Review Article

Prevalence of Drug-resistant *Pseudomonas aeruginosa* in Iranian Burned Patients: A Meta-analysis

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Abstract

The increasing prevalence of drug-resistant *Pseudomonas aeruginosa* in burned patients is one of the main public health problems worldwide. Although drug-resistant *P. aeruginosa* in burn units is frequent in some countries and unusual in others, the level of this conditions is not precisely known in Iran. Imipenem is one of the most potent agents against *P. aeruginosa*. Imipenem resistance is a major obstacle to treatment of *P. aeruginosa* infections. We aimed to determine the true prevalence of imipenem-resistant *P. aeruginosa* in Iranian burned patients according to the Preferred Reporting Items for Meta-Analyses statement. Moreover, resistance to several potent anti-*P. aerugi*nosa drugs were indicated according to the Clinical and Laboratory Standards Institute guidelines for the disc diffusion method. Several databases including Web of Science, Scopus, PubMed, Scientific Information Database, Magiran, Iranmedex, and science direct were searched to get studies addressing drug-resistant *P. aeruginosa* in Iranian burned patients from March 2006 to May 2015. A total of 34 reports available from different areas of Iran were included in the current study. The meta-analyses showed that 54.9% of *P. aeruginosa* were resistant to imipenem. The most common resistance was seen against ceftazidime (66.9%), followed by ciprofloxacin (52.9%) and cefepime (52.3%). It is necessary to know the epidemiology of drug-resistant *P. aeruginosa* because it can promote control strategies for decreasing their prevalence. The high incidence of drug-resistant *P. aeruginosa* in Iran emphasizes the need for precise drug susceptibility testing, continuous monitoring of drug resistance, especially in burn units, use of sensitive methods for the laboratory diagnosis, and close relation between physician and laboratories.

Keywords: Burn, imipenem, Iran, *Pseudomonas aeruginosa*

Introduction

Burn infections are one of the most prevalent and destructive health problems in many countries of the world, particularly in developing countries like Iran, where in some cases infection control programs are ignored. Patients with serious burn injury require immediate care to minimize complications. One of the most remarkable and serious complications of burn is wound infections.[1] It is estimated that about 75% of the mortality in burn injuries contributes to the infection.[2] According to the Centers for Disease Control and Prevention (CDC) report in 2013, *Enterobacteriaceae*, *Pseudomonas aeruginosa*, and *Acinetobacter* spp. have the appearance as significant pathogens caused infection in the burn unit. The CDC's National Healthcare Safety Network estimates that approximately 8% of all healthcare-associated infections reported are caused by *P. aeruginosa*.[3] Antibiotic therapy is considered as the major intervention in the treatment and management of burn infections. Carbapenems including imipenem and meropenem are the most important antibiotics used to treat *P. aeruginosa* infections. Imipenem is one of the most potent agents against *P. aeruginosa*. Imipenem resistance is a major obstacle to treatment of *P. aeruginosa* infections. Increasing antibiotic resistance is a serious problem for both patients and health-care systems.[4,5] Recently, this concern has been further intensified by the emergence of multidrug-resistant (MDR) strains with the mortality rate >40%–50%.[4,6] Thereby, in the past decade, major attempt has been done to establish new strategies to progress treatment of burned patients. Although numerous studies have been

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published in burn wound infections and antibiotic resistance in Iran, none of them has studied all of the countries within a comprehensive study. Having comprehensive and reliable data on antibiotic susceptibility status of *P. aeruginosa* is crucial for effective treatment and successful infection control program against this bacterium, especially in regions where an antibiotic therapy is empirical, and infection control strategy is ignored. The aim of the present study was to determine the true prevalence of imipenem-resistant *P. aeruginosa* in Iranian burned patients according to the Preferred Reporting Items for Meta-Analyses statement. Moreover, resistance to several potent anti-*P. aerugi*nosa drugs were indicated according to the Clinical and Laboratory Standards Institute (CLSI) guidelines for the disc diffusion method.

Materials and Methods

Search strategies

A database was constructed to evaluate the prevalence of drug-resistant *P. aeruginosa* in Iranian burned patients from March 2006 to May 2015 using PubMed, Web of Science, Iranmedex, Scopus, and the Scientific Information Database. The search was confined to original articles published in English and Persian that present the prevalence or incidence of *P. aeruginosa* in Iranian burned patients. 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, Iran drug susceptibility, and drug resistance. The authors searched both English published articles and relevant Persian articles. All published data in the Persian language including Magiran, Iranian National Library, Scientific Information Database, and Iranmedex were searched.

Inclusion and exclusion criteria

All research articles presenting the prevalence of drug-resistant *P. aeruginosa* in burned patients in Iran were selected. Based on titles, abstracts, and full papers, the collection of articles for review was performed. Method of antibiotic susceptibility in all of included studies was based on CLSI guidelines for *P. aeruginosa* against anti-*P. aeruginosa* drugs including imipenem, meropenem, ceftazidime, ceftriaxone, cefepime, ciprofloxacin, amikacin, gentamicin, and aztreonam. Studies were excluded from analysis for any of the following reasons: articles noted only on non-*P. aeruginosa*; studies done on regions except Iran; studies checking the nonburned patient; studies that were not performed based on the CLSI guidelines and do not use the anti-*P. aeruginosa* drugs. Review articles, congress abstracts, meta-analyses, or systematic reviews, studies reported in languages other than English or Persian, articles available only in abstract form and also duplicate publication of the same study were excluded.

Data extraction

For all studies, the data including year of publication, first author, study setting, number of burned patients, and drug resistance status were extracted by two persons, independently. The term drug resistance among *P. aeruginosa* refers to isolates that according to the CLSI guidelines show resistance to suitable antimicrobial tests and grow in the presence of antimicrobial agents that would normally kill them or limit their growth.

Statistical analysis

Comprehensive Meta-Analysis Software Version 2.0 (Biostat, Englewood, NJ) was used for statistical analysis. The prevalence of drug-resistant *P. aeruginosa* in burned patients in Iran was reported by 95% confidence intervals (CIs). Egger weighted regression and Begg's rank correlation methods were used to assess possible publication bias. The value of $P < 0.05$ was considered indicative of a statistically significant publication bias. Random effects models were chosen according to the Cochrane Q test and I^2 tests, taking into account the possibility of heterogeneity between studies.

Results

A total of 1071 research articles were selected [Figure 1]. Based on title and abstract evaluation, 652 of them were excluded, and 419 for full-paper evaluation were retained. After this screening, 34 articles describing the prevalence of drug-resistant *P. aeruginosa* in burned patients in Iran are selected for analysis and presented in Table 1. Of the included articles, 11 articles were considered the age and 13 articles reported the gender of the patients. Based on these articles, 1021 males and 617 females with a mean age between 20 and 40 years [Table 1] were analyzed. All 34 articles contained information for drug-resistant *P. aeruginosa* in burned patient in Iran. All studies had been used the disc agar diffusion method according to the CLSI protocols. Considering the

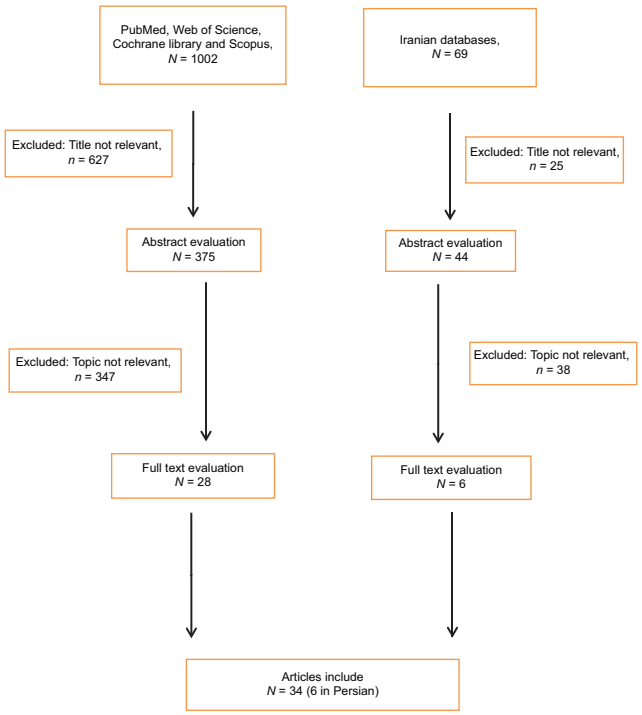

Figure 1: Diagram of the study selection process

Table 1: Status of drug-resistant *Pseudomonas aeruginosa* isolates

First author	Province	Published time	Case number	IMP	MEM	CAZ	CPM	CIP	AMK	GM	AZT
Japoni[7]	Shiraz	2006	70	47	48	11	2	19	5	-	-
Kohanteb[8]	Shiraz	2007	30	14	11	30	-	25	28	30	-
Mahini[9]	Ahvaz	2007	100	41	23	81	100	-	-	-	-
Owlia[10]	Tehran	2007	110	42	-	101	-	85	52	98	-
Khorasani[11]	Sari	2008	71	15	58	68	70	35	57	49	-
Mahouf[12]	Hamadan	2008	57	30	27	35	45	24	22	36	14
Saderi[13]	Tehran	2008	128	49	-	95	-	63	83	107	-
Mirsalhian[14]	Tehran	2008	100	63	66	85	88	83	-	-	90
Khosravi[15]	Ahvaz	2008	100	41	41	83	100	-	-	-	-
Afrasiabian[16]	Sanandaj	2008	16	1	-	13	-	5	1	6	-
Bahar[4]	Sanandaj	2010	115	115	-	115	-	89	94	115	-
Zolfaghari[17]	Qom	2011	40	20	-	21	-	19	10	12	-
Mirsalehian[18]	Tehran	2010	170	112	118	141	144	142	-	-	150
Alipour[19]	Ilam	2010	53	2	-	21	-	-	35	-	14
Alipour[19]	Kerman	2010	120	0	-	78	-	-	69	-	72
Saderi[20]	Tehran	2010	100	69	-	78	-	55	73	86	-
Jazani[21]	Urmia	2010	100	47	-	100	75	70	70	97	-
Jabalameli[22]	Tehran	2011	112	74	79	94	98	95	92	-	101
Bayat[23]	Urmia	2011	20	20	-	20	20	20	20	20	-
Ranjbar[24]	Tehran	2011	70	68	-	40	-	45	63	47	-
Rezaei[25]	Mashhad	2011	28	5	5	27	11	17	16	-	-
Vahdani[26]	Tehran	2012	220	174	-	178	191	191	174	158	178
Sepehrisereshtl[27]	Tabriz	2012	483	272	-	-	-	-	-	-	-
Nikokar[28]	Guilan	2013	86	20		59	-	57	42	32	-
Jafari[29]	Tehran	2013	100	77	100	77	100	100	100	49	100
Fallah[30]	Tehran	2013	100	83	48	48	48	48	48	49	48
Moazami-Goudarzi[31]	Tehran	2013	133	126	126	119	122	127	119	-	125
Vala[32]	Tehran	2013	47	37	35	31	32	33	-	34	33
Goudarzi[33]	Tehran	2014	73	47		72	-	73	71	72	-
Akhavan-Tafti[34]	Yazd	2014	54	40	38	-	34	-	-	40	-
Farshadzadeh[35]	Ahvaz	2014	185	55	111	149	157	55	-	-	182
Neyestanaki[36]	Tehran	2014	214	100	100	180	213	100	-	100	100
Japoni[37]	Shiraz	2014	270	60	60	207	265	265	252	265	60
Hakemi Vala[38]	Tehran	2014	47	37	35	34	32	32	-	34	39
Mean rate (%)	-		-	54.9	30.3	66. 9	52.3	52.9	42.8	41.2	35

IMP: Imipenem, MEM: Meropenem, CAZ: Ceftrixone, CPM: Cefepime, CIP: Ciprofloxacin, AMK: Amikacin, GM: Gentamycin, AZT: Aztreonam

location of the studies, most of the studies were conducted in Tehran (n = 15) and compared with studies in Shiraz and Ahvaz (each of them n = 3), Sanandaj (each n = 2), Sari, Hamadan, Qom, Ilam, Kerman, Urmia, Mashhad, Tabriz, Guilan, and Yazd (each n = 1). Figure 2 shows the distribution of imipenem-resistant *P. aeruginosa* in different regions of Iran. The prevalence of imipenem resistance was found to be 54.9% (95% CI, 46.9–62.7). However, evident heterogeneity was observed ($P < 0.226$). Figure 3 shows the forest plot of the meta-analysis on imipenem-resistant *P. aeruginosa*. As shown in Figure 4, some evidence for the publication bias was observed ($P = 0.241$ for Begg's rank correlation analysis; $P = 0.472$ for Egger weighted regression analysis). Common data of each selected studies such as first author, published time, province, number of *P. aeruginosa,* and number of imipenem resistance were shown in Table 1. Resistance to anti-*P. aeruginosa* drugs that have been selected according to the CLSI guidelines for the disc diffusion method was shown in Table 1. Considering resistance to anti-*P. aeruginosa* drugs, the most common resistance was seen against ceftazidime (66.9%), followed by ciprofloxacin (52.9%), and cefepime (52.3%).

Discussion

P. aeruginosa is one of the most important nosocomial agents and clinical isolates of this opportunistic pathogen cause serious infections in burn units.[39] The current meta-analysis showed the prevalence and distribution of drug-resistant *P. aeruginosa* in burned patients in Iran. Our analyses showed that 54.9% of the *P. aeruginosa* strains from burned patients were resistant to imipenem. Considering that the carbapenems are still the drug of choice for MDR *P. aeruginosa*, this high rate of resistance is very alarming.[40] Poorabbas *et al*. performed a study in Iran on antibiotic resistance and reported resistance to imipenem (85%), ciprofloxacin (76%), amikacin (70%),

Figure 2: Distribution of imipenem-resistant *Pseudomonas aeruginosa* in different regions of Iran

gentamicin (67%), cefepime (40%), and ceftazidime (74%) in burn patients.[41] Other study from India, in 2015, indicated resistance to gentamicin (84%), ceftazidime (76.79%), amikacin (73.2%), ciprofloxacin (71.4%), and imipenem (61%) in burn patients.[42] The development of imipenem resistance among *P. aeruginosa* strains in burn units may contribute to the factors such as the severity of burn infection which result in long hospitalization time in particular intensive care unit stay, previous broad-spectra antibiotics use or monotherapy that increase risk of resistance, poor laboratory diagnosis of resistance isolates that can cause to increase transferring resistance to other susceptible germs and higher costs that may lead to prescribe inappropriate and cheaper drug or use of monotherapy.[43,44] Carbapenem-resistance mechanisms in *P. aeruginosa* isolates are in association with resistance to other antibiotic classes such as penicillins, cephalosporins, and monobactams probably due to similar resistance mechanisms and make treatment very challenging.[45,46] Hence, identifying and detection of carbapenem-resistant strains and using the infection control procedures are very important.[47] In addition, resistance can be transferred to *P. aeruginosa* by mobile elements such as plasmids or integrons. In low hygiene condition on burn units, colonization of other microorganisms such as *Enterobacteriaceae* and *A. baumannii* may lead to transfer the resistance coding elements to the *P. aeruginosa*.[48,49] According to the geographic areas, classified analyses were done in the current study. Most of the studies were performed in Tehran, where high rates of imipenem resistance (65.8%) compared to other regions have been reported by researchers. These findings may supported that Tehran, the capital of Iran, with many health-care centers play a referral role for other regions of Iran and burned patients with drug-resistant *P. aeruginosa* are mostly referred to this province. The Central and Northwest of Iran showed almost high imipenem resistance (50%), whereas the South and West of Iran were moderate (almost 30%) and the East of Iran was experienced the lowest rate of imipenem resistance (<20%). Based on this finding, distribution of imipenem resistance in Iran is not homogeneous that reported in range of 0% (Southeast of Iran) to 88.5% (West of Iran). This pattern is similar to India where based on different studies the imipenem-resistance rate varies from 10% to 95.7%. According to data released from CDC, several ways exist to prevent drug-resistant *P. aeruginosa* infections including knowledge about resistance trends in a specific region, and coordinating the local and regional infection control efforts; the results should be made available more rapidly to clinicians for suitable treatment.[50] Moreover, hospitalization time should be shortened if possible; effective and appropriate antibiotic policies should be implemented; staff should be educated about the significance of right antibiotic use; and some strategies are necessary to optimize the use of antibiotics, for example, the prescription of carbapenem.[43,51] Finally, essentials of the standard precautions should be taken.[52] Every assay should be done to reduce spreading and emerging of resistant organisms.[53] We suggest that the infection control program recommended by the World Health Organization be implemented according to local conditions to be more effective. In the other words, countries with low- and middle-income are not able to apply

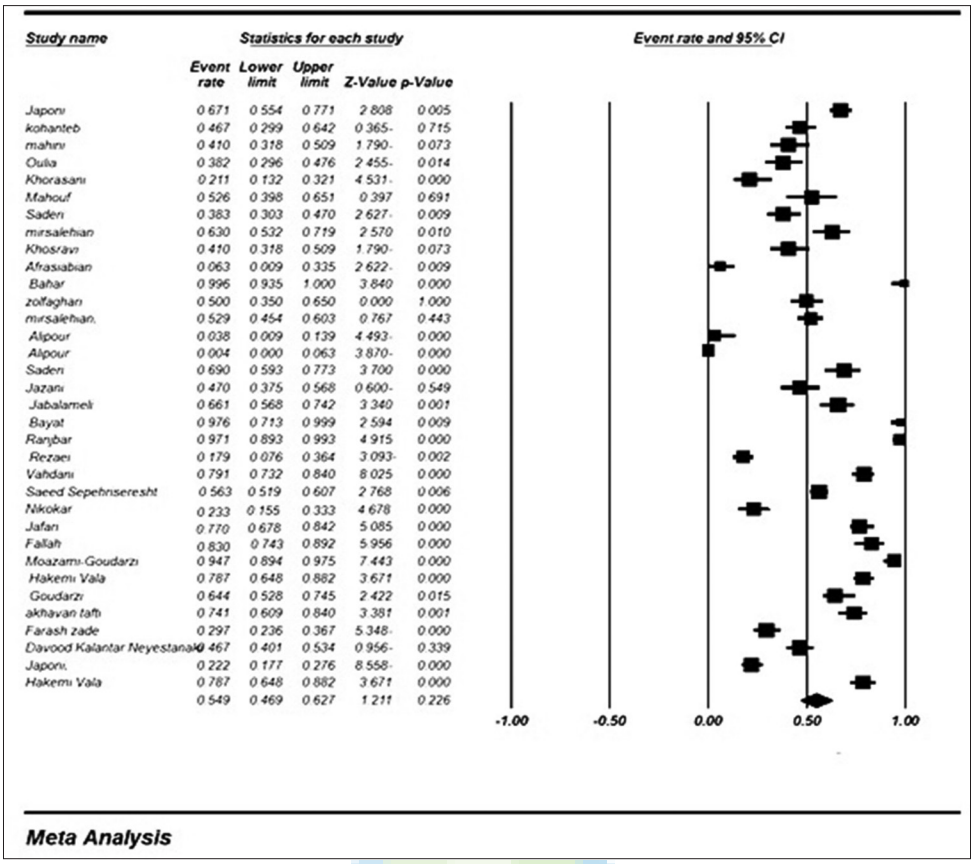

Figure 3: Forest plot of the meta-analysis on imipenem-resistant *Pseudomonas aeruginosa*. CI: confidence interval

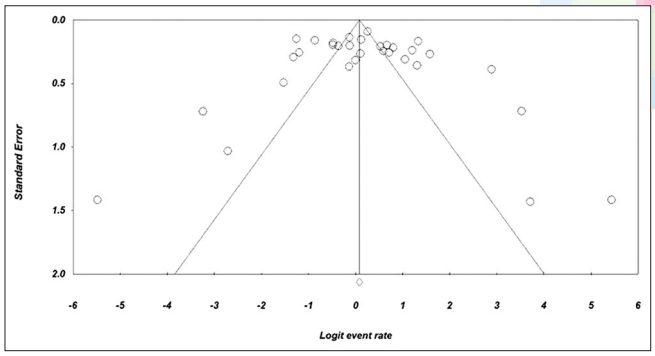

Figure 4: Funnel plot of the meta-analysis on imipenem-resistant *Pseudomonas aeruginosa*

infection control programs as developed countries in terms of cost and cultural requirements.[54,55] Close cooperation of clinicians with the microbiology laboratory, rapid reporting, and effective treatment using combination regimens is necessary to prevent spread of resistant *P. aeruginosa* isolates in burned patients.[54,56,57] However, combination regimens should be used very carefully only in inpatient who has indication, otherwise may lead to new resistance.[58] The limitations of this review should be discussed as follows: (a) it cannot fully represent the prevalence of imipenem resistance in *P. aeruginosa* in Iran due to the imipenem resistance is not yet investigated in many areas of Iran. (b) The potential influence of age and sex could not be analyzed because of the limited information obtained from the studied articles. (c) Only the disc diffusion test was used in selected studies and other confirmatory tests such as *E*-test or minimal inhibitory concentration were not used. (d) The heterogeneity exists among the included studies. (e) As with any meta-analysis, limitations associated with potential publication bias should be considered.

Conclusion

This meta-analysis showed that *P. aeruginosa* resistance was high among isolates with burn infection, which may lead to more cost and high rate of mortality. Thereby, attention to infection control guidelines, creating close relation between physicians and laboratory, and continuous monitoring of drug resistance are highly recommended. It is necessary to know the epidemiology of drug-resistant *P. aeruginosa* because it can promote control strategies for decreasing their prevalence. The high incidence of drug-resistant *P. aeruginosa* in Iran emphasizes the need for precise drug susceptibility testing, continuous monitoring of drug resistance, especially in burn units, use of sensitive methods for the laboratory diagnosis, and close relation between physician and laboratories.

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Conflicts of interest

There are no conflicts of interest.

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