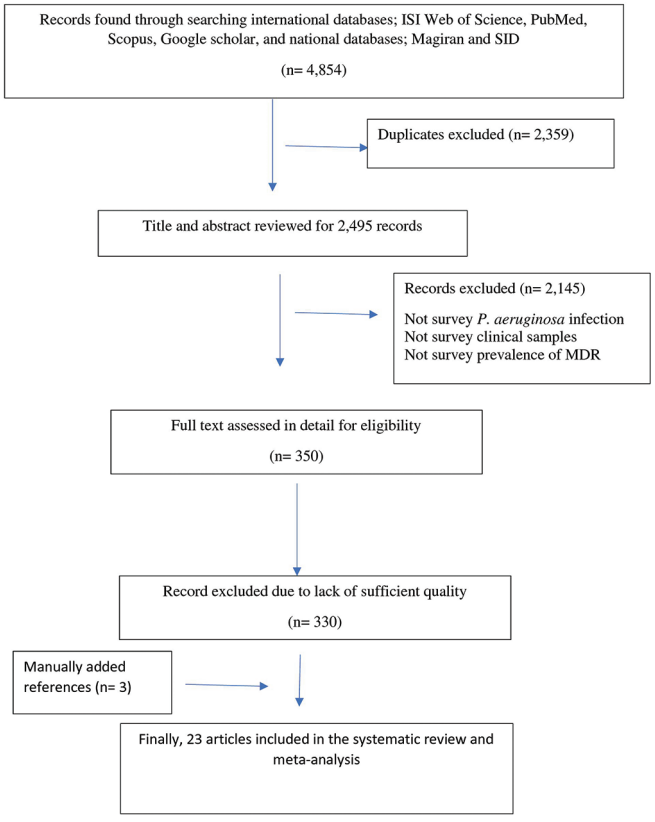

Figure 1: Schematic flow diagram for literature review and study selection

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]
Tavajjohi *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 Corehtash *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-Taher *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]
Moazami 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]
Bokaeian *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]
Alikhani *et al*.	2014	Hamedan	2009	106	88.7	[11]

MDR: Multidrug resistant

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 till 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. aeruginos*a infection in different parts of Iran is high.[34] 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].

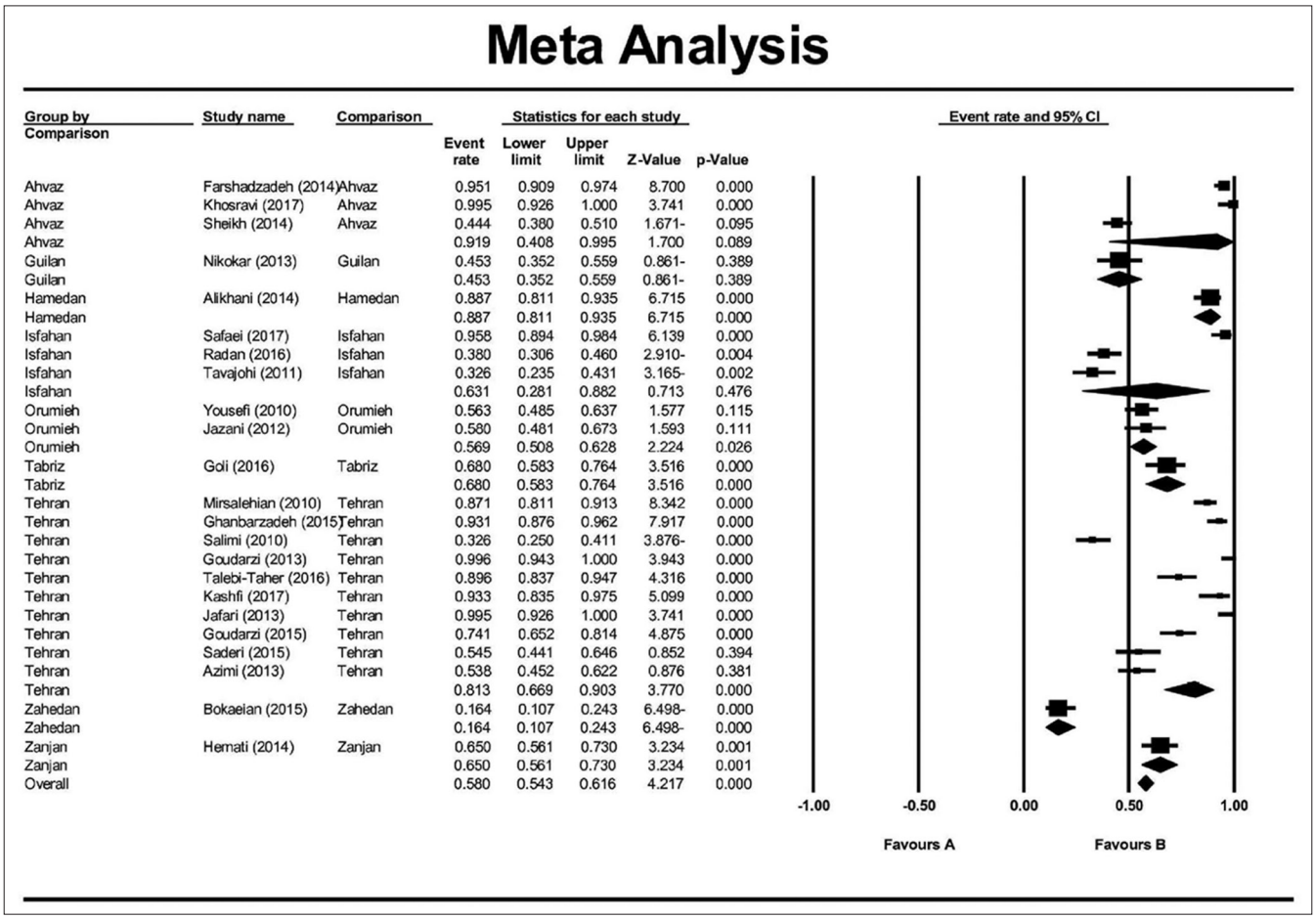

Figure 3: Meta-analysis examining the overall prevalence of multidrug-resistant *Pseudomonas aeruginosa* on studies conducted in Iran. The analysis revealed that the overall prevalence was about 58%

Table 2: Antibiotic resistance patterns of *Pseudomonas aeruginosa* in different provinces of Iran

Province	Antibiotic							
	CAZ (%)	IMP (%)	MP (%)	CIP (%)	PIP/TZ (%)	AMC (%)	GM (%)	AZ (%)
Tehran	72.4	70.4	78.8	81.5	68.7	80	62.5	83.7
Isfahan	66.5	76.1	93	78.7	75.2	95.5	55	69
Orumieh	55.4	30.8	39.4	34.2	44.4	30.7	45.8	56.3
Guilan	68.6	23.3	NA	66.3	NA	48.8	37.2	NA
Zahedan	14.7	17.2	NA	3.4	NA	NA	12.1	14.7
Ahvaz	77	42.9	44.1	46.8	59.3	55.2	66.8	91.3
Zanjan	29.2	29.2	NA	32.5	NA	21.7	37.5	37.5
Hamedan	50.9	7.5	13.2	4.7	NA	30.2	36.8	27.4
Tabriz	55	49	NA	65	34	NA	55	60
Total	50.4	31.6	40	47.3	49.4	50.6	46.9	46.8

NA: Not available

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.[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.[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%,[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).[38] Sixteen countries (Germany, Bulgaria, Austria, Lithuania, Malta,

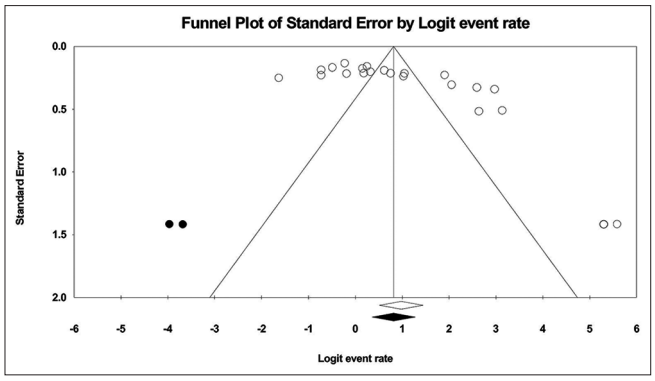

Figure 4: Funnel plot with pseudo 95% confidence interval demonstrating the effect sizes derived from each study (logit event rate) against their corresponding standard errors

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, piperacillin/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.[38]

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 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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Nil.

Conflicts of interest

There are no conflicts of interest.

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