Prevalence of Class 1 Integron and Antibiotic Resistance Pattern in Pseudomonas aeruginosa Isolated from Iranian Clinical Specimens; a Systematic Review and Meta-Analysis

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Abstract

Background The role of integrons has been shown in the horizontal transmission of antibiotic resistance genes among bacterial isolates especially Gram-negative microorganisms in clinical settings. Objectives The aim of this study was to systematically review the prevalence of class 1 integrons and antibiotic resistance in Pseudomonas aeruginosa isolates of clinical samples of Iranian patients. Methods The Web of Science, PubMed, Scopus, and Science Direct databases were searched using preferred keywords based on the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines. The cross-sectional studies addressing the frequency of class 1 integrons and antibiotic-resistance in P. aeruginosa isolates from clinical samples of Iranian patients published from 1 January 2000 until 31 December 2018 were included. Meta-analysis was performed using Comprehensive Meta-Analysis¬ (CMA) software. The random effects model was used for meta-analysis. The Cochran's Q and I2 tests were applied for statistical analyses. Publication bias was assessed using Funnel plot and Egger's linear regression test. Results Out of 911 studies retrieved in the initial search, 17 articles met the eligibility standards for being included in the meta-analysis. The Egger's linear regression test indicated no publication bias (P = 0.95). The combined prevalence of class 1 integrons in P. aeruginosa isolates was obtained as 58.9% (95% CI: 46.3–70.4%). The highest rate of combined antibiotic resistance was related to Carbenicillin with a resistance rate of 79.9%. On the other side, the most effective antibiotic against P. aeruginosa was Polymyxin B with the resistance rate of 0%. The pooled prevalence of multi-drug resistant (MDR) P. aeruginosa isolates was 55% (¬95% CI: 33.8-75.3%). Conclusions Our findings indicated the high prevalence of class 1 integrons and antibiotic resistance among P. aeruginosa isolates of Iranian patients' clinical samples. Also, the prevalence of MDR P. aeruginosa isolates was noticeable requiring prompt action.

Background

Pseudomonas aeruginosa is a non-fermentative aerobic Gram-negative bacillus and a common nosocomial pathogen. *P. aeruginosa* is one of the dreadful causes of severe infections in clinical settings particularly in immune-compromised patients, as well as individuals hospitalized in Intensive Care Unit (ICU), patients with cystic fibrosis, and those with severe burns [1]. Although the antibiotics are the main therapeutics to control the infections caused by this microorganism, the inherent resistance of *P. aeruginosa* to antibiotics is increasing [2].

The selective pressure of inappropriate antibiotic consumers on one hand, and the increasing use of antibiotics on the other hand are probably the main causes for the development of multidrug-resistant (MDR) *P. aeruginosa* in hospital settings [3]. MDR P. aeruginosa isolates are those showing resistant against three classes of conventional antibiotics particularly aminoglycosides, carbapenems, and fluoroquinolones [4].

Infections caused by MDR-*Pseudomonas aeruginosa* strainspresent clinically significant challenges. The empirical antibiotic therapy for MDR *P. aeruginosa* has represented poor outcomes with high morbidities, mortalities, long hospital stays and high economic and therapeutic burden on both health systems and the patients [5].

According to the reports of the European Centre for Disease Prevention and Control(CDC), *P. aeruginosa* comprises 9% of all hospital-based infections presenting the fourth most common hospital pathogen in Europe [6]. Also, CDC reported similar findings in the United States with the frequency of about 7% for *P. aeruginosa* infections in hospital settings [7]. A survey in Spain in 2016 reported a higher prevalence about 13% for this microorganism in ICU units of hospitals [8]. In European countries, the prevalence of MDR *P. aeruginosa* isolates was reported nearly 30% [9]. The rate of MDR *P. aeruginosa* isolates in Iran; however, has been reported between 30-100% [10].

Some possible antimicrobial resistance mechanisms in *P. aeruginosa* include the production of beta-lactamases, overexpression of efflux pumps, down regulation of outer membrane porins, production of AmpC or loss of OprD, genetic mutations, and finally expression of integrons on plasmids and transposons [6, 11]. The integrons are specialized genetic structures by which bacteria can acquire resistance genes through horizontal transmission [12].

Integrons can acquire external drug resistance gene cassettes and integrate them by site-specific recombination. In clinical settings, integrons facilitate rapid horizontal transmission of antibiotic resistance genes among bacterial isolates especially Gram-negative microorganisms [13, 14]. Generally, integrons comprise of an integrase gene, two conserved sequences called sul1 and int1, and a variable region harboring gene cassettes between the two conserved fragments [15].

Based on the structure of integrase gene, several classes of integrons have been recognized. Three main classes of integrons (i.e. class 1, 2, and 3) have been identified in Gram-negative bacteria including *Enterobacteriaceae*, and *Pseudomonas*. Among these, class 1 integrons are the most frequent in these microorganisms. Class 1 integrons usually carry one or several gene cassettes conferring resistance to a broad spectrum of antibacterial agents such as β-lactams, aminoglycosides and fluoroquinolones [16, 17].

It is necessary to comprehend the prevalence of MDR *P. aeruginosa* and the mechanisms associated with antibiotic resistance (such as the presence of integrons) to eradicate infections caused by this organism. Regarding the significance of *P. aeruginosa* in hospital acquired infections, and the lack of a comprehensive study on the prevalence of class 1 integrons in *P. aeruginosa* isolates and antimicrobial resistance patterns of this organism in Iran, we aimed to investigate the prevalence of class 1 integrons and antibiotic resistance patterns of *P. aeruginosa* recovered from clinical samples of Iranian patients.

Results

A total of 911 relevant articles were obtained in the primary literature search (Figure 1). Out of these, 456 duplicate studies were excluded. Also, 90 records with irrelevant titles were deleted. After reading the abstracts of 365 remained papers, 259 were excluded owing to justified reasons. Then, 106 full text studies assessed. From these, 89 studies were omitted due to either lack of data accessibility, missing data, or not reporting the frequency of class 1 integrons. Finally, 17 articles were included in the meta-analysis (Figure 1).

The combined prevalence of class 1 integrons in *P. aeruginosa* isolated from clinical specimens of Iranian patients varied from 13.3% to 99.1% (Figure 2). The clinical samples were mostly collected from ICU and Burn units. The pooled prevalence of MDR *P. aeruginosa* isolates varied from 13.1 to 100%. Overall, 11 out of the 17 included studies (64.7%) described a correlation between the presence of class 1 integrons and antibiotic resistance (Table 1, *P value < 0.05*).

Overall effects

There was a statistically significant heterogeneity among the included studies (Q2=341.7, I^2=95.3, t=1.2, *P=0.00*). Accordingly, the random effects model was applied to combine the prevalence of class 1 integrons in *P. aeruginosa* isolates. The combined prevalence of class 1 integrons was obtained as 58.9% (95% CI: 46.3–70.4%) in Iranian patients' clinical specimens (Table 2). The publication bias was checked using Funnel plot. Concerning possible asymmetrical data distribution in the selected studies, the Egger's linear regression test was used to further evaluate any publication bias. Nevertheless, the results of the Egger's linear regression test revealed no publication bias

(*P=0.95*). The pooled prevalence of MDR *P. aeruginosa* isolates was obtained as 55% (95% CI: 33.8-75.3%). Subgroups analysis revealed that the highest combined antibiotic resistance belonged to Carbenicillin following by Cloxacillin and Cefotaxime with respective resistance rates of 79.9%, 77.4%, and 76.6%. On the other hand, the most effective antibiotics against *P. aeruginosa* were Polymyxin B and Colistin each with resistance rate of 0% (Table 3).

Discussion

The non-lactose fermentative Gram-negative pathogens, especially *P. aeruginosa,* are emerging causes of nosocomial infections in patients hospitalized in ICU and Burn units [19].

In the present study, the combined prevalence of class 1 integrons in *P. aeruginosa* isolates was obtained as 58.9% ranging from 13.3% to 99.1%. About 64.7% of the included studies described a correlation between the presence of class 1 integrons and antibiotic resistance among *P. aeruginosa* isolates.

The noticeable differences and variability in the distribution of class 1 integrons among the Iranian studies included in the current systematic review may be partly due to the heterogeneities in the patterns of antibiotics usage, as well as the sources of infections and geographical locations [20]. Integrons carrying gene cassettes provide a powerful vehicle for the fast horizontal transmission of antibiotic resistance genes among different bacterial populations, and in this manner, contribute to the dissemination of antibiotic resistance in hospital settings which delivers a serious concern for human health services [12]. Similar to our findings, several researchers such as Ren *et al.* (2012) in the United States [21], Cholley *et al.* (2011) in France[22], and Taccone *et al.* (2012) in Brooklyn [23] have reported an association between the expression of class 1 integrons and antibiotic resistance in bacterial strains. In accordance with our findings, the class 1 integrons have been reported as the most common integrons expressed in *P. aeruginosa* isolates in studies conducted in Japan [24], Spain [12], and China[13].

The high frequency of integrons; particularly class 1 integrons, among resistant *P. aeruginosa* isolates highlights a role for these genetic elements in resistance to antimicrobial agents. We here encountered relatively high rates of resistant *P. aeruginosa* inthe ICU and burn units of hospitals, patients in these units are particularly susceptible to infections by MDR *P. aeruginosa.* Inappropriate empirical antibiotic therapy in infections caused by MDR *P. aeruginosa* strainshas resulted in increased mortality, prolonged hospitalization and elevated hospital costs [7]. Thus, particular strategies should be implemented to prevent the colonization of Gram-negative bacteria such as *P. aeruginosa* and transmission of resistance genes among these microorganisms through integrons in hospital settings [25].

Nevertheless, some included studies showed no relationship between the presence of integrons and antibiotic resistance in *P. aeruginosa*. This may partially be related to the contribution of other mechanisms involved in antibiotic resistance such as the overexpression of AmpC beta lactamase (which is encoded by chromosomal genome), the repression or inactivation of Carbapenem porin OprD, and the up-regulation of different efflux pumps [6].

In the present review, the pooled prevalence of MDR *P. aeruginosa* isolates recovered from clinical specimens of Iranian patients was 55%. In comparison, the frequency of MDR *P. aeruginosa* isolateswas reported 30% in eastern European countries [9] that was lower than the ratio obtained here. In line with our findings; however, other studies in China [26], and Brazil [27] reported the high frequency of MDR *P. aeruginosa* isolates. In accordance with our results, Fonseca *et al*. showed that more than half of Imipenem-resistant and almost all MDR *P. aeruginosa* isolates expressed class 1 integrons [27].

In the current study, the most effective antibiotics against *P. aeruginosa* isolates were Polymyxin B and Colistin each with susceptibility rate of 100%. This is while most of *P. aeruginosa* isolates represented the high resistance toward

Carbenicillin (79.9%), Cloxacillin (77.4%), and Cefotaxime (76.6%). Polymyxin B and colistin are among the most important anti-pseudomonal antibiotics with the highest effects against MDR *P. aeruginosa* isolates. However, both of these antibiotics have been associated with side effects and toxicities [6]. In fact, the restricted prescription of Polymyxins because of their toxicity is probably the most important reason for the high susceptibility rate (100%) of *P. aeruginosa* isolatesin exposure to these antibiotics [28]. Accordingly, a report from Spain in 2015 revealed a high rate of combined resistance to three or more frequently prescribed antimicrobial agents (piperacillin–tazobactam, Ceftazidime, fluoroquinolones, aminoglycosides and Carbapenems) among *P. aeruginosa* isolates[29]. As well, polymyxins have shown the highest antibacterial activity among XDR *P. aeruginosa* isolates [9] which is in agreement with our results.

To the best of our knowledge, fluoroquinolones (such as Ciprofloxacin) are among the most effective available antibiotics for the treatment of *P.aeruginosa* infections, particularly urinary tract infections [30]. In this study; however, more than 50% of *P. aeruginosa* isolates showed resistance against Ciprofloxacin. According to the studies conducted in Latin America and Europe, 25-30% of *P. aeruginosa* isolates were also resistant to Ciprofloxacin [31, 32]. In addition, we encountered a broad resistance rate against beta-lactams and aminoglycosides in *P. aeruginosa* strainswhich is in line with the results of previous studies [26, 33]. On the contrary, others have described low resistance rates of *P. aeruginosa* against aminoglycosides [25, 27].

It is noteworthy that hospital acquired infections caused by MDR bacterial isolates are relatively frequent in developing countries such as Iran in comparison with developed nations such as the USA and most European countries. This difference can be explained by the effective programs implemented to prevent and control nosocomial hospital infections in developed countries [34]. This is while the hospital-based committees for controlling infections are either unavailable or their members are inexperienced and untrained in developing countries. Therefore, it is advisable to recruit clinical microbiologists for effective management of nosocomial infections in hospitals [35, 36].

Overall, the prevalence of MDR *P. aeruginosa* isolates was high in clinical samples obtained from Iranian patients especially those hospitalized in critical care units (i.e. ICU and Burn). Furthermore, a high penetrance of class 1 integrons was noted in the MDR *P. aeruginosa* isolates delineating their association with antibiotic resistance in these bacteria. Timely reporting of antibiotic resistance patterns in these bacteria is recommended to prescribe appropriate antibiotics. Also, it is recommended to develop hospital-based infection control committees and educate their members regarding the nosocomial infections control programs.

In this review, we included only the articles published in English which is a limitation of our study. Also, we did not include unpublished literatures in the present review.

Conclusions

Our findings indicated the high prevalence of class 1 integrons and antibiotic resistance among *P. aeruginosa* isolates of Iranian patients' clinical samples. Also, the prevalence of MDR *P. aeruginosa* isolates was noticeable requiring prompt action.

Materials And Methods

Search strategy

The studies addressing the prevalence of class 1 integrons and antibiotic resistance pattern of *P. aeruginosa* isolatesfrom Iranian patients' clinical specimens published from January 2000 to the end of 2018 were included. The

search was carried out in Web of Science, Cochrane Library, Scopus, PubMed, and Google Scholar databases. The search was restricted to the English original articles reporting either the prevalence or incidence of *P. aeruginosa*. The following keywords from Medical Subject Headings or titles or abstracts were used with the help of Boolean operators (and, or): *P. aeruginosa*, burned patients, drug susceptibility, and drug resistance. The keywords of Integrons, *Pseudomonas aeruginosa* or *P. aeruginosa,* prevalence/incidence and distribution of INT1 in *Pseudomonas aeruginosa*, Iran, Int1, antibiotic resistance, and local studies were used alone or in combination to conduct a complete search antibiotic resistance.

Inclusion and exclusion criteria

All the original articles reporting the prevalence, incidence and distribution of integrons in *P. aeruginosa* isolated from Iranian patients' clinical specimens were included. Only those studies that performed antibiotic susceptibility test based on CLSI guidelines were considered. Foreign studies (i.e. not performed in Iran) and those studies that did not follow CLSI directions in performing antibiotic susceptibility test were excluded. Also, narrative and systematic reviews, meta-analyses, editorials, prospective studies, congress abstracts, case reports, and letters to the editors were omitted. Studies published in languages other than English, articles only available in abstract form and also duplicate publications were excluded.

Data extraction

The intended data including first author's name, year of publication, location of study, sample size, the frequencies of MDR and class 1 integrons, hospital wards, and correlation between the presence of integrons and antibiotic resistance were recorded in a data extraction form designed by the researchers.

Qualification of the studies

The strengthening the reporting of observational studies in epidemiology (STROBE) checklist was utilized for qualifying the methodology of the included studies [18]. Based on the qualification criteria, the studies were categorized as high, medium or low quality.

Statistical analysis

The data was analyzed using Comprehensive Meta-Analysis software (Version 3.3.070). The prevalence of class 1 integrons in *P. aeruginosa* isolated from Iranian patients' clinical samples was reported with 95% confidence interval (CI). The random effects model was used for meta-analysis. The statistical heterogeneity among the studies was determined by Cochrane Q and I^2 tests. To evaluate possible publication bias, the funnel plot and quantitative Egger weighted regression test were applied. P value<0.05 was considered as the statistical significance cut off for detecting any publication bias.

Abbreviations

PRISMA: Preferred Reporting Items for Systematic Review and Meta-Analyses, CMA: Comprehensive Meta-Analysis, MDR: multi-drug resistant, ICU: Intensive Care Unit, CDC: Centre for Disease Prevention and Control, STROBE: Strengthening the reporting of observational studies in epidemiology, CI: Confidence interval.

Declarations

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Availability of data and materials

The data can be accessible to the interested researchers by the corresponding authors on reasonable request.

Authors' contributions

EZ and designed the study. YEK and AK contributed in the searching process, and drafting the work. MR and MB performed the analysis of the data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table1. Characteristics of selected studies from Iranian patients

Study	Publication Year	Location	Sample Size (N)	MDR N (%)	Int1 in total N (%)	Units	Correlation between Int1 And antibiotic resistance
Yousefi[37]	2010	Orumieh	160	21(13.1)	90 (56.3)	Different wards	Yes
Moradian[25]	2013	Babol	54	53 (98.1)	20 (37)	ICU	Yes
Nikokar[38]	2013	Guilan	86	11(13.3)	37 (43)	Burn	Yes
Moazami[39]	2015	Tehran	112	15(13.4)	79 (70.5)	Burn and non-burn	Yes
Goudarzi[40]	2016	Tehran	140	19(13.3)	56 (40)	Burn	Yes
Aryanezhad[41]	2016	Bandar Abbas	90	12(13.3)	12(13.3)	ICU, non-ICU	yes
Hosseini[2]	2016	Tehran	100	-	90(90)	Burn	No
Mirahsani[42]	2016	Isfahan	231	192 (83.1)	146 (63.2)	Burn and non-burn	-
Goli[43]	2017	Tabriz	100	71(71)	66(66)	Burn and different wards	Yes
Khosravi[44]	2017	Ahvaz	93	93(100)	89 (95.7)	Burn,	-
Mohammadzadeh[45]	2017	Gonabad	95	-	29 (30.5)	different wards	-
Mobaraki[3]	2018	Tabriz	200	106(53)	55 (27.5)	Different wards	Yes
Faghri[20]	2018	Isfahan	72	-	40(55.6)	ICU, non-ICU	Yes
Goli et al[46]	2018	Tabriz	57	57(100)	57(99.1)	ICU	Yes
Pournajaf[47]	2018	Iran	143	12(8.4)	27(18.9)	CF Patient(Iran)	-
Zarei-Yazdeli[48]	2018	Yazd	144	108(75)	119 (82.6)	Burn and non-burn	No
Salimizadeh[49]	2018	Tehran	21	21(100)	19(90.5)	Different	Yes

Table 2. Analysis of prevalence of class 1 integron in *P. aeruginosa* recovered from clinical specimens of Iranian patients

Subgroups	Number of studies	Heterogeneity test			Egger's test			Random model	
Overall effect									
		Prevalence (95% CI) (%)	Z	P	Q	P	I2	T	P
Int1	**17**	58.9(46.3-70.4)	1.3	0.00	341.7	0.24	95.3	1.2	0.16
MDR	**14**	55(33.8-75.3)	0.48	0.00	474.1	0.95	97.2	0.05	0.62

Note: Int1: Class1 Integron; MDR: Multi-Drug Resistant.

Table 3. Subgroups analysis for antibiotic resistance in *P. aeruginosa* isolated from Iranian burn patients

Subgroups	Number of studies	Heterogeneity test			Egger's test			Random model	
		Prevalence (95% CI) (%)	Z	P	Q	P	I2	T	P
Imipenem	14	47.5(32.8-62.7)	0.31	0.00	352.6	0.42	96.3	0.83	0.75
Ciprofloxacin	17	62.4(48.6-74.5)	1.7	0.00	406.7	0.2	96.06	1.1	0.07
Gentamicin	15	60.5(47.4-72.2)	1.5	0.11	288.9	0.37	95.1	0.9	0.11
Amikacin	16	57.4(46.4-67.8)	1.3	0.00	262.2	0.9	94.2	0.1	0.18
Ceftriaxone	5	58.6(29.8-82.5)	0.56	0.00	129.8	0.72	96.9	0.37	0.57
Ceftazidime	14	57.8(44.4-70.2)	1.14	0.00	289.6	0.99	95.5	0.00	0.25
Cefepime	9	46.4(26.6-67.4)	0.32	0.00	250.9	0.34	96.8	1	0.74
Piperacillin/ tazobactam	10	50.6(40.4-60.8)	0.11	0.00	102.9	0.35	91.2	0.97	0.9
Aztreonam	7	48.1(27.9-68.9)	0.17	0.00	180.7	0.1	96.6	1.9	0.86
Cloxacillin	4	77.4(62.8-87.4)	3.4	0.00	32.8	0.23	90.8	1.6	0.001
Tobramycin	9	65.8(51.2-77.9)	2.1	0.00	160.8	0.78	95	0.28	0.035
Ticarcillin	8	55.4(40.1-69.7)	0.68	0.00	102.5	0.70	93.1	0.39	0.49
Carbenicillin	3	79.9(72.7-85.6)	6.7	0.00	2.7	0.80	28.3	0.32	0.00
Cefotaxime	3	76.6(72.1-80.6)	9.7	0.00	9.6	0.96	79.3	0.05	0.00
Norfloxacin	4	57.3(11.5-93.3)	0.24	0.00	180.9	0.45	98.3	0.91	0.81
Polymyxin B	3	1(1-2.5)	6.4	0.00	0.001	0.05	0.00	121	0.00
Colistin	3	1(1-1.25)	4.1	0.00	0.001	0.06	0.00	102	0.00