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

**ABSTRACT**

**Objective:** *Pseudomonas aeruginosa* is one of the most opportunistic pathogens 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

**ÖZET**

**Amaç:** *Pseudomonas aeruginosa*, kistik fibrozis (KF) hastalarında solunum yolu enfeksiyonuna karşı en fırsatçı patojenlerden biridir. Bu çalışma, sistematik bir incelleme ve meta-analiz kullanarak İranlı KF hastalarından izol edilen *P. aeruginosa* suşlarının antibiyotik direnç paternini değerlendirdi. Dahil edilen çalışmalar Iran’ın Kuzeydoğu (Meshed) bölgesindeki rapor edilmiştir. Piperaslin-tazobaktam %7.3 (%95 GA: %1.8–25.4%) ile en düşük direnç oranına sahipti, seftazidim %34.7 (%95 GA: %11.9–67.6%) ile en yüksek direnç oranına sahipti.

**Sonuç:** Sonuçlarımızda seftazidim ve gentamizin’i karşı yüksek düzeyde antibiyotik direnci endişe vericidir ve KF hastalarında *P. aeruginosa* enfeksiyonlarının neden olduğu ciddi ve kompleksiyona bağlı olabilir. Ayrıca piperaslin-tazobaktam, tobramisin ve amikasin popüloşonumuzdaki solunum yolu enfeksiyonlarının tedavisini için en uygun antibiyotiklerdir. Ancak, kontrol stratejilerinin ve gözlem programlarının yönetimini şiddetle tavsiye edilir.

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

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INTRODUCTION

Pseudomonas aeruginosa is one of the most opportunistic pathogens 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-β-lactamases (MBLs), extended-spectrum-β-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 assessed 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 (I²) 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.

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

| Subgroup               | Sample size | Penicillins | β-Lactam Combination agents | Cephalosporins | Carbapenem | Fluoroquinolone | Aminoglycosides |
|------------------------|-------------|-------------|-----------------------------|----------------|------------|----------------|-----------------|
|                        |             | P. aeruginosa | 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              | -              | 1           | 0         |
| 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 (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** |             |             | 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**       |             |             | 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      |
| Study name          | P. aeruginosa | Event rate and 95% CI | Study name          | P. aeruginosa-Tasabaxin | Event rate and 95% CI |
|--------------------|--------------|-----------------------|--------------------|-----------------------|-----------------------|
|                    | Total Event  | Lower limit           | Upper limit        | Weight                | Total Event  | Lower limit           | Upper limit        | Weight                |
| Ethelbar, 2003     | 4/21         | 0.0643                | 0.073              | 0.412                | 0.06           | 0.073              | 0.412               | 0.061                |
| Ethelbar, 2009     | 1/21         | 0.0622                | 0.073              | 0.412                | 0.06           | 0.073              | 0.412               | 0.061                |
| Fazl, 2013         | 2/21         | 0.0643                | 0.073              | 0.412                | 0.06           | 0.073              | 0.412               | 0.061                |
| Nadaregani, 2016   | 6/82         | 0.0711                | 0.073              | 0.412                | 0.06           | 0.073              | 0.412               | 0.061                |

| Study name          | Ceftaroline  | Event rate and 95% CI | Study name          | Imipenem               | Event rate and 95% CI |
|--------------------|--------------|-----------------------|--------------------|-----------------------|-----------------------|
|                    | Total Event  | Lower limit           | Upper limit        | Weight                | Total Event  | Lower limit           | Upper limit        | Weight                |
| Ethelbar, 2003     | 2/21         | 0.0831                | 0.0831             | 0.0831                | Ethelbar, 2003 | 2/21         | 0.0831                | 0.0831             | 0.0831                |
| Khabbiab, 2008     | 1/12         | 0.0831                | 0.0831             | 0.0831                | Ethelbar, 2009 | 3/25         | 0.0831                | 0.0831             | 0.0831                |
| Ethelbar, 2009     | 28/105       | 0.0831                | 0.0831             | 0.0831                | Khabbiab, 2012 | 0/10        | 0.0831                | 0.0831             | 0.0831                |
| Farzi, 2008        | 1/7          | 0.0831                | 0.0831             | 0.0831                | Farzi, 2012   | 0/7          | 0.0831                | 0.0831             | 0.0831                |
| Nadaregani, 2016   | 0/25         | 0.0831                | 0.0831             | 0.0831                | Shahri, 2018  | 0/25         | 0.0831                | 0.0831             | 0.0831                |
| Shahri, 2018       | 2/25         | 0.0831                | 0.0831             | 0.0831                | Shahri, 2018  | 2/25         | 0.0831                | 0.0831             | 0.0831                |

| Study name          | Ciprofloxacin | Event rate and 95% CI | Study name          | Gentamicin        | Event rate and 95% CI |
|--------------------|--------------|-----------------------|--------------------|------------------|-----------------------|
|                    | Total Event  | Lower limit           | Upper limit        | Weight            | Total Event  | Lower limit           | Upper limit        | Weight            |
| Ethelbar, 2003     | 2/21         | 0.0831                | 0.0831             | 0.0831            | Ethelbar, 2002 | 8/21         | 0.0831                | 0.0831             | 0.0831            |
| Khabbiab, 2008     | 5/15         | 0.0831                | 0.0831             | 0.0831            | Ethelbar, 2008 | 3/21         | 0.0831                | 0.0831             | 0.0831            |
| Ethelbar, 2009     | 20/105       | 0.0831                | 0.0831             | 0.0831            | Khabbiab, 2012 | 7/10         | 0.0831                | 0.0831             | 0.0831            |
| Fazl, 2013         | 3/21         | 0.0831                | 0.0831             | 0.0831            | Fazl, 2013    | 3/21         | 0.0831                | 0.0831             | 0.0831            |
| Nadaregani, 2016   | 10/50        | 0.0831                | 0.0831             | 0.0831            | Shahri, 2018  | 3/25         | 0.0831                | 0.0831             | 0.0831            |
| Shahri, 2018       | 4/25         | 0.0831                | 0.0831             | 0.0831            | Shahri, 2018  | 4/25         | 0.0831                | 0.0831             | 0.0831            |

| Study name          | Ampicillin   | Event rate and 95% CI | Study name          | Tobramycin        | Event rate and 95% CI |
|--------------------|--------------|-----------------------|--------------------|------------------|-----------------------|
|                    | Total Event  | Lower limit           | Upper limit        | Weight            | Total Event  | Lower limit           | Upper limit        | Weight            |
| Ethelbar, 2003     | 4/21         | 0.1031                | 0.1121             | 0.1211            | Ethelbar, 2003 | 0/21         | 0.0707                | 0.0707             | 0.0707            |
| Khabbiab, 2008     | 4/13         | 0.1031                | 0.1121             | 0.1211            | Ethelbar, 2009 | 2/21         | 0.0707                | 0.0707             | 0.0707            |
| Ethelbar, 2009     | 1/10         | 0.1031                | 0.1121             | 0.1211            | Khabbiab, 2012 | 2/10         | 0.1031                | 0.1121             | 0.1211            |
| Fazl, 2013         | 2/21         | 0.1031                | 0.1121             | 0.1211            | Fazl, 2013    | 2/21         | 0.1031                | 0.1121             | 0.1211            |
| Shahri, 2018       | 3/25         | 0.1031                | 0.1121             | 0.1211            | Shahri, 2018  | 3/25         | 0.1031                | 0.1121             | 0.1211            |

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

**Figure 3:** Funnel plots of publication bias for the included studies
The significant presence 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, 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 vaee 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.

Conflict of interest

No conflict of interest was declared by the authors.

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