Epidemiology of Antibiotic Resistance Pattern of *Pseudomonas Aeruginosa* in Cystic Fibrosis Patients in Iran: A Systematic Review and Meta-Analysis

İran'daki Kistik Fibrozis Hastalarında Pseudomonas Aeruginosa'nın Antibiyotik Direnç Paterninin Epidemiyolojisi: Sistematik Bir İnceleme ve Meta-Analiz

Tofigh Yaghubi Kalurazi[1], Ali Nazari-Alam [2], Hadi Sedigh Ebrahim-Saraie [3], Farzaneh Mohammadzadeh Rostami[4]
Masoud Yousefi [5], Kourosh Delpasand[3], Mehrdad Halaji [6]

[1]Department of Health, Nutrition & Infectious Diseases, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran
[2]Infectious Diseases Research Center, Kashan University of Medical Sciences, Kashan, I.R.Iran
[3]Razi Clinical Research Development Unit, Razi Hospital, Guilan University of Medical Sciences, Rasht, Iran
[4] Department of Microbiology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran
[5] Birjand University of Medical Sciences, Infectious Diseases Research Center, Birjand, Iran
[6] Department of Microbiology, Faculty of Medicine, Babol University of Medical Sciences, Babol, Iran

ABSTRACT

Objective: *Pseudomonas aeruginosa* is one of the most opportunistic pathogen involved in respiratory tract infection in cystic fibrosis (CF) patients. The present study aimed to assess the antibiotic resistance pattern of *P. aeruginosa* strains isolated from Iranian CF patients in using a systematic review and meta-analysis.
Methods: A systematic search was done to identify studies which met our inclusion criteria in the Web of Science, PubMed, Embase, Scopus, and Google Scholar electronic databases from the beginning to the end of July 2019. Finally, seven articles with appropriate criteria was chosen for data extraction and analysis by Comprehensive Meta-Analysis Software.
Results: Seven studies assessed antibiotic resistance pattern of *P. aeruginosa* in CF patients. Included studies were reported from North (Tehran), Central (Isfahan), and Northeast (Mashhad) of Iran. Piperacillin-tazobactam had the lowest resistance rate at 7.3% (95% CI: 1.8–25.4%), while ceftazidime had the highest resistance rate at 34.7% (95% CI: 11.9–67.6%).
Conclusion: A high level of antibiotic resistance against ceftazidime and gentamicin in our results is an alarming and may be due to severe and complication caused by *P. aeruginosa* infections in CF patients. Moreover, piperacillin-tazobactam, tobramycin and amikacin are the most suitable antibiotics for the treatment of respiratory infections in our population. However, administration of control strategies and surveillance programs highly recommended.

Keywords: *Pseudomonas aeruginosa*; Antibiotic resistance; Cystic fibrosis, Meta-analysis, Iran

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ÖZET

Amaç: *Pseudomonas aeruginosa*, kistik fibrozis (KF) hastalarında solunum yolu enfeksiyonuna karışan en fırsatçı patojenlerden biridir. Bu çalışma, sistematik bir inceleme ve meta-analiz kullanarak İranlı KF hastalarından izole edilen P. aeruginosa suşlarının antibiyotik direnç paternini değerlendirmeyi amaçlamıştır.
Yöntemler: 2019 yılının başından sonuna kadar Web of Science, PubMed, Embase, Scopus ve Google Scholar elektronik veritabanlarında dahil edilme kriterlerimizi karşılayan çalışmaları belirlemek için sistematik bir arama yapıldı. Son olarak uygun kriterlere sahip yedi makale belirlendi. Kapsamlı Meta-Analiz Yazılımı tarafından veri çıkarma ve analiz için seçilmiştir.
Bulgular: Yedi çalışma, KF hastalarında P. aeruginosa'nın antibiyotik direnç paternini değerlendirdi. Dahil edilen çalışmalar İran'ın Kuzey (Tahran), Orta (İsfahan) ve Kuzeydoğu (Meşhed) bölgelerinden rapor edilmiştir. Piperasilin-tazobaktam %7.3 (%95 GA: %1.8–25.4) ile en düşük direnç oranına sahipken, seftazidim %34.7 (%95 GA: %11.9–67.6) ile en yüksek direnç oranına sahipti.
Sonuç: Sonuçlarımızda seftazidim ve gentamisin'e karşı yüksek düzeyde antibiyotik direnci endişe vericidir ve KF hastalarında P. aeruginosa enfeksiyonlarının neden olduğu ciddi ve komplikasyona bağlı olabilir. Ayrıca piperasilin-tazobaktam, tobramisin ve amikasin popülasyonumuzdaki solunum yolu enfeksiyonlarının tedavisi için en uygun antibiyotiklerdir. Ancak, kontrol stratejilerinin ve gözetim programlarının yönetimi şiddetle tavsiye edilir.

Anahtar Sözcükler: *Pseudomonas aeruginosa*; Antibiyotik direnci; Kistik fibroz, Meta-analiz, İran

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ORCID IDs: T.Y.K.0000-0002-6042-2331, A.N.A.0000-0003-4770-5836, H.S.E.S.0000-0001-8339-5199, F.M.R.0000-0003-0536-6071, M.Y.0000-0002-8992-8424, K.D.0000-0001-6842-3374, M.H.0000-0002-4576-8203

Address for Correspondence / Yazışma Adresi: Mehrdad Halaji, MD Department of Microbiology, Faculty of Medicine, Babol University of Medical Sciences, Babol, Iran E-mail: mehrdad.md69@gmail.com

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INTRODUCTION

Pseudomonas aeruginosa is one of the most opportunistic pathogen involved in respiratory tract infection in cystic fibrosis (CF) patients (1). It is commonly associated with chronic lung infection following that respiratory failure, decline in lung function, and finally increased morbidity and mortality (2). CF is accounted as a human genetic disorder caused by mutations in the CF-transmembrane conductance regulator. After colonization of bacteria, the main defense mechanisms of lung tissue against those are mucociliary clearance, polymorphonuclear neutrophil (3) which are poorly effective under conditions of increased viscosity and osmolarity (4). These viscosity and osmolarity is caused by bacterial infection especially *P. aeruginosa* infection. According to previous reports, *P. aeruginosa* strains may be acquired from several sources such as the environmental source, and person-to-person transmission in CF patients (5). In recent years, the cross-infection and epidemic strains of *P. aeruginosa* have been reported in different countries such as Iran, United Kingdom, Germany, Canada, United States and Australia (6-14).

To control and prevent *P. aeruginosa* infections among CF patients, high-dose antibiotic therapy is necessary to eradicate *P. aeruginosa* from the lower respiratory tract during the early stage of infection (15). However, treatment of infections caused by *P. aeruginosa* is of increasing concern and currently considered as one of the major problems in the healthcare setting worldwide (5). Although aggressive antibiotic therapy reduce the bacterial burden, the elimination of chronic *P. aeruginosa* infections usually fail and is extremely difficult (16).

A reason for the dissemination of antibiotic resistance in CF patients is the spread of multidrug resistant (MDR) clones. The report MDR isolates returns to 1996 where Liverpool epidemic strain (LES) described for the first time. One of the important complications of CF patient is the use of an inappropriate antimicrobial agent and the subsequent emergence of resistant strain has been confirmed in several studies (17). *P. aeruginosa* possesses acquired and intrinsic antibiotic resistance to a broad spectrum of antimicrobials, such as β-lactams. Usually, antimicrobial resistance of *P. aeruginosa* isolates is due to several mechanism such as metallo-b-lactamases (MBLs), extendedspectrum-b-lactamases (ESBLs) and aminoglycoside modifying enzymes (AMEs) (18, 19). Therefore, accurate and updated information investigating the antibiotic resistance patterns of *P. aeruginosa* in CF patients can help to clarify and the development of national policies to control of these in each country. Although antibiotic susceptibility patterns of *P. aeruginosa* isolated from CF patients have been stated in some studies in different parts of Iran, a comprehensive analysis of these data is needed. Thus, the present study aimed to assist the antibiotic susceptibility pattern of *P. aeruginosa* isolated from CF patients in Iran using a systematic review and meta-analysis.

METHODS

Search strategies

A systematic review was performed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines using a multiple of electronic databases including Web of Science, PubMed, Embase, Scopus, and Google Scholar from the beginning to end of July 2019 to find published studies from the Iran.

The keywords search was conducted in the title or abstract or within the full text of the articles. The Medical Subject Headings (MeSH), Non-MeSH terms and keywords including "*Pseudomonas aeruginosa"* OR "*P. aeruginosa*" AND "Cystic fibrosis" OR "CF" AND "Antibiotic resistance "OR "Antibiotic susceptibility pattern" AND "Iran" were searched in the titles, abstracts and keywords fields.

Selection criteria

Two reviewers independently checked and screened the results of search in the databases with the related keywords and analyzed the titles, abstracts and full texts to apply eligibility for inclusion according to inclusion criteria, and discrepancies were resolved by consensus. The searches were limited to articles published in English or Persian language with English available abstract. Also, the study must be limited to cross-sectional studies which indexed in the Web of Science or PubMed or Scopus and reported the prevalence of antibiotic resistance among *P. aeruginosa* strains isolated from Iranian CF patients. In addition, review articles, case reports, congress abstracts, duplicate reports and studies which the results of antibiotic resistance pattern was unclear in them were excluded. Moreover, the references lists of investigated studies were checked.

Quality assessment and data extraction

The quality assessment of the study was also judged independently by two authors using a checklist provided by the Joanna Briggs Institute (JBI) and disagreements were resolved by consensus. Items related to title and abstract, introduction, methods, results, discussion, and other data were assessment and a score was assigned to each item. The following data were extracted from all selected studies by two researchers: authors' names, publication time, performed time, the location of the study, sample size, source of isolation, and antibiotic resistance pattern of *P. aeruginosa.*

Statistical analysis

Meta-analysis was performed using Comprehensive Meta-Analysis (CMA) software version 2.2 (Biostat, Englewood, NJ). The pooled prevalence of antibiotic resistance pattern of *P. aeruginosa*, with 95% confidence intervals (95%CI) was estimate by the random-effects model. Statistical heterogeneity groups were calculated using Cochrane Q-test and I-squared (I^2) index. The possibility of publication bias was checked by Egger's weighted regression test in combination with a visual funnel plot. A *P* value <0.05 was considered as an indication of a statistically significant publication bias.

RESULTS

Literature search

A total of 85 articles were collected from aimed databases. As shown in Figure 1, after screening the titles, abstracts and full texts of the articles, and removing duplicates and non-relevant studies, seven eligible articles were selected for the meta-analysis (6, 20-25). The characteristics of seven eligible studies are accessible in Table 1. Included studies were reported from North (Tehran), Central (Isfahan), and Northeast (Mashhad) of Iran.

Table 1: Characteristics of studies included in the meta-analysis

Study	Publication Year	Years of Study	Location	Source of sample	References
Eftekhar	2003	-	Tehran	Sputum	[30]
Khodadad	2006	-	Tehran	Sputum or pharyngeal swab	[21]
Eftekhar	2009	2004-2005	Tehran	Sputum	[22]
Khalilzadeh	2012	2006-2010	Tehran	Sputum	[23]
Fazeli	2013	2003-2008	Isfahan	Sputum	[24]
Nobandegani	2016	2011-2012	Tehran	Sputum	[6]
Sharifi	2018	2016-2017	Mashhad	-	[25]

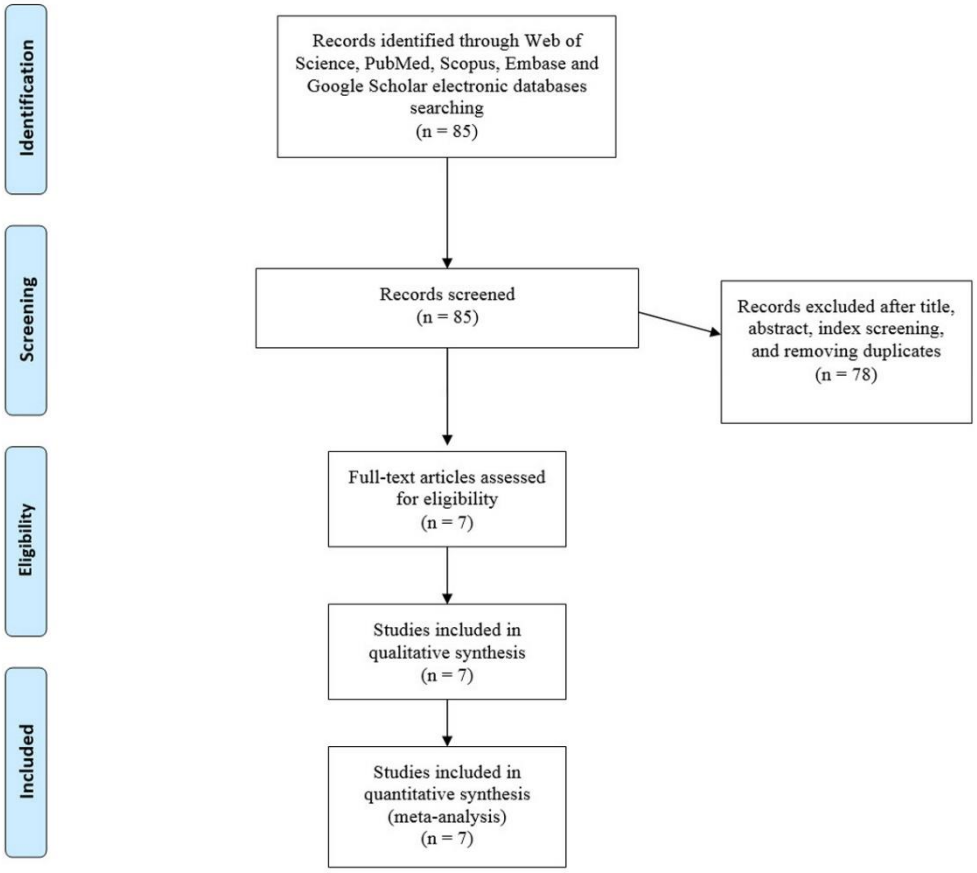

Figure 1. Flow chart of study selection for inclusion in the systematic review

Characteristics of P. aeruginosa antibiotic resistance

Finally, seven studies assessed antibiotic resistance pattern of *P. aeruginosa* in CF patients. These studies used disk agar diffusion methods for antimicrobial susceptibility testing on *P. aeruginosa* isolates according to Clinical and Laboratory Standards Institute (CLSI) guidelines. According to antibiotic resistance pattern, antibiotic resistance rate to the inhibition of cell wall synthesis agents were 34.7% (95% CI: 11.9–67.6%) for ceftazidime, 17.6% (95% CI: 9.6–33.9%) for imipenem, 13.6% (95% CI: 7.9–22.5%) for piperacillin and 7.3% (95% CI: 1.8–25.4%) for piperacillin-tazobactam. Antibiotic resistance rates to aminoglycoside antibiotics were 24.3% (95% CI: 10.6–46.4%) to gentamicin, 16.5% (95% CI: 7.1–33.9%) to amikacin, and 13.7% (95% CI: 5.7–29.5%) to tobramycin.

Antibiotic resistance rates to nucleic acid synthesis inhibitors was 20.4% (95% CI: 9.2–39.1%) to ciprofloxacin. On the other hand, piperacillin-tazobactam had the lowest resistance rate at 7.3% (95% CI: 1.8–25.4%), while ceftazidime had the highest resistance rate at 40.2% (95% CI: 14–73.6%). The full results of pooled prevalence and heterogeneity analysis of antibiotic resistance in *P. aeruginosa* had been shown in Table 2. According to heterogeneity test, among seven studies, there was a significant heterogeneity against amikacin, imipenem and ceftazidim. In addition, the funnel plot showed no evidence of strong publication bias and confirmed by the results of Egger's weighted regression tests (Figure 2,3).

Table 2: The pooled prevalence of antibiotic resistances among *P. aeruginosa* isolates

Subgroup	Sample size P. aeruginosa	Penicillins	β-Lactam Combination agents	Cephalosporins	Carbapenem	Fluoroquinolone	Aminoglycosides		
		Piperacillin	Piperacillin-Tazobactam	Ceftazidime	Imipenem	Ciprofloxacin	Gentamicin	Amikacin	Tobramycin
Eftekhar (2003)	21	4	4	3	0	2	8	4	3
Khodadad (2006)	13	-	-	1	-	5	11	4	-
Eftekhar (2009)	31	1	-	28	22	0	2	1	0
Khalilzadeh (2012)	10	-	-	3	-	7	-	5	-
Fazeli (2013)	21	4	-	18	-	3	2	2	-
Nobandegani (2016)	52	6	2	10	3	5	9		10
Sharifi (2018)	21	-	0	2	7	6	4	1	-
Prevalence of resistance (95% CI)		13.6 (7.9-22.5)	7.3 (1.8-25.4)	34.7 (11.9-67.6)	20.6 (3.8-63.0)	20.4 (9.2-39.1)	24.3 (10.6-46.4)	16.5 (7.1-33.9)	13.7 (5.7-29.5)
Heterogeneity test	I^2	15.9	60.1	88.9	90.8	73.5	79.2	62.9	42.6%
	Q	3.565	5.010	54.021	32.645	22.670	24.052	13.480	3.482
	P	0.312	0.082	<0.001	<0.001	0.001	<0.001	0.019	0.175
Egger's test	t	0.98	1.11	0.19	1.48	0.49	0.21	2.39	4.24
	P	0.43	0.47	0.86	0.28	0.64	0.84	0.08	0.15

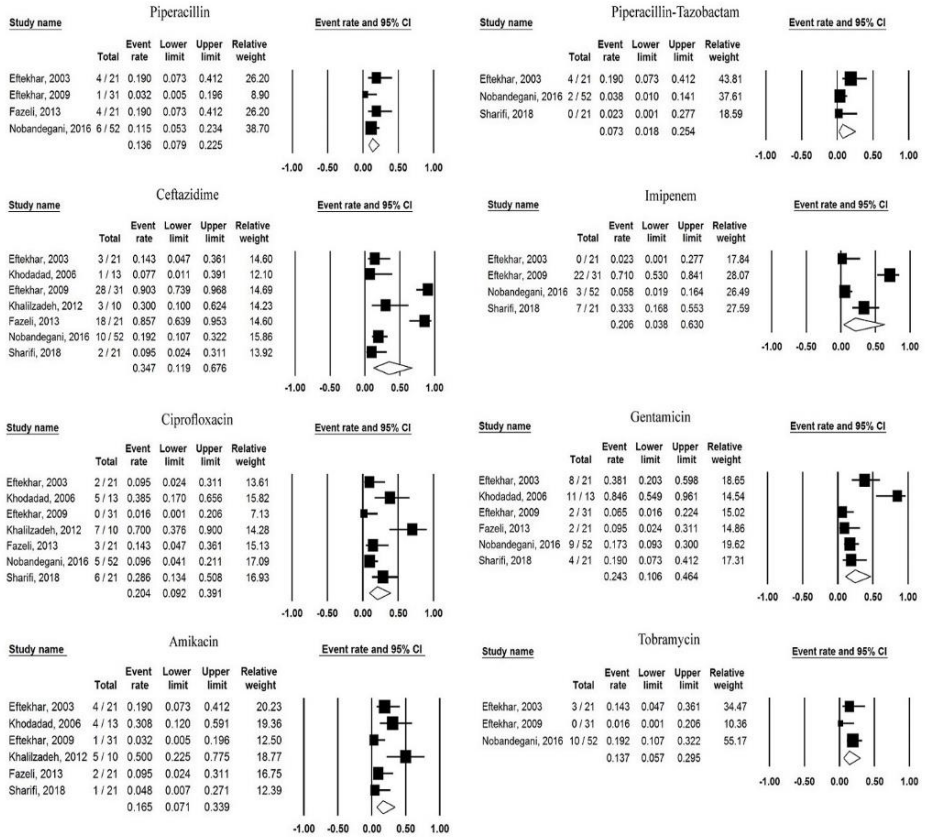

Figure 2. Forest plots of the pooled prevalence of antibiotic resistances

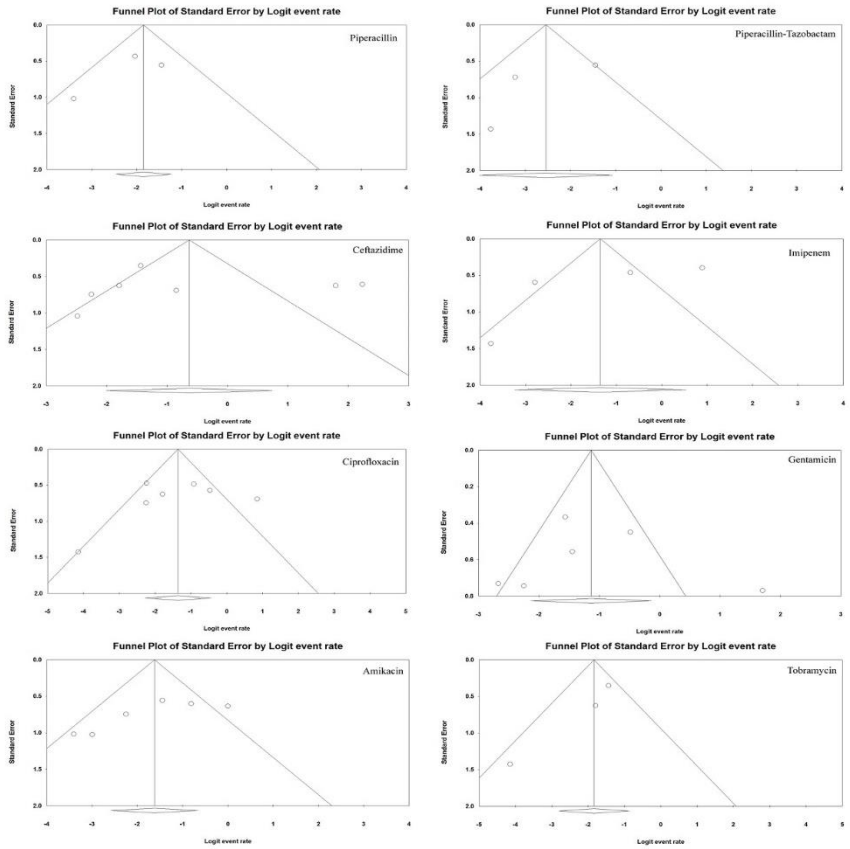

Figure 3: Funnel plots of publication bias for the included studies

DISCUSSION

The emergence of *P. aeruginosa* as the most common pathogen in respiratory infection associated with CF remains the leading cause of morbidity and mortality in these patients. In CF population, the respiratory chronic infection is related to failure in lung function (26). Due to the significant presence of this opportunistic pathogen, antibiotic therapy is a basis of CF treatment, and these patients are exposed to multiple options of a range of antibiotics over long periods and following that the increase of antibiotic resistance (27). Although the administration of antibiotic prophylaxis is an effective option for decreasing the prevalence of respiratory infection in CF patients, resistance to used antibiotics is a significant and concerning problem in a medical setting and is a common complication in CF patients for the development of recurrent respiratory infections (28, 29). Therefore, in this study, we investigated antibiotic susceptibility patterns within a collection of *P. aeruginosa* isolates from CF patients in Iran, which provides a broader vision than the previous surveys, which have focused on a single study or center. According to the antibiotic resistance pattern, piperacillin-tazobactam had the lowest resistance rate while ceftazidime had the highest resistance rate followed by gentamicin.

In spite of the good therapeutic effects of carbapenems such as imipenem, aminoglycoside such as amikacin and fluoroquinolones against *P. aeruginosa*, in recent decades, resistance to these drugs has emerged [48]. Based on our results, the resistance rate to imipenem and amikacin had different range and the pooled prevalence were 20.6% and 16.5%, respectively and both agents had also significant heterogeneity (6, 22, 25, 30). Moreover, the resistance rate to cephalosporins including ceftazidime (40.2%) was high and can be a therapeutic concern in CF patients.

Therefore, bearing findings in this population, physicians should be caution in prescribing these drugs. However, we observed that resistance to imipenem, amikacin, ciprofloxacin, and gentamycin was relatively at the low level for *P. aeruginosa* isolates which suggest that these agents may be the drug of choice in this population.

However, the antibiotic resistance rate of *P. aeruginosa* to different antibiotic classes was variable in Iran and worldwide (31-33) . In this regards, in a meta-analysis conducted by vaez et al in Iran, the antibiotic resistance patterns of *P. aeruginosa* among clinical isolates were investigated. The results of this analysis showed the highest resistance rate was against ceftazidime (50%) and amikacin (50%) followed by piperacillin/tazobactam (49%) while, the lowest rate was against imipenem (31%) (32). The result was relatively different from our results except about ceftazidime which in our results had also the highest resistance rate. Furthermore, Ding et al reported the prevalence of antimicrobial-resistant *P. aeruginosa* in patients with pneumonia. In this meta-analysis, *P. aeruginosa* revealed a high level of resistance to gentamicin and a low level of resistance to amikacin that is partially in agreement with our reports (34). According to reports from different countries, the results of the resistance rate of piperacillin; and piperacillin-tazobactam are controversial and in contrast to ours (35, 36). For instance, Mustafa et al investigated the antimicrobial susceptibility of *P. aeruginosa* isolated from CF patients in the UK. Their results showed 76% and 71% of isolates were resistance against piperacillin; and piperacillin-tazobactam, respectively, which is in contrast to ours (17). Also, Acar et al studied the prevalence of antimicrobial resistance of *P. aeruginosa* among clinical isolates over the past 10 years in Turkey. This meta-analysis revealed that the pooled resistance rates of piperacillin and piperacillin-tazobactam were to be 49.8% and 44.9%, respectively, which is higher when compared with our studies (33). The reasons for the discrepancy in antibiotic resistance rate could be related to the differences in source of the isolates, the characteristics of the studied population, infection control polices, the in the antibiotic prescription pattern and geographical distribution.

The present study had some limitation which must be acknowledged. Due to lack of sufficient studies in CF patients, results mostly originated from major cities and results may not reveal the actual antibiotic resistance of *P. aeruginosa* among Iranian CF patients. Moreover, a same antibiotic resistance pattern according to was not used in all studies.

In conclusion, a high level of antibiotic resistance against ceftazidime and gentamicin in our results is an alarming and may be due to severe and complication caused by *P. aeruginosa* infections in CF patients. Moreover, piperacillin-tazobactam, tobramycin and amikacin are the most suitable antibiotics for the treatment of respiratory infections in our population. However, administration of control strategies and surveillance programs highly recommended.

Conflict of interest

No conflict of interest was declared by the authors.

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