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In Vitro Efficacy of Ceftazidime-Avibactam on Carbapenem-Resistant *Pseudomonas aeruginosa* Isolates

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ABSTRACT: *Pseudomonas aeruginosa* is the primary Pseudomonas species responsible for hospital-acquired infections. Ceftazidime-avibactam (CZA) is a new beta-lactam/beta-lactamase inhibitor combination effective against carbapenem-resistant *P. aeruginosa* isolates. The aim of this study was to evaluate the in vitro activity of CZA against carbapenem-resistant *P. aeruginosa* isolates. In hospitalized patient culture samples, 190 isolates that were evaluated as significant growth and identified as *P. aeruginosa* with the Vitek 2 Compact automated system (BioMérieux, France) and determined as imipenem resistant (≥ 8 mg/L) and meropenem resistant (≥ 16 mg/L)with the same system were included in the study. 88% (167/190) of *P. aeruginosa* strains were isolated from patients in intensive care units and 78% (148/190) from respiratory tract samples. CZA activity was studied using the disk diffusion test (10-4 µg disk) and zone diameters <17 mm were accepted as resistant. 20% (38/190) of the isolates were found to be resistant to CZA. The difference in resistance rates between CZA and all of the studied antimicrobials except amikacin is highly significant (p: 0.006 - <0.001). The low resistance rate found in our study indicates that CZA is a good option for the treatment of carbapenem-resistant *P. aeruginosa* isolates. In addition, amikacin treatment with a low resistance rate may be an appropriate approach for patients requiring combination therapy. Given the growing challenge of carbapenem resistance and multidrug resistance, further studies are warranted to assess the efficacy of new antimicrobials and drug combinations.

Keywords: *Pseudomonas aeruginosa*, ceftazidime-avibactam, carbapenem resistance.

1 INTRODUCTION

Pseudomonas aeruginosa is a Gram-negative, opportunistic pathogen that is responsible for 5–14% of hospital-acquired infections. The risk of infection is particularly high in cases of immunodeficiency, severe burns, prolonged stays in Intensive Care Units (ICUs), cystic fibrosis and bronchiectasis [1]. The development of resistance to antimicrobials—including antipseudomonal cephalosporins, monobactams, beta-lactam/beta-lactamase inhibitors, carbapenems fluoroquinolones, aminoglycosides, and polymyxins—poses significant challenges in the treatment of infections [2,3]. In particular, carbapenem-resistant isolates are defined as critically important pathogens by the World Health Organization (WHO) [4]. *P. aeruginosa* can develop carbapenem resistance through various mechanisms, including gene mutations that regulate the expression of membrane porins, upregulation of efflux pump systems (e.g., MexAB-OprM), and acquisition

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of transferable genes encoding carbapenemases, such as metallo-beta-lactamases (e.g., VIM, IMP, and NDM) [5].

Ceftazidime is an antipseudomonal, semisynthetic third-generation cephalosporin that binds to penicillin-binding proteins and inhibits bacterial cell wall synthesis. However, resistance to third-generation cephalosporins has been increasing due to the emergence of multidrug-resistant Gram-negative bacteria capable of producing extended-spectrum beta-lactamases, chromosomal AmpC cephalosporinases, carbapenemases and metallo-beta-lactamases. Consequently, ceftazidime alone may be insufficient for the treatment of *P. aeruginosa* infections [1,6,7]. Ceftazidime-avibactam (CZA) is a novel beta-lactam/beta-lactamase inhibitor combination effective against carbapenem-resistant *P. aeruginosa* isolates. The combination of ceftazidime with avibactam may be effective against strains producing carbapenemases other than metallo-beta-lactamases [7].

This study aims to evaluate the in vitro activity of CZA against carbapenem-resistant *P. aeruginosa* isolates.

2 MATERIAL AND METHOD

Our study included 190 isolates from Gram-negative, oxidase-positive, R-type colonies that were classified as significant growth in inpatient culture samples sent from various clinics to the Microbiology Laboratory of Malatya Education and Research Hospital in 2022. The isolates were identified as *P. aeruginosa* using the Vitek 2 Compact automated system (BioMérieux, France) and determined to be imipenem-resistant (≥ 8 mg/L) and meropenem-resistant (≥ 16 mg/L) by the same system. The antimicrobial activities of the isolates were evaluated according to ‘‘The European Committee on Antimicrobial Susceptibility Testing’’ (EUCAST) criteria. CZA activity was assessed with disk diffusion test (10–4 µg disk) and zone diameters < 17 mm were accepted as resistant [8]. For statistical analysis, the SPSS 17 software (SPSS Inc., Chicago, IL, USA) was used. Categorical variables were expressed as numbers and percentages, and differences between categorical variables were analyzed using Chi-square tests.

3 RESULT

88% (167/190) of *P. aeruginosa* strains were isolated from patients in intensive care units and 78% (148/190) from respiratory tract samples. Blood (9%), urine (5%), wound (5%) and catheter (3%) samples were the other sources from which the strains were isolated. 20% (38/190) of the isolates were found to be resistant to CZA. The resistance rates of carbapenem-resistant isolates to other antimicrobials are presented in Table 1.

The difference in resistance rates tween CZA and all other studied antimicrobials, except amikacin, was highly significant ($p = 0.006$ to <0.001). The difference in resistance

Table 1. Antimicrobial resistance rates of 190 carbapenem-resistant *P. aeruginosa* isolates.

Antimicrobial	Rates of resistant isolates (%)
Ceftazidime-avibactam (< 17 mm)	38/190 (20)
Amikacin (>16 mg/L)	54/189 (28.6)
Ceftazidime (>8 mg/L)	80/190 (42.1)
Aztreonam (>16 mg/L)	88/180 (48.9)
Cefepime (>8 mg/L)	141/189 (74.6)
Levofloxacin (>2 mg/L)	150/184 (81.5)
Piperacillin/tazobactam (>16 mg/L)	168/187(89.8)

rates between CZA and amikacin is not statistically significant (p:0.052). 15 (39.5%) of 38 CZA-resistant isolates were found to be susceptible to amikacin.

4 DISCUSSION

The limited treatment options for carbapenem-resistant P. aeruginosa infections pose a significant clinical challenge. Although colistin remains one of the most effective antimicrobials for treating these infections, its nephrotoxicity and unfavorable pharmacokinetic properties limit its widespread use [9]. CZA treatment, one of the combination therapies recommended to solve the treatment problem, has been reported to be effective in many studies [6,7,10,11]. One of these studies was conducted in the United States (US) with 1151 multidrug-resistant isolates, and the CZA resistance rate was reported as 11.8% [11]. Similarly, studies conducted in the US with meropenem-resistant *P. aeruginosa* isolates, the CZA resistance rate was reported as 19% and 26% [12,13].

In studies performed with carbapenem-resistant P. aeruginosa isolates in Turkey, Aydemir et al. reported a CZA resistance rate of 21.8%, Bilgin et al. reported 7.7%, and Mirza et al. reported 16.7% [14–16]. In the present study, we determined a CZA resistance rate of 20% in our hospital, which was found to be consistent with the rates reported in both domestic and international studies.

The low resistance rate observed in our study indicates that CZA may be a valuable treatment option for carbapenem-resistant *P. aeruginosa* isolates. In addition, amikacin treatment with a low resistance rate may be an appropriate approach for patients requiring combination therapy. The increasing problem of carbapenem resistance and multidrug resistance requires more studies to evaluate the effectiveness of new antimicrobials and drug

combinations.

5 AUTHOR CONTRIBUTIONS

Hypotesis: A.M., A.G; Design: A.M., A.G; Literature review: A.M.; Data Collection: A.M., A.G; Analysis and/or interpretation: A.M., A.G; Manuscript writing: A.M.

6 CONFLICT OF INTEREST

Authors declare that there is no conflict of interest.

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