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Evaluation of the in vitro efficacy of ceftazidime-avibactam against *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* isolates from respiratory tract cultures in intensive care units

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ABSTRACT

Aims: Worldwide, an increase in multidrug resistance is observed in *Escherichia coli (E. coli), Klebsiella pneumoniae (K. pneumoniae),* and *Pseudomonas aeruginosa (P. aeruginosa)* isolates, leading to challenges in the treatment of infections caused by these pathogens. This study aims to investigate the in vitro efficacy of ceftazidime-avibactam (CZA) against isolates containing *K. pneumoniae*, *E. coli,* and *P. aeruginosa* strains obtained from respiratory tract samples sent from intensive care units.

Methods: A retrospective analysis was conducted on 653 *Enterobacterales* (*E. coli*, *K. pneumoniae*) and *P. aeruginosa* isolates obtained from respiratory tract cultures, including sputum, tracheal aspirates, and bronchial lavage, from patients over 18 years old admitted to the intensive care units of Ordu University Training and Research Hospital between May 1, 2021, and May 1, 2024. Automated systems were used to identify the pathogens and perform antibiotic susceptibility testing. Discriptive data analysis was conducted using SPSS version 24.0.

Results: A total of 653 isolates from respiratory tract samples were included in the study, consisting of 368 *Enterobacteriaceae* [61 *E. coli* (9.3%) and 307 *K. pneumoniae* (47%)] and 285 *P. aeruginosa* (43.7%). These samples were isolated from endotracheal aspirate (69.5%), sputum (27.9%), and bronchoalveolar lavage (2.6%). Among all isolates, 364 (55.7%) were found to be sensitive to carbapenems, while 289 (44.3%) were carbapenem-resistant. Of the samples, 631 (96.6%) were sensitive to CZA, while 22 (3.4%) were resistant. Although resistance to CZA was detected in 3.6% of *K. pneumoniae* isolates and 3.9% of *P. aeruginosa* isolates, no resistance was detected in *E. coli*. Colistin resistance was observed in 15.3% of *K. pneumoniae* and 5.6% of *P. aeruginosa* isolates, but was absent in *E. coli* isolates. Resistance rates to other antibiotics were as follows for *E. coli*, *K. pneumoniae*, and *P. aeruginosa* isolates, respectively: amikacin (3.3%, 46.6%, 8.1%), ciprofloxacin (73.8%, 73.6%, 85.9%), ceftazidime (67.2%, 77.8%, 35.8%), piperacillin-tazobactam (26.2%, 70%, 37.2%), and trimethoprim-sulfamethoxazole (52.5%, 66.4%, 0%).

Conclusion: In our study, CZA was found to be the most effective antibiotic against multidrug-resistant *Enterobacterales* and *P. aeruginosa* isolates, followed by colistin.

Keywords: Multidrug resistance, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, ceftazidime-avibactam

INTRODUCTION

Concerns regarding antibacterial resistance continue to rise worldwide, and the management of secondary infections caused by multidrug-resistant (MDR) organisms has become a global health issue. The primary pathogens that pose treatment challenges are MDR gram-negative bacteria, and infections caused by these microorganisms are associated with increased mortality and morbidity, especially in patients with significant comorbidities.[1] Furthermore, the increasing prevalence of antibiotic resistance has led to the widespread and often inappropriate use of antibiotics globally. Carbapenems are frequently used as first-line antibiotics in the treatment of infections caused by extended-spectrum beta-lactamase (ESBL)-producing microorganisms isolated from respiratory tract samples, as they are highly effective against these pathogens. However, the rising incidence of infections caused by ESBL-producing *Enterobacteriaceae* over the years has resulted in increased carbapenem usage and higher rates of carbapenem resistance.[2]

In the treatment of carbapenem-resistant microorganisms, ceftazidime-avibactam (CZA), a combination of the third-generation broad-spectrum cephalosporin ceftazidime and

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the β-lactamase inhibitor avibactam, is used as an antibiotic therapy.[3] The use of CZA for gram-negative bacterial infections was approved in 2018. The European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) have approved it for adult patients with infections caused by aerobic gram-negative bacteria, particularly in cases with limited therapeutic options. In Turkiye, it was licensed for use in October 2019.[4] Recently, the World Health Organization listed the multidrug-resistant *Pseudomonas aeruginosa (*P. *Aeruginosa)*, *Klebsiella pneumoniae (K. Pneumoniae)*, and *Escherichia coli* (*E. Coli)* included in our study among the bacterial species for which the development of new antibiotics is critically needed to treat infections.[5,6]

The aim of this study is to investigate the in vitro efficacy of CZA against carbapenem-resistant *K. pneumoniae*, *E. coli*, and *P. aeruginosa* strains isolated from respiratory tract samples sent from intensive care units to the Microbiology Laboratory of Ordu University Faculty of Medicine Training and Research Hospital. Given the significance of resistance development in combating infections caused by these microorganisms and the limited number of studies in Turkiye examining CZA's activity against MDR strains of these pathogens, further research on this topic is essential.

METHODS

Ethics Approval

This study was approved by the Ordu University Non-interventional Scientific Researches Ethics Committee (Date: 26.07.2024, Decision No: 2024/109). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Design

This retrospective study examined 653 isolates of *E. coli, K. pneumoniae* and *P. aeruginosa* isolated from respiratory culture samples such as sputum, tracheal aspirates, and bronchoalveolar lavage from patients admitted to the intensive care units of Ordu University Training and Research Hospital between May 1, 2021, and May 1, 2024. All patients aged 18 and older were included in the study, and the first culture results from similar clinical samples of the same patient, as well as culture results from different clinical samples, were included in the analysis. Repeated cultures from the same patients were excluded from the study.

Automated systems were used for the identification of pathogens and the results of the antibiograms. In addition to classical methods for species-level identification and antimicrobial susceptibility testing, the BD Phoenix 100 automated system (Becton Dickinson and Company, USA) was utilized to determine the production of extended-spectrum beta-lactamases (ESBL). For ESBL confirmation testing, disk diffusion tests (combined disk method) were performed according to Clinical and Laboratory Standards Institute (CLSI) documents, using both ceftazidime, ceftazidime-clavulanic acid, and cefotaxime, cefotaxime-clavulanic acid disks. Among these, isolates determined to be multidrug-resistant (MDR) were evaluated for susceptibility to ceftazidime-avibactam 10/4 mg (Bioanalyse, Turkiye) using the Kirby-Bauer disk diffusion method. Antimicrobial susceptibility results were reported according to the breakpoints recommended by the European Committee on Antimicrobial Susceptibility Testing (EUCAST). Categorical variables are described as frequencies (percentages), while continuous variables are presented as mean and standard deviation. Discriptive data analysis was conducted using SPSS version 24.0.

RESULTS

A total of 653 isolates were included in our study, with 69.5% from endotracheal aspirates, 27.9% from sputum, and 2.6% from bronchoalveolar lavage; of these, 61 (9.3%) were *E. coli* and 307 (47%) were *K. pneumoniae*, resulting in a total of 368 Enterobacteriaceae and 285 (43.7%) *P. aeruginosa* (**Table 1**). All patients from whom respiratory cultures were obtained were adults aged 18 and older who were hospitalized in the intensive care unit.

Table 1. Sample sites of isolated bacterial agents

Sample site	n (%)
Endotracheal aspirate	454 (69.5%)
Sputum	182 (27.9%)
Bronchoalveolar lavage	17 (2.6%)

Among all isolates, 364 (55.7%) were found to be susceptible to carbapenems, while 289 (44.3%) were resistant. Of the *E. coli* isolates, 4.9% (3/61) were resistant to carbapenems, 56% (172/307) of *K. pneumoniae* isolates, and 53% (152/285) of *P. aeruginosa* isolates were found to be carbapenem-resistant.

Of the samples, 631 (96.6%) were susceptible to CZA, while 22 (3.4%) were resistant. Resistance to CZA was found in 3.6% of *K. pneumoniae* isolates and 3.9% of *P. aeruginosa* isolates, while no resistance was detected in *E. coli* isolates. No resistance to CZA was observed in any of the bronchoalveolar lavage samples.

When investigating colistin resistance, 15.3% of *K. pneumoniae* isolates and 5.6% of *P. aeruginosa* isolates were found to be resistant to colistin. No colistin resistance was observed in *E. coli* isolates, similar to the findings for CZA. Among the 63 isolates with detected resistance to colistin, 6 (9.5%) were also resistant to CZA.

Resistance rates were found to be as follows: amikacin 3.3%, 46.6%, and 8.1% for *E. coli*, *K. pneumoniae*, and *P. aeruginosa*, respectively; ciprofloxacin 73.8%, 73.6%, and 85.9%; ceftazidime 67.2%, 77.8%, and 35.8%; piperacillin/tazobactam 26.2%, 70%, and 37.2%; and trimethoprim-sulfamethoxazole 52.5%, 66.4%, and 0%. The detected antibiotic resistances in microorganisms are shown in **Table 2**.

In our study, CZA was found to be the most effective antibiotic against multidrug-resistant Enterobacterales and *P. aeruginosa* isolates, followed by colistin.

DISCUSSION

Members of Enterobacterales are among the primary causes of healthcare-associated and community-acquired infections.

Table 2. Antibiotic resistance rates by microorganism

Microorganism	Carbapenem n (%)	Ceftazidime-avibactam, n (%)	Colistin n (%)	Amikacin n (%)	Ciprofloxacin n (%)	Ceftazidime n (%)	Piperacillin/tazobactam n (%)	Trimethoprim-sulfamethoxazole, n (%)
Klebsiella pneumoniae	172 (56%)	11 (3.6%)	47 (15.3%)	143 (46.6%)	226 (73.6%)	239 (77.8%)	215 (70%)	204 (66.4%)
Escherichia coli	3 (4.9%)	-	-	2 (3.3%)	45 (73.8%)	41 (67.2%)	16 (26.2%)	32 (52.5%)
Pseudomonas aeruginosa	152 (53%)	11 (3.9%)	16 (5.6%)	23 (8.1%)	245 (85.9%)	102 (35.8%)	106 (37.2%)	-
Total	327 (50.0%)	22 (3.3%)	63 (9.6%)	168 (25.7%)	516 (79.0%)	382 (58.5%)	337 (51.6%)	236 (36.1%)

The most frequently isolated Enterobacteriaceae agents from cultures are *K. pneumoniae* and *E. coli*.[7] The most effective treatment for these microorganisms has been carbapenems; however, increased resistance due to their widespread use has posed significant challenges for treatment in clinical practice.[8] Carbapenem antibiotics, which belong to the beta-lactam group, are bactericidal, fast-acting, and have broad-spectrum activity, making them widely used in the treatment of infectious diseases. Carbapenem-resistant bacteria are typically resistant not only to penicillins and cephalosporins but also may carry genes encoding resistance to aminoglycosides and quinolones. Multidrug-resistant Gram-negative bacilli develop resistance mechanisms that lead to resistance against multiple antimicrobial agents, not just a single antibiotic class. Initially, carbapenem resistance was more commonly detected in *Acinetobacter baumannii* and *P. aeruginosa* isolates, but in recent years, *K. pneumoniae* has become the most frequently reported agent of carbapenem resistance and a significant contributor to the spread of carbapenem resistance.[9]

Colistin, tigecycline, and aminoglycosides are nearly the last-line therapeutic agents for treating multidrug-resistant (MDR) isolates.[10] Consequently, there is an increasing need for new antibiotics effective against MDR isolates. In the treatment of carbapenem-resistant microorganisms, CZA, a new antibiotic combining the broad-spectrum cephalosporin ceftazidime with the non-beta-lactam beta-lactamase inhibitor avibactam, is being utilized.

In a study evaluating the antibiotic resistance profiles of *K. pneumoniae*, resistance rates for gentamicin, amikacin, amoxicillin/clavulanate, piperacillin/tazobactam, cefepime, ceftriaxone, and ceftazidime were found to be 37%, 33%, 63%, 53%, 74%, 62%, and 61%, respectively[11]. Another study examining the resistance profiles of carbapenem-resistant Enterobacterales isolates from 2015 to 2018 reported resistance rates in *K. pneumoniae* of 28.10% for amikacin, 51.08% for amoxicillin/clavulanate, 98.37% for ceftazidime, 51.08% for gentamicin, 99.72% for piperacillin/tazobactam, 80.81% for cefepime, and 99.72% for ceftriaxone. The highest resistance rates among carbapenem-resistant *K. pneumoniae* isolates were observed against ceftriaxone and piperacillin/tazobactam (99.72%).[12] In a study conducted by Altay Koçak et al.[13] from 2016 to 2018 on respiratory samples and antibiotic resistance profiles in hospitalized patients, resistance rates in *K. pneumoniae* isolates for amikacin, amoxicillin/clavulanate, gentamicin, colistin, levofloxacin, netilmicin, piperacillin/tazobactam, cefazolin, cefepime, cefoxitin, ceftazidime, ceftriaxone, cefuroxime, ciprofloxacin, and trimethoprim/sulfamethoxazole were reported as 30.6%, 60.9%, 52.9%, 11%, 51.8%, 39.5%, 55.8%, 77.9%, 73.3%, 48.8%, 74.1%, 74.1%, 76.5%, 51.2%, and 65.1%, respectively.

In our study, resistance rates for *K. pneumoniae* isolates were 3.6% for CZA, 15.3% for colistin, 46.6% for amikacin, 73.6% for ciprofloxacin, 77.8% for ceftazidime, 70% for piperacillin/tazobactam, and 66.4% for trimethoprim/sulfamethoxazole. The highest resistance rates in *K. pneumoniae* isolates in our study were observed against ciprofloxacin, ceftazidime, and piperacillin/tazobactam, while the most effective antibiotics were CZA and colistin.

According to a study conducted in İstanbul in 2012, ciprofloxacin, cotrimoxazole, amikacin, and gentamicin resistance rates in ESBL-positive *K. pneumoniae* were reported as 66.2%, 68.6%, 16.2%, and 43.0%, respectively. Resistance rates in ESBL-positive *K. pneumoniae* were reported as 10.5% for imipenem, 7% for meropenem, and 11.6% for ertapenem, with no colistin-resistant isolates detected.[14] The low resistance rates in this study were attributed to its completion in 2012.

In a study conducted in Turkiye, fluoroquinolone resistance was reported at 86.1%, suggesting that empirical use of this class of antibiotics is not recommended.[15] Due to the development of multidrug resistance linked to fluoroquinolone use in gram-negative bacteria, avoiding fluoroquinolones and reverting to other empirical agents is considered one of the most reliable approaches[16]. Similarly, in our study, fluoroquinolone resistance was found to be 79%, and we do not recommend its use in empirical treatment.

In a study by Özkul Koçak et al.,[17] the colistin resistance rate in 81 carbapenem-resistant *K. pneumoniae* isolates was 39.51%. Agyar,[18] in Ankara in 2020, reported colistin resistance of 36.4% in carbapenem-resistant *K. pneumoniae*, while Tartar et al.,[19] in 2017, reported a colistin resistance rate of 5% in *Klebsiella spp.* isolated from endotracheal aspirate samples based on antibiogram results. In our study, colistin resistance in *K. pneumoniae* isolates was detected as 15.3%.

Although studies and case reports on CZA-a combination developed and approved for combating bacterial resistance caused by ESBL and carbapenemases-show promising results, resistance may develop in the near future.[20] Research based on clinical data has shown that CZA is an effective treatment option for MDR gram-negative bacteria, reducing mortality rates and improving quality of life.[21] A recent study conducted in Turkiye reported a CZA susceptibility rate of 95.7% in ESBL-positive strains.[5] Another study found CZA susceptibility rates of 87.5% for *K. pneumoniae* and 95.2% for *E. coli*.[2] As these studies suggest, CZA appears to be a viable option for ESBL-producing and carbapenem-resistant Enterobacteriaceae isolates.[22] Similarly, in our study, 96.6%

of the isolates were susceptible to CZA, while 3.4% showed resistance.

In another study, 22.5% of carbapenem-resistant *K. pneumoniae* isolates were found to be resistant to CZA. Nevertheless, CZA is considered a viable option for suitable cases.[23] Following the use of ceftazidime-avibactam as an alternative therapeutic agent, clinical practice has demonstrated the proliferation of CZA-resistant strains. Given the increase in strains resistant to this antibiotic, it is important to emphasize the prudent use of CZA.[24]

A study conducted in Turkiye found CZA susceptibility rates for *E. coli*, *K. pneumoniae*, and *P. aeruginosa* strains to be 93.8%, 95.7%, and 36.2%, respectively. Despite CZA's introduction in Turkiye in October 2019, the high in vitro resistance rate of MDR *P. aeruginosa* strains (63.8%) found in this study is concerning.[5] Another study in Turkiye determined that, among MDR *P. aeruginosa* strains, colistin was the most effective antibiotic, with similar susceptibility rates to gentamicin, amikacin, and CZA. However, *P. aeruginosa* showed higher resistance rates to CZA than other Gram-negative pathogens.[25] These findings suggest that while CZA may be an alternative for treating infections caused by MDR *Enterobacterales*, susceptibility testing results are critical for MDR *P. aeruginosa* strains. Other studies have similarly shown that the in vitro susceptibility rate of CZA for MDR *P. aeruginosa* is lower than for MDR *Enterobacterales.*[26] In contrast, in our study, 3.6% of *K. pneumoniae* and 3.9% of *P. aeruginosa* isolates were resistant to CZA, with no resistance detected in *E. coli*. Contrary to the literature, our study did not find higher CZA resistance in *P. aeruginosa* isolates compared to other microorganisms.

In a study by Shields et al.,[27] CZA was used to treat carbapenemase-producing, meropenem-resistant *Klebsiella* infections in patients. In recurrent infections, the same patients developed meropenem-susceptible, CZA-resistant *Klebsiella*, showing both beneficial and adverse impacts of CZA on antibiotic resistance genes. The absence of CZA resistance is thought to be related to naive strains that had not previously encountered this antibiotic.[15]

In the study by Hoşbul et al.,[28] susceptibility results for 100 *Pseudomonas* strains were 100% for colistin and 90% for CZA, respectively. In our study, similar results were observed, with *P. aeruginosa* isolates showing 94.4% and 96.1% susceptibility to colistin and CZA, respectively. Studies by Camargo et al.[29] and Wu et al.[30] observed successful treatment and microbiological cure in cases unresponsive to alternative treatments, including combinations of colistin and carbapenems, when treated with CZA. The rational use of CZA, along with older antibiotics such as colistin and meropenem, forms an essential part of infection control and antimicrobial stewardship.[31] Therefore, in vivo studies are needed to evaluate the antimicrobial activity of CZA in combination therapies, particularly in bacteria with various resistance genes.

Limitations

The main limitation of our study is that it was conducted in a single center, which restricts its generalizability to national data. Another important limitation is the lack of genomic analysis and molecular testing in evaluating antibiotic susceptibilities. Limiting the study to carbapenem-resistant bacterial strains reduced the number of bacterial species included in the study. Additionally, clinical patient data and treatment outcomes were not analyzed.

CONCLUSION

Surveillance of local epidemiology and antimicrobial susceptibility is a crucial step in determining empirical treatment options to combat infections. Increasing the use of narrow-spectrum antibiotics minimizes the development of resistance mechanisms associated with antibiotic use. Regular monitoring of antibiotic resistance patterns is essential to guide future antibiotic choices. Similar to other studies, our findings confirm the in vitro activity of CZA against MDR *K. pneumoniae*, *E. coli*, and *P. aeruginosa* strains.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was approved by the Ordu University Non-interventional Scientific Researches Ethics Committee (Date: 26.07.2024, Decision No: 2024/109).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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REFERENCES

1. Cerceo E, Deitelzweig SB, Sherman BM, Amin AN. Multidrug-resistant gram-negative bacterial infections in the hospital setting: overview, implications for clinical practice, and emerging treatment options. *Microbial Drug Resistance.* 2016;22(5):412-431. doi:10.1089/mdr.2015.0220
2. Bilgin M, İşler H, Başbulut E, Görgün S. Genişlemiş spektrumlu beta-laktamaz üreten *Enterobacteriaceae* izolatlarına karşı seftazidim-avibaktamin in vitro etkinliğinin araştırılması. *J Immunol Clin Microbiol.* 2023;8(1):17-23. doi:10.58854/jicm.1249716
3. van Duin D, Bonomo RA. Ceftazidime/avibactam and ceftolozane/tazobactam: second-generation β-lactam/β-lactamase inhibitor combinations. *Clin Infect Dis.* 2016;63(2):234-241. doi:10.1093/cid/ciw243
4. Ayhan M. New therapeutic options for treatment of multi-drug resistant gram-negative microorganisms. *J Ankara Univ Fac Med.* 2020;73(2):96-101. doi:10.4274/atfm.galenos.2020.92408

5. Kaya F, Ölçü M. Yoğun bakım ünitelerinde çoklu ilaca dirençli *Klebsiella pneumoniae, Escherichia coli* ve *Pseudomonas aeruginosa* suşlarında seftazidim-avibactam direnç oranlarının değerlendirilmesi. *Flora J Infec Dis Clin Microbiol*. 2024;29(1):45-51. doi:10.5578/flora.202401843
6. Wong D, van Duin D. Novel beta-lactamase inhibitors: unlocking their potential in therapy. *Drugs*. 2017;77(6):615-628. doi:10.1007/s40265-017-0725-1
7. Martin RM, Bachman MA. Colonization, infection, and the accessory genome of *Klebsiella pneumoniae*. *Front Cell Infect Microbiol*. 2018;8:4. doi:10.3389/fcimb.2018.00004
8. Zhang W, Guo Y, Li J, et al. In vitro and in vivo bactericidal activity of ceftazidime-avibactam against carbapenemase-producing *Klebsiella pneumoniae*. *Antimicrob Resist Infect Control*. 2018;7(1):142. doi:10.1186/s13756-018-0435-9
9. Liao CH, Lee NY, Tang HJ, et al. Antimicrobial activities of ceftazidim-avibactam, ceftolozane-tazobactam, and other agents against *Escherichia coli, Klebsiella pneumoniae* and *Pseudomonas aeruginosa* isolated from intensive care units in Taiwan: results from the surveillance of multicenter antimicrobial resistance in Taiwan in 2016. *Infect Drug Resist*. 2019;12:545-552. doi:10.2147/IDR.S193638
10. Chen D, Xiao L, Hong D, et al. Epidemiology of resistance of carbapenemase-producing *Klebsiella pneumoniae* to ceftazidime-avibactam in a Chinese hospital. *J Appl Microbiol*. 2022;132(1):237-243. doi:10.1111/jam.15166
11. Kahraman EP, Karakeçe E, Erdoğan F, Uluyurt H, Köroğlu M, Çiftci İH. The evaluation of antibiotic resistance status of *Klebsiella pneumoniae*. *Ortadoğu Tıp Derg*. 2017;9(1):12-18. doi:10.21601/ortadogutipdergisi.291133
12. Tanrıverdi Çaycı Y, Bıyık İ, Çınar C, Birinci A. Antimicrobial resistance of carbapenem-resistant enterobacteriaceae isolates between the years of 2015-2018. *Turk Mikrobiyol Cemiy Derg*. 2020;50(3):134-140. doi:10.5222/TMCD.2020.134
13. Altay Koçak A, Yayla B, Üsküdar Güçlü A, et al. Evaluation of respiratory pathogens isolated in a university hospital in Adana and their antibiotic resistance profiles. *Turk Mikrobiyol Cemiy Derg*. 2019;49(4):226-232. doi:10.5222/TMCD.2019.226
14. Haciseyitoğlu D, Çağ Y, Başgönül S, Özer S. Antibiotic resistance patterns of *Escherichia coli* and *Klebsiella pneumoniae* strains isolated from clinical specimens. *Turk Mikrobiyol Cemiy Derg*. 2014;44(3):101-106. doi:10.5222/TMCD.2014.101
15. Tuna A, Bulut H. Yoğun bakım ünitesinden izole edilen karbapenem dirençli *Pseudomonas* ve *Klebsiella* suşlarının seftazidim/avibaktam duyarlılıklarının saptanması. *KÜ Tıp Fak Derg*. 2023;25(3):408-413. doi:10.24938/kutfd.1318977
16. FDA. Drug safety communication: FDA advises restricting fluoroquinolone antibiotic use for certain uncomplicated infections; warns about disabling side effects that can occur together. Press release. Silver Spring: US Food and Drug Administration; 2016.
17. Özkul Koçak C, Çetin Hazırolan G. Colistin resitance in carbapenem resistant *K. pneumoniae* clinical isolates. *Turk Mikrobiyol Cemiy Derg*. 2019;49(1):17-23. doi:10.5222/TMCD.2019.017
18. Aygar İS. In Vitro evaluation of the increase in MIC value of colistin in the carbapenem resistant klebsiella pneumoniae strains over the years. *Turk Mikrobiyol Cemiy Derg*. 2020;50(3):164-171. doi:10.5222/TMCD.2020.164
19. Sagmak-Tartar A, Ozer AB, Ulu R, Akbulut A. Microbiological evaluation of the pathogens isolated from the endotracheal aspirate samples of the patients followed in the intensive care units: a one-year retrospective analysis. *Klimik J*. 2018;31(1):56-60. doi:10.5152/kd.2018.14
20. Gaibani P, Re MC, Campoli C, Viale PL, Ambretti S. Bloodstream infection caused by KPC-producing Klebsiella pneumoniae resistant to ceftazidime/avibactam: epidemiology and genomic characterization. *Clin Microbiol Infect*. 2020;26(4):516.e1-516.e4. doi:10.1016/j.cmi.2019.11.011
21. Balandín B, Ballesteros D, Pintado V, et al. Multicentre study of ceftazidime/avibactam for Gram-negative bacteria infections in critically ill patients. *Int J Antimicrob Agents*. 2022;59(3):106536. doi:10.1016/j.ijantimicag.2022.106536
22. Isler B, Aslan AT, Akova M, Harris P, Paterson DL. Treatment strategies for OXA-48-like and NDM producing *Klebsiella pneumoniae* infections. *Expert Rev Anti Infect Ther*. 2022;20(11):1389-1400. doi:10.1080/14787210.2022.2128764
23. Öztaş S, ER DK, Dündar D. Karbapenemlere dirençli ve duyarlı *Klebsiella pneumoniae* izolatlarının çeşitli antimikrobiyallere direnç oranları. *KOU Sag Bil Derg*. 2022;8(3):229-232. doi:10.30934/kusbed.1163427
24. Di Bella S, Giacobbe DR, Maraolo AE, et al. Resistance to ceftazidime/avibactam in infections and colonisations by KPC-producing *Enterobacterales:* a systematic review of observational clinical studies. *J Glob Antimicrob Resist*. 2021;25:268-281. doi:10.1016/j.jgar.2021.04.001
25. Akbaş E, Keskin BH, Kayman H, et al. Çok ilaca dirençli gram negatif bakterilerdeki seftazidim-avibaktam duyarlılığının araştırılması. *ANKEM Derg*. 2023;37(3):103-108. doi:10.54962/ankemderg.1406287
26. Stone GG, Seifert H, Nord CE. In vitro activity of ceftazidime-avibactam against gram-negative isolates collected in 18 European countries, 2015–2017. *Int J Antimicrob Agents*. 2020;56(3):106045. doi:10.1016/j.ijantimicag.2020.106045
27. Shields RK, Chen L, Cheng S, et al. Emergence of Ceftazidime-Avibactam Resistance Due to Plasmid-Borne *bla*KPC-3 Mutations during Treatment of Carbapenem-Resistant Klebsiella pneumoniae Infections. *Antimicrob Agents Chemother*. 2017;61(3):e02097-16. doi:10.1128/AAC.02097-16
28. Hoşbul T, Aydoğan C, Kaya S, Bedir O, Özcan H, Gümral R. In vitro activity of ceftazidime-avibactam and colistin against carbapenem-resistant *Pseudomonas aerugınosa* clinical isolates. *J Ist Faculty Med*. 2022;85(3):355-361. doi:10.26650/IUITFD.1092556
29. Wu G, Abraham T, Lee S. Ceftazidime-avibactam for treatment of carbapenem-resistant *Enterobacteriaceae Bacteremia:* table 1. *Clin Infect Dis*. 2016;63(8):1147-1148. doi:10.1093/cid/ciw491
30. Camargo JF, Simkins J, Beduschi T, et al. Successful treatment of carbapenemase-producing pandrug-resistant *Klebsiella pneumoniae* bacteremia. *Antimicrob Agents Chemother*. 2015;59(10):5903-5908. doi:10.1128/AAC.00655-15
31. Akalın H. Karbapenem dirençli Enterobacteriaceae enfeksiyonlarının tedavisi. Görenek L, editör. Karbapenem dirençli gram-negatif bakteri enfeksiyonları. 1. Baskı. Ankara: Türkiye Klinikleri; 2023;45-60.