Journal of Global Antimicrobial Resistance 18 (2019) 64–70

Contents lists available at ScienceDirect

Journal of Global Antimicrobial Resistance

journal homepage: www.elsevier.com/locate/jgar

# Pooled prevalence and trends of antimicrobial resistance in *Pseudomonas aeruginosa* clinical isolates over the past 10 years in Turkey: A meta-analysis

Ali Acar[a,*], Gökhan Karaahmetoğlu[b], Halis Akalın[c], Aybala F. Altay[a]

[a] Health Science University, Diskapi Yildirim Beyazit Education and Training Hospital, Department of Infectious Disease and Clinical Microbiology, Ankara, Turkey
[b] Ilker Çelikcan Physical Therapy Hospital, Department of Infectious Disease and Clinical Microbiology, Bursa, Turkey
[c] Uludağ University, Faculty of Medicine, Department of Infectious Disease and Clinical Microbiology, Bursa, Turkey

ARTICLE INFO

*Article history:*
Received 3 September 2018
Received in revised form 16 January 2019
Accepted 31 January 2019
Available online 10 February 2019

*Keywords:*
*Pseudomonas aeruginosa*
Antibiotic resistance
Meta-analysis
Turkey

ABSTRACT

*Objectives:* This meta-analysis aimed to evaluate the current prevalence and trends over the past 10 years of *Pseudomonas aeruginosa* (*P. aeruginosa*) antimicrobial resistance. Two researches independently searched two national (ULAKBİM, Türk Medline) and two international databases (PubMed, Web of Science) to identify studies on *P. aeruginosa* resistance to antimicrobials from 2007 to 2017.

*Methods:* Homogeneity across studies was assessed using Cochrane guidelines, and total variability due to between-study variations was reflected in the $I^2$ index. A random effects model was developed to estimate the antimicrobial resistance rates and their corresponding 95% CI. Pooled antibiotic resistance rates between 2007–2011 and 2012–2016 were compared to calculate the change in antibiotic resistance over time. Electronic searches with MeSH terms and text words identified 1017 papers. After applying exclusion and inclusion criteria, 45 articles were selected.

*Results:* Pooled resistance prevalence of *P. aeruginosa* to piperacillin-tazobactam, ceftazidime, cefepime, meropenem, imipenem, ciprofloxacin, gentamicin, amikacin, tobramycin and colistin were 33.9%, 38.6%, 35.6%, 30.1%, 28.0%, 30.7%, 28.2%, 17.8%, 15.7% and 2.2%, respectively. The resistance rates of piperacillin, piperacillin-tazobactam, imipenem, meropenem, amikacin and colistin significantly increased in the second 5 years ($P < 0.05$); however, gentamicin, tobramycin and ciprofloxacin resistance rates significantly decreased ($P < 0.05$). Comparing the resistance rates between the isolates of intensive care unit (ICU) patients and non-ICU patients, meropenem and piperacillin-tazobactam resistance in ICU isolates were significantly higher than non-ICU ($P < 0.05$).

*Conclusions:* These results suggest that antibiotic resistance is high in *P. aeruginosa* and the trends in antimicrobial resistance continue to increase, mainly in carbapenems and penicillins, in Turkey.


## 1. Introduction

*Pseudomonas aeruginosa* (*P. aeruginosa*) is a ubiquitous environmental bacterium, classified as an opportunistic pathogen, and remains a significant cause of morbidity and mortality in patients with underlying conditions such as an immunosuppression or chronic disease [1].

*P. aeruginosa* is among the top three pathogens that most commonly cause nosocomial infections in Turkey [2–4]. *P. aeruginosa* infections are becoming more difficult to treat because this bacterium is naturally resistant to many antibiotics and the number of multidrug and pandrug-resistant strains is increasing worldwide [5]. Antibiotic resistance rates vary, depending on: where the infection is acquired (nosocomial, community); the clinical sample in which bacteria are isolated; patient characteristics; and the antibiotic usage policy, which can differ by country, region and hospital. For this reason, a national database should be introduced where relevant data are reliably recorded using scientific methods. There is a need for a reliable and continuous surveillance system to better understand and respond to antimicrobial resistance patterns and key drivers. In Turkey, the following are major barriers to cumulative resistance data assessment deficiencies: capacities of some laboratories, local differences in methods of surveillance and microbiological

* Corresponding author.
*E-mail address:* dracarali@gmail.com (A. Acar).

https://doi.org/10.1016/j.jgar.2019.01.032

analyses, and gaps in surveillance practices. These barriers, which avoid the proper management of antibiotic resistance, can be overcome by standardising the data by meta-analysis. In this context, a meta-analysis was undertaken to determine the resistance profile and course of *P. aeruginosa* in Turkey.

In Turkey, there have been some meta-analyses undertaken to assess the cumulative resistance of *P. aeruginosa*, but they were studied on isolates from one system (e.g., urinary tract) or isolates from unidentified clinical samples [6]. In contrast to these studies, the current study analysed pooled prevalence of resistance in pseudomonas according to the source of pathogenic isolates; therefore, this study is the first meta-analysis to reveal the antibiotic resistance pattern of *P. aeruginosa* in Turkey. This meta-analysis aimed to provide a guide to the development of strategies for antimicrobial resistance, by showing the national dimension of change in the current resistance profile and resistance rates of *P. aeruginosa* isolates, and a high level of evidence for empirical antibiotic selection for clinicians.

## 2. Methods

This systemic review and meta-analysis was carried out in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [7].

### 2.1. Literature peer review

Two national (ULAKBİM and Türk Medline) and two international (PubMed and Web of Science) databases were searched for peer review. Search terms included "*Pseudomonas aeruginosa*" or "*Pseudomonas* spp." as the title word, in combination with "antibiotic resistance" or "antibiotic susceptibility" and "Turkey" or "Türkiye" including all possible combinations of these keywords. Additional articles were identified by manually searching the reference lists of included reviews.

### 2.2. Selection criteria

The inclusive selection criteria set out in Table 1 were applied for meta-analysis.

### 2.3. Review of the literature and data collection

The studies that corresponded to eligibility criteria were included in the meta-analysis (Fig. 1). Two independent reviewers (A.A. and G.K.) screened all publications for eligibility. The discrepancies between reviewers were resolved by discussions with a senior reviewer (H.A.). For each of the articles: year of publication, first author, name of the published journal and design of each of the studies were noted, as well as time interim, and cities or provinces where the studies had taken place. Type of clinical samples, source of infection (nosocomial or community), patients' hospitalisation status (intensive care unit, inpatient clinic or outpatient clinic), and methods used for determining the microorganisms, antibiotic susceptibility criteria and methods were also recorded. To homogenate the antibiotic resistance data, only the studies that provided the total number of isolates and the number of resistant isolates were included in the meta-analysis. Intermediate susceptible isolates were included in the resistant isolates group and the number and ratio of resistant isolates were recalculated. According to Cochrane guideline recommendations, power and heterogeneity of each of the studies were assessed and pooled prevalence of resistance was calculated [8].

To minimise bias, the studies having less than 20 isolates were excluded [9]. Studies that did not specify from which clinical specimens the isolates were obtained were excluded. In addition, the studies reporting about the sources of clinical isolates without any distinction were also excluded to avoid probable bias because antibiotic susceptibility profiles could significantly differ due to origin of clinical sample. Where a study reported results for years separately, these were regarded as separate reports (e.g., for a study performed between 2007–2010, susceptibility analyses of each of the years 2007, 2008, 2009 and 2010 were reported as a separate study). On the other hand, studies in which the susceptibility of isolates were provided cumulatively (e.g., susceptibility profiles of *P. aeruginosa* strains isolated between 2013 and 2016) were recorded as a single study. Studies in the meta-analysis were separated into two groups based on the year of publication. Pooled antibiotic resistance rates between 2007–2011 and 2012–2016 were compared to calculate the change in antibiotic resistance over time.

Subgroup analyses of the antibiotic susceptibility profiles of the isolates were performed according to: year of isolation, clinical specimen of the isolates (bacteraemia or sepsis, pneumonia, skin-soft tissue infection, urinary), units (intensive care unit, inpatient clinic, outpatient clinic), and geographic region. Antipseudomonal antibiotics, which the Clinical and Laboratory Standards Institute (CLSI) and/or European Committee on Antimicrobial Susceptibility Testing (EUCAST) recommends to report, were chosen for antibiotic resistance investigation in the scope of meta-analysis: piperacillin (PIP), piperacillin-tazobactam (TZP), cefepime (FEB), ceftazidime (CAZ), aztreonam (ATM), imipenem (IPM), meropenem (MEM), gentamicin (GEN), tobramycin (TOB), amikacin (AMK), netilmicin (NET), ciprofloxacin (CIP), levofloxacin (LVX), colistin (CST) [9,10].

### 2.4. Statistical analysis

A statistical analysis of the data that met the inclusion criteria was carried out using SPSS-23.0 and MedCalc software. A random effects model was developed to estimate the antimicrobial resistance rates and their corresponding 95% confidence intervals. The pooled prevalence of antibiotic resistance for each antibiotic was analysed by two periods (2007–2011 and 2012–2016). In

**Table 1**
Selection criteria for meta-analysis.

| | |
|---|---|
| 1 | *Pseudomonas aeruginosa* strains isolated from patients referred to Turkish hospitals. |
| 2 | Studies included strains assigned for analysis between 1 January 2007 and 31 December 2016. |
| 3 | Specification of the clinical samples from which *Pseudomonas aeruginosa* were isolated. |
| 4 | Tested on more than 20 isolates. |
| 5 | Original full text research articles published in Turkish or English. |
| 6 | Reported methods used for susceptibility analysis (disc diffusion, Etest, Commercial microdilution, agar or broth dilution, etc.). |
| 7 | Used NCCLS and/or EUCAST breakpoints for determining antibiotic sensitivity and resistance. |
| 8 | Susceptibility analyses included at least three of the major antipseudomonal antibiotic groups being used in treatment (carbapenems, quinolones, aminoglycosides, antipseudomonal penicillins, cefalosporins, aztreonam). |
| 9 | Statistical data were verified in terms of count and rate. |

EUCAST, European Committee on Antimicrobial Susceptibility Testing; NCCLS, National Committee for Clinical Laboratory Standards.

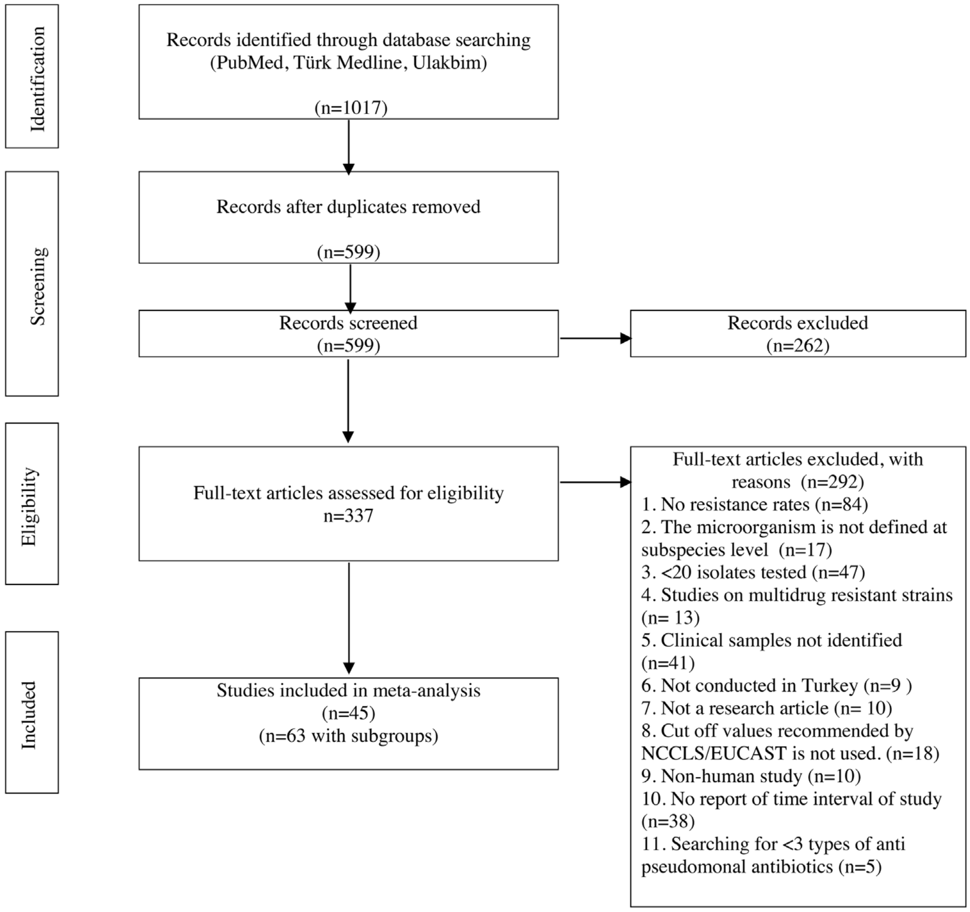


**Fig. 1.** Flow diagram of study inclusion.
EUCAST, European Committee on Antimicrobial Susceptibility Testing; NCCLS, National Committee for Clinical Laboratory Standards.

addition, subgroup analyses for the differences in drug resistance prevalence of *P. aeruginosa* were performed using pre-defined variables, including: clinical samples, clinical department (intensive care or clinics), and the geographical region of the country.

Homogeneity across the studies was assessed using Cochrane guidelines, and total variability due to between-study variation was reflected in the $I^2$ index. Regarding Cochrane recommendations, heterogeneity was determined as low (25%), intermediate (50%) or high (75%) measured with $I^2$ value [8]. All tests were two-sided with a significance level of 0.05.

## 3. Results

A total of 1017 articles was found by searching in databases using keyword combinations. Following the application of the eligibility criteria, 45 articles were included in the meta-analysis (Fig. 1). Because resistance data were subanalysed according to the year of the study, clinical sample type, and patient profile (inpatient/outpatient), these subanalyses were accepted as separate studies (e.g., the resistance rates of blood and urine isolates that were separately recorded in the same study were accepted as two independent studies); 63 studies were reviewed. The properties and references of the articles included in the meta-analysis are shown in Table S (Supplementary Material).

The 10-year (between 2007–2016) pooled resistance rates of *P. aeruginosa* isolates were highest in aztreonam (57.5%), piperacillin (40.5%), ceftazidime (38.6%), cefepime (35.6%) and piperacillin-tazobactam (33.9%). The change in pooled resistance rates between the first 5 years (2007–2011) and the second 5-year (2012–2016) period is shown in Table 2. In the second 5 years, the rates of resistance to piperacillin, piperacillin-tazobactam, imipenem, meropenem, amikacin and colistin increased, which were found to be statistically significant ($P < 0.05$). Conversely, pooled resistance rates to gentamicin, tobramycin and ciprofloxacin were significantly decreased in the second 5-year period ($P < 0.05$).

When the studies were classified according to the source of the isolates, the articles were searched in which 20 blood, 13 urine, 17 lower respiratory tracts, 12 skin soft tissues (wound) and one cerebrospinal fluid (CSF) specimen were studied. Resistance rates regarding clinical samples are shown in Table 3. When resistance rates were compared according to geographical regions, significant differences were found for ceftazidime and aztreonam (Table 4). Ceftazidime resistance was higher in the Aegean region when compared with the Mediterranean, central Anatolian and Black Sea regions. Similar findings were found when the south-eastern Anatolian region was compared with the central Anatolian and Black Sea regions ($P < 0.05$).

When the resistance rates of isolates of ICU and non-ICU patients were compared, meropenem and piperacillin-tazobactam resistance rates were significantly higher ($P < 0.05$) for ICU isolates (Table 5).

## 4. Discussion

This meta-analysis found the pooled resistance rates of piperacillin and piperacillin-tazobactam in the last 10 years (2006–2017) to be 40.5% and 33.9%, respectively. The resistance rates were seen to have significantly increased in the last 5 years

**Table 2**
Pooled mean prevalence and temporal differences of antimicrobial resistance of *P. aeruginosa*, 2007–2016.

| Antimicrobial agents | 2007–2016 | | | | | 2007–2011 | | | | | 2012–2016 | | | | | $P^*$ | 95% CI |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Study (n) | Sample size (n) | Resistance (%) | 95% CI | $I^2$ (%) | Study (n) | Sample size (n) | Resistance (%) | 95% CI | $I^2$ (%) | Study (n) | Sample size (n) | Resistance (%) | 95% CI | $I^2$ (%) | | |
| Piperacillin | 11 | 1612 | 40.5 | 22.1–60.4 | 98.4 | 7 | 862 | 31.8 | 13.3–53.9 | 97.7 | 7 | 750 | 49.8 | 22.5–77.2 | 98.3 | **0.0001** | 13.2–22.7 |
| Piperacillin-tazobactam | 33 | 3942 | 33.9 | 25.4–42.9 | 97.1 | 23 | 2262 | 27.4 | 19.4–36.3 | 95.2 | 16 | 1680 | 44.9 | 29.0–61.5 | 97.8 | **0.0001** | 14.5–20.5 |
| Ceftazidime | 44 | 5520 | 38.6 | 30.9–46.5 | 97.2 | 30 | 2792 | 38.4 | 95.3–96.9 | 96.2 | 22 | 2778 | 38.0 | 27.5–49.5 | 97.0 | 0.08 | −2.2–2.9 |
| Cefepime | 32 | 3413 | 35.6 | 29.0–42.4 | 93.9 | 21 | 1857 | 35.0 | 26.5–44.1 | 93.9 | 16 | 1556 | 34.9 | 25.2–43.4 | 92.6 | 0.95 | −3.1–3.3 |
| Cefoperazone-sulbactam | 17 | 1613 | 32.3 | 19.1–47.2 | 97.3 | 10 | 878 | 32.3 | 21.9–43.6 | 92.0 | 8 | 735 | 32.4 | 9.1–61.8 | 98.3 | 0.97 | −4.5–4.7 |
| Imipenem | 44 | 4719 | 28.0 | 23.6–32.7 | 91.5 | 30 | 2781 | 25.6 | 21.5–30.0 | 85.0 | 21 | 1938 | 32.9 | 23.7–42.9 | 95.0 | **0.0001** | 4.7–10.0 |
| Meropenem | 29 | 2798 | 30.1 | 23.9–36.7 | 92.7 | 17 | 1624 | 25.8 | 18.2–34.1 | 92.7 | 17 | 1174 | 36.3 | 25.8–47.4 | 93.2 | **0.0001** | 7.2–14.2 |
| Aztreonam | 12 | 1183 | 57.5 | 41.8–72.5 | 96.6 | 11 | 1009 | 55.4 | 43.7–66.8 | 92.9 | 3 | 174 | 61.8 | 5.6–100 | 98.8 | 0.12 | −1.6–14.0 |
| Gentamicin | 36 | 4398 | 28.2 | 23.4–33.3 | 92.0 | 22 | 1939 | 30.6 | 24.5–37.1 | 89.0 | 20 | 2459 | 25.5 | 18.4–33.4 | 94.0 | **0.0002** | 2.4–7.8 |
| Amikacin | 44 | 5610 | 17.8 | 13.9–22.2 | 93.7 | 29 | 2725 | 17.0 | 13.4–20.9 | 85.3 | 22 | 2875 | 19.7 | 12.7–28.0 | 96.0 | **0.01** | 0.7–4.7 |
| Tobramycin | 8 | 1124 | 15.7 | 9.2–23.4 | 89.3 | 5 | 561 | 20.2 | 8.6–35.0 | 93.6 | 6 | 563 | 11.4 | 8.9–14.3 | 25.8 | **0.0001** | 4.6–13.0 |
| Netilmicin | 8 | 941 | 27.9 | 17.6–39.5 | 92.7 | 5 | 570 | 29.5 | 17.8–42.8 | 90.6 | 3 | 371 | 24.4 | 5.3–51.6 | 94.8 | 0.09 | −0.8–10.7 |
| Ciprofloxacin | 40 | 4931 | 30.7 | 24.6–37.2 | 95.6 | 25 | 2208 | 33.6 | 26.1–41.5 | 93.4 | 22 | 2723 | 25.9 | 18.2–34.6 | 95.4 | **0.0001** | 5.1–10.3 |
| Levofloxacin | 14 | 1102 | 32.3 | 25.8–39.1 | 81.3 | 6 | 427 | 33.7 | 24.8–43.3 | 75.8 | 10 | 675 | 31.4 | 22.9–40.6 | 81.5 | 0.43 | −3.3–8.0 |
| Colistin | 16 | 1257 | 2.2 | 1.5–3.1 | 40.1 | 6 | 419 | 0.3 | 0.0–1.4 | 0.0 | 12 | 838 | 3.3 | 2.2–4.7 | 0.0 | **0.0008** | 1.5–4.5 |

* Comparison of antibiotic resistance prevalence between 2007–2011 and 2012–2016.

(2011–2017): from 31.8% to 49.8% for piperacillin and from 27.4% to 44.9% for piperacillin-tazobactam ($P$ = 0.0001 for each of the agents). In multicentre studies from Turkey, piperacillin-tazobactam resistance was found in ranges from 18.1 to 22.7% [11,12]. In a review of antibiotic resistance of *P. aeruginosa* from 2003 to 2013 in Turkey, the cumulative resistance of piperacillin-tazobactam was 34.1% and decreased to 28.9% in last 5 years [6]. The pooled resistance rate of piperacillin-tazobactam in the current meta-analysis was significantly higher when compared with multicentre studies in Turkey, and the increase in resistance rates was prominent.

In the current meta-analysis, the highest resistance to piperacillin-tazobactam was detected in skin-soft tissue isolates (46.1%) followed by respiratory (36.4%), urine (27.1%) and blood isolates (26.7%). In contrast, in the International nosocomial infection control consortium (INICC) report, including data from Turkey, the highest resistance to piperacillin-tazobactam was found in bloodstream infections (37%) [13]. It is surprising that piperacillin-tazobactam resistance was lowest in blood stream infections in the current meta-analysis. This could be explained by the high heterogeneity among studies included in this research. Besides, most of the wound isolates were from infected burn wounds or surgical site infections and this could lead to high resistance rates.

Pooled prevalence resistance to cefepime, ceftazidime, and cefoperazone-sulbactam was 35.6%, 38.6% and 32.3%, respectively. There were no significant changes for these three agents over the years. The highest resistance rates were at wound infection and lower respiratory tract isolates. In Turkey, resistance to cefepime and ceftazidime was found to be 32.9% and 25.3%, respectively, in a multicentre study, while it was found to be 41.4% and 43.9%, respectively, in a review covering the years 2003–2013 [6,11]. Resistance to antipseudomonal cephalosporin has been stable for the last 10 years.

Carbapenems are one of the most preferred and most effective antibiotic groups for the treatment of pseudomonas infections. However, resistance development during carbapenem treatment is being reported and imipenem is the riskiest agent in this respect [14].

Pooled prevalence of resistance to meropenem was 30.1% and resistance to imipenem was 28.0% in the current meta-analysis. These rates were 25.8% and 25.6%, respectively, in the first 5 years and they significantly increased in the second 5 years to 36.3% and 32.9%, respectively ($P$ = 0.0001). Resistance to meropenem was highest in respiratory tract isolates, with a rate of 33.4%. In a multicentre study and a meta-analysis conducted in Turkey, resistance to imipenem was reported at rates of 28.9% and 29.4%, respectively [6,11]. These results are consistent with the first 5 years of results in the current data. However, the current meta-analysis shows that there is a tendency towards increasing resistance rates against imipenem in Turkey.

Risk factors for carbapenem resistance have been well studied, including: prior carbapenem use, being bedridden or in the ICU, a history of *P. aeruginosa* infection or colonisation within the previous year, length of hospital stay, and long-term catheterisation [15]. In multicentre studies investigating the use of antibiotics in hospitalised patients in Turkey, it was reported that carbapenems were the most commonly used antibiotics [16,17]. Inappropriate use of antibiotics is one of the major reasons that cause antibiotic resistance in Turkey. In a multicentre meta-analysis, inappropriate antibiotic use in a hospital was found to be 68% [18]. Carbapenems are the leading antimicrobial agents that are overused and misused in Turkey [19]. The upward trend in carbapenem use as a first choice, as well as its widespread inappropriate use, may explain the increase in carbapenem resistance, which was found in the current meta-analysis.

**Table 3**
Pooled antibiotic resistance rate of *P. aeruginosa* according to the source of isolates.

| Antimicrobial agents | Blood | | | | | Urine | | | | | Respiratory tract specimen | | | | | Wound | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Study (n) | Sample size (n) | Resistance (%) | 95%CI (%) | $I^2$ (%) | Study size (n) | Sample (n) | Resistance % | 95%CI % | $I^2$ (%) | Study (n) | Sample size (n) | Resistance % | 95%CI % | $I^2$ (%) | Study (n) | Sample size (n) | Resistance % | 95%CI % | $I^2$ (%) |
| Piperacillin | 2 | 177 | 56.7 | 4.5–99.4 | 98.7 | 1 | Insufficient data | | | | 3 | 676 | 27.3 | 14.8–42.1 | 89.4 | 4 | 670 | 54.4 | 23.7–83.3 | 98.6 |
| Piperacillin/ tazobactam | 15 | 1389 | 26.7 | 17.5–43.6 | 96.6 | 5 | 462 | 27.1 | 3.6–61.7 | 93.3 | 9 | 1644 | 36.4 | 25.4–48.7 | 95.5 | 4 | 447 | 46.1 | 18.7–74.9 | 97.2 |
| Ceftazidime | 16 | 1402 | 34.0 | 24.9–43.9 | 92.8 | 9 | 1397 | 34.3 | 14.1–58.0 | 98.3 | 11 | 1796 | 39.6 | 29.1–50.7 | 95.1 | 9 | 912 | 45.8 | 24.2–68.3 | 97.9 |
| Cefepime | 12 | 1179 | 38.5 | 26.8–50.9 | 94.4 | 6 | 351 | 36.1 | 21.3–52.3 | 89.5 | 9 | 1292 | 38.5 | 25.3–52.6 | 95.7 | 5 | 568 | 22.7 | 13.0–34.2 | 88.5 |
| Cefoperazone–sulbactam | 9 | 915 | 36.7 | 14.2–62.8 | 98.3 | 3 | 303 | 28.1 | 7.2–56.1 | 96.0 | 5 | 374 | 31.2 | 16.1–48.8 | 52.0 | 1 | Insufficient data | | | |
| Imipenem | 16 | 1418 | 29.1 | 22.5–36.1 | 87.0 | 8 | 587 | 19.2 | 13.1–26.2 | 75.0 | 12 | 1817 | 29.4 | 22.0–37.4 | 91.5 | 8 | 874 | 31.3 | 16.4–48.6 | 96.3 |
| Meropenem | 9 | 593 | 29.6 | 17.6–43.2 | 91.8 | 4 | 376 | 22.5 | 18.5–27.0 | 0.0 | 10 | 1246 | 33.4 | 22.9–44.9 | 93.6 | 6 | 583 | 31.1 | 14.4–50.9 | 95.5 |
| Aztreonam | 7 | 650 | 57.9 | 39.3–75.4 | 95.7 | 2 | 132 | 22.4 | 2.8–53.1 | 93.1 | 3 | 401 | 79.0 | 42.7–99.2 | 97.7 | 0 | Insufficient data | | | |
| Gentamicin | 13 | 1200 | 22.9 | 14.4–32.7 | 92.7 | 5 | 1064 | 32.8 | 20.4–46.7 | 91.2 | 11 | 1154 | 31.2 | 25.9–37.6 | 75.7 | 7 | 957 | 27.4 | 14.5–42.6 | 95.9 |
| Amikacin | 15 | 1363 | 13.3 | 8.0–19.6 | 89.6 | 9 | 1347 | 18.1 | 12.0–25.2 | 85.2 | 12 | 1819 | 19.5 | 12.6–27.6 | 93.2 | 9 | 1058 | 23.9 | 10.5–40.6 | 97.1 |
| Tobramycin | 1 | Insufficient data | | | | 2 | 170 | 20.3 | 14.5–27.0 | 0.0 | 4 | 746 | 17.1 | 5.5–33.5 | 94.5 | 1 | Insufficient data | | | |
| Netilmicin | 2 | 230 | 20.4 | 9.9–33.4 | 78.5 | 0 | 0 | Insufficient data | | | 5 | 501 | 33.1 | 17.9–50.3 | 92.2 | 1 | Insufficient data | | | |
| Ciprofloxacin | 15 | 1385 | 29.9 | 26.7–37.7 | 89.1 | 8 | 1338 | 31.7 | 13.9–53.0 | 97.8 | 10 | 1365 | 30.0 | 17.2–44.6 | 96.5 | 8 | 820 | 32.5 | 21.3–44.8 | 91.9 |
| Levofloxacin | 4 | 286 | 31.7 | 14.6–51.8 | 91.2 | 1 | 1 | Insufficient data | | | 7 | 602 | 32.5 | 23.7–42.0 | 79.6 | 1 | Insufficient data | | | |
| Colistin | 7 | 552 | 1.4 | 0.3–3.3 | 57.2 | 0 | 0 | Insufficient data | | | 5 | 393 | 2.6 | 1.3–4.7 | 0.0 | 4 | 312 | 3.3 | 1.6–5.0 | 25.8 |

In the current meta-analysis, the pooled resistance rate was 30.7% for ciprofloxacin and 32.3% for levofloxacin. When the resistance rates were evaluated between the first and the second 5 years, resistance rates for ciprofloxacin were seen to decrease from 30.7% to 25.9%, with a significant downfall ($P = 0.0001$), while there was no significant change for levofloxacin. The rate resistance to ciprofloxacin in strains isolated from ICU and non-ICU patients were 38.3% and 40%, respectively, above the pooled prevalence of resistance. This indicates that ciprofloxacin is becoming less effective in ICU isolates.

In this meta-analysis, the resistance rates of ICU isolates were found to be as follows: meropenem 46.7%, ciprofloxacin 38.3%, ceftazidime 50.4%, and gentamycin 40.6%. In a multicentre study in 2013 from Turkey, which investigated the prevalence of antibiotic resistance of healthcare-associated Gram-negative bloodstream infections, the *P. aeruginosa* resistance rates to carbapenem, quinolone, third-generation cephalosporin, and aminoglycoside were 32%, 36%, 37%, and 19%, respectively [20]. The current resistance rates are very high compared with the rates reported in the multicentre study from Turkey. The number of the isolates that were subjected to the resistance test affected the results of the resistance comparisons. However, it can be concluded that there is an increase in the resistance rates of antipseudomonal agents in Turkish ICUs, as the current results provide powerful evidence and are more up-to-date.

Aminoglycosides are active against *P. aeruginosa* but are generally not used as single agents because of inadequate clinical efficacy at most sites. Instead, aminoglycosides are frequently used in combination with other antibiotics for the treatment of serious infections. The current study found that pooled resistance rates to gentamicin, amikacin, tobramycin and netilmicin were 28.2%, 17.8%, 15.7% and 27.9%, respectively. Comparing the first and second 5-year periods, the pooled resistance rates to gentamicin and tobramycin were significantly lower, while there was a significant increase in amikacin. The highest level of resistance to aminoglycosides was observed in urine isolates. Tobramycin and amikacin were found to be the most active agents against *P. aeruginosa* in this meta-analysis; however, tobramycin has not been used in Turkey for a long time. According to this result, amikasin is clearly a very useful addition to drugs that are used to treat pseudomonas infections in hospitalised patients.

Colistin is an effective alternative agent for treating multidrug-resistant *P. aeruginosa*. Thus, colistin is increasingly being used, despite its well-known propensity for causing nephrotoxicity and ototoxicity. In the current meta-analysis, pooled resistance to colistin was 0.3% in the first 5 years and it was found to be 3.3% in the second 5 years ($P < 0.0008$). Due to the increase in resistance to colistin, it is expected that the use of this agent will be limited in the future.

This meta-analysis determined significantly higher resistance rates for piperacillin-tazobactam and meropenem in isolates from ICU patients when compared with non-ICU patients ($P = 0.005$ and $P = 0.007$). Intensive care unit stay, invasive device use, recent use of wide-spectrum antimicrobial agents (cephalosporin, aminoglycoside, carbapenem or quinolone), diabetes mellitus, and surgery are risk factors for infections with resistant *P. aeruginosa* [21]. Patients in ICUs usually have the risk of being hospitalised in the ICU and also have other risk factors that increase the risk of becoming infected with resistant strains. Therefore, it likely that the current results are consistent with international data. The reason why the rates of resistance of meropenem and piperacillin-tazobactam are higher in ICUs may be that they are the usual first preference in critically ill patients and consequent selection of resistant strains. Carbapenems and β-lactam-β-lactamase inhibitor combinations are the most common antibiotics used in inpatients in Turkey [19]. In a study comparing the use of antipseudomonal

**Table 4**
Comparison of antibiotic resistance rates by geographical area.

| | | Marmara | Aegean | Mediterranean | Central Anatolia | South–eastern Anatolia | Eastern Anatolia | Black sea | Multicentre | *P*[a] |
|---|---|---|---|---|---|---|---|---|---|---|
| Piperacillin | N | 2 | 1 | | 4 | | 1 | 3 | | 0.1 |
| | Xm (Min–Max) | 18.6 (15.0–22.2) | 81.0 (81.0–81.0) | | 56.5 (25.0–86.1) | | 6.1 (6.1–6.1) | 25.0 (20.3–58.3) | | |
| Piperacillin/tazobactam | N | 7 | 9 | 1 | 7 | 3 | 2 | 2 | 2 | 0.09 |
| | Xm (Min–Max) | 19.1 (2.4–76.9) | 67.5 (22.9–82.8) | 7.1 (7.1–7.1) | 15.2 (6.3–85.9) | 27 (7.7–31.0) | 16.0 (4.8–27.1) | 18.2 (17.9–18.5) | 24.7 (23.2–26.2) | |
| Ceftazidime | N | 8 | 12 | 2 | 10 | 4 | 2 | 4 | 2 | **0.03**[b] |
| | Xm (Min–Max) | 36.0 (9.8–41.0) | 57.3 (32.0–66.0) | 20.7 (5.0–36.4) | 23.2 (8.5–65.8) | 57.1 (32.0–66.0) | 22.8 (4.5–41.4) | 23.3 (12.9–30.2) | 25.7 (22.6–28.9) | |
| Cefepime | N | 5 | 10 | 2 | 5 | 2 | 2 | 5 | 1 | 0.9 |
| | M ± SD | 25.2 ± 16.9 | 46.3 ± 16.6 | 21.0 ± 21.8 | 39.2 ± 15.1 | 37.5 ± 17.7 | 31.7 ± 35.9 | 40.7 ± 25.6 | 22.6 | |
| Cefoperazone-sulbactam | N | 4 | 6 | 1 | 1 | 2 | – | 1 | 2 | 0.2 |
| | M ± SD | 25.9 ± 18.6 | 59.8 ± 24.9 | 13.8 | 73.6 | 28.9 ± 30.0 | | 21.7 ± 12.9 | 19.1 ± 12.8 | |
| Imipenem | N | 8 | 12 | 2 | 9 | 4 | 2 | 5 | 2 | 0.2 |
| | Xm (Min–Max) | 20.0 (10.0–59.1) | 21.1 (18.0–45.0) | 20.9 (11.1–30.7) | 35.0 (20.3–72.0) | 31.7 (26.0–46.0) | 14.4 (4.5–24.3) | 20.3 (8.9–70.8) | 20.7 (15.1–26.2) | |
| Meropenem | N | 6 | 7 | 1 | 8 | 2 | 1 | 3 | 1 | 0.5 |
| | Xm Min–Max) | 25.9 (20.0–56.8) | 29.1 (9.3–45.0) | 11.1 (11.1–11.1) | 29.8 (14.5–70.6) | 22.0 (19.0–25.0) | 16.7 (16.7–16.7) | 70.8 (2.5–79.3) | 16.7 (16.7–16.7) | |
| Aztreonam | N | 1 | 5 | – | 5 | – | 1 | – | – | **0.002**[c] |
| | SD | 37.0 | 80.4 ± 17.3 | | 43.7 ± 4.5 | | 9.7 | | | |
| Gentamicin | N | 6 | 11 | 2 | 10 | 1 | 1 | 5 | | 0.3 |
| | SD | 22.2 ± 15.0 | 35.9 ± 12.7 | 12.1 ± 2.2 | 28.5 ± 16.3 | 36.0 | 19.4 | 22.2 ± 15.0 | | |
| Amikacin | N | 8 | 12 | 2 | 10 | 3 | 2 | 5 | 2 | 0.9 |
| | SD | 20.2 ± 14.0 | 17.4 ± 13.9 | 8.9 ± 5.1 | 20.8 ± 19.9 | 31.0 ± 9.6 | 13.2 ± 1.6 | 17.4 ± 20.9 | 22.6 ± 0.1 | |
| Tobramycin | N | 2 | 3 | – | 1 | – | 1 | – | – | 0.6 |
| | SD | 9.5 ± 3.4 | 27.3 ± 25.1 | | 8.0 | | 13.9 | | | |
| Netilmicin | N | 1 | 6 | – | 1 | – | – | – | – | 0.6 |
| | M ± SD | 47.1 | 27.0 ± 19.1 | | 19.6 | | | | | |
| Ciprofloxacin | N | 7 | 12 | 1 | 10 | 42.5 ± 24.7 | 2 | 4 | 2 | 0.12 |
| | M ± SD | 19.7 ± 11.6 | 39.2 ± 14.2 | 11.9 | 30.8 ± 16.8 | 2 | 21.8 ± 1.6 | 26.2 ± 12.1 | 29 ± 4.0 | |
| Levofloxacin | N | 3 | 3 | | | | | 3 | – | 0.84 |
| | M ± SD | 34.8 ± 12.6 | 33.8 ± 19.8 | 21.3 ± 13.3 | 32.6 ± 16.0 | – | – | 36.6 ± 12.0 | | |
| Colistin | N | 2 | 5 | – | 5 | 1 | – | 2 | 1 | 0.5 |
| | Xm (Min–Max) | 1.1 (0.0–2.1) | 0.0 (0.0–10.0) | | 3.9 (0.0–4.9) | 0.0 (0.0–0.0) | | 2.0 (0.0–4.0) | 4.2 (4.2–4.2) | |

N, number of studies; Xm, median; Min, minimum; Max, maximum; M, mean; SD, standard deviation.

[a] The One-Way ANOVA test was used to compare normal distribution averaged samples. The Kruskal-Wallis test was used to compare non-normal distribution samples.

[b] AZT: There is a significant difference between groups and within the group. There is a statistical difference between eastern Anatolia and Aegean, Aegean and central Anatolian regions.

[c] CAZ: Significant differences were found within the group. Post Hoc tests between the groups revealed a significant difference between the Aegean and Mediterranean, Aegean and Black Sea, central Anatolia and south-eastern Anatolia, Black Sea and south-eastern Anatolia regions.

**Table 5**
Comparison of antimicrobial resistance rates of isolates from intensive care and clinics.

| Antimicrobial agents | Intensive care units Mean ± SD | Non-intensive care units Mean ± SD | *P* |
|---|---|---|---|
| Piperacillin-tazobactam | 57.9 ± 18.0 | 19.0 ± 11.7 | **0.005** |
| Ceftazidime | 50.4 ± 18.2 | 35.8 ± 19.3 | 0.24 |
| Cefepime | 52.7 ± 18.1 | 38.5 ± 19.1 | 0.34 |
| Imipenem | 39.8 ± 24.9 | 30.8 ± 11.5 | 0.5 |
| Meropenem | 46.7 ± 24.2 | 20.0 ± 1.4 | **0.007** |
| Gentamicin | 40.4 ± 21.7 | 36.4 ± 13.4 | 0.77 |
| Amikacin | 31.1 ± 18.3 | 15.1 ± 5.9 | 0.17 |
| Ciprofloxacin | 38.3 ± 17.5 | 40.0 ± 21.2 | 0.97 |

penicillin in ICUs in Turkey with US National Nosocomial Infection Surveillance System (NNIS) data, the use of antipseudomonal penicillin and carbapenem in Turkey was found to be above the 90th percentile according to NNIS [17]. These results confirm that there is a correlation between antipseudomonal penicillin and carbapenem use and resistance rates.

Antibiotic resistance varies among countries, provinces and hospitals. To demonstrate this difference, pooled resistance was calculated according to the seven geographical regions in Turkey. There was a statistically significant difference in the resistance rates of ceftazidime and aztreonam according to the regions. However, median values were compared for both agents, as the data did not fit the normal distribution. According to this, ceftazidime resistance was higher in the Aegean region than the Mediterranean, central Anatolia and Black Sea regions, while it was higher in the eastern Anatolian region than central Anatolian and Black Sea regions.

In conclusion, the rates of antibiotic resistance in pathogenic *P. aeruginosa* strains are substantially high in Turkey, and continue to increase compared with previous years.

Carbapenem and antipseudomonal penicillin resistance rates in *P. aeruginosa* have reached alarming proportions. Local data and strict infection control practices can only control the spread of virulent and resistant organisms; therefore, it is essential to strengthen the surveillance of antibiotic resistance of *P. aeruginosa* and to timeously update treatment guidelines in Turkey.

## Funding

The authors received no specific funding for this work.

## Competing interests

The authors have declared that no competing interests exist.

## Ethical approval

No ethical approval required.

## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jgar.2019.01.032.

## References


[1] Ruiz M, Ewig S, Torres A, Arancibia F, Marco F, Mensa J, et al. Severe community-acquired pneumonia. Risk factors and follow-up epidemiology. Am J Respir Crit Care Med 1999;160(3):923.

[2] Dereli N, Ozayar E, Degerli S, Sahin S, Koc F. Three-year evaluation of nosocomial infection rates of the ICU. Braz J Anesthesiol 2013;63(1):73–8.

[3] Ak O, Batirel A, Ozer S, Colakoglu S. Nosocomial infections and risk factors in the intensive care unit of a teaching and research hospital: a prospective cohort study. Med Sci Monit 2011;17(5):PH29–34.

[4] Keten D, Aktas F, Tunccan OG, Dizbay M, Kalkanci A, Biter G, et al. Catheter-associated urinary tract infections in intensive care units at a university hospital in Turkey. Bosn J Basic Med Sci 2014;14(4):227–33.

[5] Nathwani D, Raman G, Sulham K, Gavaghan M, Menon V. Clinical and economic consequences of hospital-acquired resistant and multidrug-resistant *Pseudomonas aeruginosa* infections: a systematic review and meta-analysis. Antimicrob Resist Infect Control 2014;3:32.

[6] Aykan SB, Ciftci IH. Changes in antibiotic resistance of *Pseudomonas aeruginosa* isolates over the past 11 years in Turkey: a meta-analysis. Mikrobiyol Bul 2015;49(3):352–65.

[7] Moher D, Liberti A, Tetzlaff J, Altman DG, Group PRISMA. Preferred reporting items for systemic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6:e1000097.

[8] Higgins JP, Green S. Cochrane handbook for systematic reviews of Interventions. 2011 Available from: https://handbook-5-1.cochrane.org. [Accessed 23 February 2018]..

[9] National Committee for Clinical Laboratory Standards. Analysis and presentation of cumulative antimicrobial susceptibility test data; approved guideline Document M39-A. Wayne, PA: NCCLS; 2002.

[10] http://www.eucast.org. [Accessed 23 February 2018].

[11] Gür D, Gülay Z, Akan OA, Aktaş Z, Kayacan CB, Cakici O, et al. Resistance to newer beta-lactams and related ESBL types in Gram-negative nosocomial isolates in Turkish hospitals: results of the multicentre HITIT study. Mikrobiyol Bul 2008;42(4):537–44.

[12] Gur D, Hascelik G, Aydin N, Telli M, Gültekin M, Ogülnç D, et al. Antimicrobial resistance in Gram-negative hospital isolates: results of the Turkish HITIT-2 Surveillance Study of 2007. J Chemother 2009;21(4):383–9.

[13] Rosenthal VD, Maki DG, Mehta YM, Leblebicioglu H, Memish ZA, Al-Mousa HH, et al. International nosocomial infection control consortium (INICC) report, data summary of 43 countries for 2007-2012. Device associated module. Am J Infect Control 2014;42(9):942–56.

[14] Carmeli Y, Troillet N, Elipoulos GM, Samore MH. Emergence of antibiotic-resistant *Pseudomonas aeruginosa*: comparison of risk associated with different antipseudomonal agents. Antimicrob Agents Chemoter 1999;43(6):1379.

[15] Tuon FF, Gortz LW, Rocha JL. Risk factor for pan-resistant *Pseudomonas aeruginosa* bacteremia and the adequacy of antibiotic therapy. Braz J Infect Dis 2012;16(4):351–6.

[16] Guclu E, Ogutlu A, Karabay O, Demirdal T, Hosoglu S, Turhan V, et al. Antibiotic consumption in Turkish hospitals; a multi-centre point prevalence study. J Chemother 2017;29(1):19–24.

[17] Saba R, İnan D, Turhan Ö, Yalçın AN, Günseren F, Mamıkoğlu L. Surveillance of antimicrobial use in a Turkish university hospital. Türk J Med Sci 2011;41(4):701–10.

[18] Ozgenç O, Genç VE, Ari AA, Sibel EI, Saçar S, Ozunlu H, et al. Evaluation of the therapeutic use of antibiotics in Aegean region hospitals of Turkey: a multicentric study. Indian J Med Microbiol 2011;29(2):124–9.

[19] Bozkurt F, Kaya S, Tekin R, Gulsun S, Deveci O, Dayan S, et al. Analysis of antimicrobial consumption and cost in a teaching hospital. J Infect Public Health 2014;7(2):161–9.

[20] Ergönül Ö, Aydin M, Azap A, Başaran S, Tekin S, Kaya Ş, et al. Healthcare-associated Gram-negative bloodstream infections: antibiotic resistance and predictors of mortality. J Hosp Infect 2016;94(4):381–5.

[21] Aloush V, Navon-Venezia S, Seigman-Igra Y, Cabii S, Carmeli Y. Multidrug-resistant *Pseudomonas aeruginosa*: risk factors and clinical impact. Antimicrob Agents Chemother 2008;50(1):43.