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Evaluation of Ceftazidime-Avibactam Susceptibility in Carbapenem-Resistant Gram-Negative Bacteria

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Abstract

Objective

Resistance to carbapenem antibiotics, commonly preferred to treat infections caused by multidrug-resistant (MDR) Gram-negative bacteria, is gradually increasing. Ceftazidime-avibactam (CZA) is a novel beta-lactam/beta-lactamase inhibitor combination, proposed as an alternative treatment option for severe infections caused by carbapenem-resistant Gram-negative bacteria. This study aimed to determine the susceptibility of carbapenem-resistant *Klebsiella pneumoniae* (CR-KP), carbapenem-resistant *Escherichia coli* (CR-EC), and carbapenem-resistant *Pseudomonas aeruginosa* (CR-PA) isolates to CZA using the Kirby-Bauer disk diffusion method (DDM) and the BD Phoenix automated system, and to compare the results.

Material and Method

A total of 320 strains (209 CR-KP, 53 CR-EC, and 58 CR-PA) resistant to at least one carbapenem (ertapenem, imipenem, and meropenem), collected between August 2021 and August 2023, were included in the study. CZA susceptibility testing was performed using the DDM and the CPO detect panel of the BD Phoenix automated system (Becton Dickinson, USA). Results were interpreted in accordance with the European Committee on Antimicrobial Susceptibility Testing (EUCAST) standards.

Results

While CZA susceptibility rates determined by the automated system were 74.1% for CR-KP, 64.5% for CR-EC, and 90.9% for CR-PA, the DDM method yielded susceptibility rates of 87.8% for CR-KP, 94.4% for CR-EC, and 81.3% for CR-PA. Categorical agreement was observed in 86.9% of 115 isolates tested by both methods. Although not statistically significant, a declining trend in CZA susceptibility was observed over the years with both methods.

Conclusion

CZA susceptibility rates among carbapenem-resistant Gram-negative isolates in our hospital were consistent with current global data. Determining accurate CZA susceptibility results is important for guiding effective treatment strategies against infections caused by carbapenem-resistant bacteria. The observed discrepancies in susceptibility results between the DDM and the automated system, particularly across different species, underscore the need for further species-specific studies to identify the most reliable testing methodology for CZA susceptibility.

Keywords: ceftazidime-avibactam, antibiotic susceptibility test, automated system, disk diffusion method

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Introduction

The increasing antimicrobial resistance in Gram-negative bacteria leads to multidrug-resistant (MDR) bacterial infections, limits treatment options, and thus contributes to higher morbidity and mortality (1). Resistance to carbapenem antibiotics, which are among the important alternatives in the treatment of infections caused by MDR Gram-negative bacteria, is also increasing and spreading rapidly (2). Options such as aminoglycosides, fosfomycin, and colistin are preferred for treating infections caused by carbapenem-resistant Gram-negative bacteria (3). Due to the limited benefits of these antibiotics, finding alternative antibacterials for treating infections caused by carbapenem-resistant bacteria has become a priority (4). Ceftazidime-avibactam (CZA) is a β-lactam/β-lactamase inhibitor combination effective against Ambler class A, C, and D carbapenemases, but inactive against class B. It was approved by the United States Food and Drug Administration (FDA) for the treatment of Gram-negative bacterial infections with limited treatment options. These include complex intra-abdominal and urinary tract infections, as well as hospital-acquired pneumonia caused by carbapenem-resistant Enterobacterales (CRE) and hard-to-treat resistant *Pseudomonas aeruginosa* strains (3). Although CZA is a relatively new antibiotic, there are reports of resistance to CZA, and this issue requires close attention (5). Assessment of CZA susceptibility is important to determine and monitor the effectiveness of the antibiotic and to detect possible resistance during treatment (6). Various susceptibility testing methods, such as broth microdilution (BMD), broth disk elution, the Kirby-Bauer disk diffusion method (DDM), gradient strip test, and an automated system, can be used to determine CZA susceptibility. (7). While the minimum inhibitory concentration (MIC) value of CZA for the tested isolate can be determined with the CPO detect panel of the BD Phoenix automated system (Becton Dickinson, USA), the inhibition zone diameter, which shows the inhibition of bacterial growth in the presence of the CZA disk, can be determined with DDM (8). This study aimed to determine the susceptibility of carbapenem-resistant *Klebsiella pneumoniae* (CR-KP), carbapenem-resistant *Escherichia coli* (CR-EC), and carbapenem-resistant *P. aeruginosa* (CR-PA) strains, isolated from various clinical samples, to CZA using the DDM and the BD Phoenix automated system, and to compare the results of both methods.

Material and Method

Clinical samples submitted to the Medical Microbiology Laboratory from various clinics between August 2021 and August 2023 were routinely cultured on 5% sheep blood agar (RTA, Turkey), eosin methylene blue agar (RTA, Turkey), and, when required, chocolate agar (RTA, Turkey). All cultures were incubated at 35±2°C for 24-48 hours. Blood cultures were incubated in an automated blood culture system (BacT/ALERT 3D, bioMérieux, France), and upon detection of a growth signal, subcultures were performed and incubated under the same conditions. Bacterial identification and antimicrobial susceptibility testing of strains isolated from the culture and evaluated as causative agents were performed using the BD Phoenix automated system (Becton Dickinson, USA). Isolates identified as *K. pneumoniae*, *E. coli*, and *P. aeruginosa* and determined to be resistant to at least one carbapenem antibiotic (ertapenem, imipenem, and meropenem) were included in the study. Susceptibility to CZA was determined using the DDM and/or the CPO detect panel of the BD Phoenix automated system. For DDM, a 0.5 McFarland standard suspension was prepared from fresh colonies and spread evenly on Mueller-Hinton agar (MHA) (RTA, Turkey) plates. A CZA disk (10/4 µg, Bioanalyse, Turkey) was placed on an MHA plate within 15 minutes and left to incubate in the incubator at 35±2°C. Inhibition zone diameters were read from the back of the plate against a dark background illuminated with reflected light after 18-24 hours of incubation. Simultaneously, the BD Phoenix automated system was loaded with the CPO panel, and results were obtained after 18-24 hours. The results obtained by both methods were interpreted in accordance with the current European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines (9-11). E. coli ATCC 25922 was used as the quality control strain for CZA susceptibility testing. Repeated isolations of the same species from different specimens of the same patient were excluded from the study. The data obtained in the study were analyzed using the IBM SPSS Statistics 31.0 program. Pearson's chi-square test was applied to compare CZA susceptibility rates between 2021-2022 and 2022-2023, and a p-value <0.05 was considered statistically significant. Cohen's Kappa (κ) analysis was performed to assess the degree of agreement between the two methods.

Results

A total of 320 carbapenem-resistant isolates, including 209 CR-KP, 53 CR-EC, and 58 CR-PA, were included in the study. Among these, 161 were obtained from the intensive care unit, 82 from the internal medicine ward, 47 from the surgical ward, and 30 from outpatient clinics. The most frequent specimen types were urine, endotracheal aspirate, and blood. The distribution of isolates by sample type is shown in Table 1.

A total of 199 isolates, including 135 CR-KP, 31 CR-EC, and 33 CR-PA, were tested with the automated system, and a total of 236 isolates, including 157 CR-KP, 36 CR-EC, and 43 CR-PA, were tested with DDM, while 115 of the isolates (83 CR-KP, 14 CR-EC, and 18 CR-PA) were tested with both DDM and the automated system.

Of the 199 isolates tested for CZA susceptibility by the automated system, 150 (75.4%) were found to be susceptible and 49 (24.6%) were found to be resistant.

Table 1 Distribution of isolates tested for ceftazidime-avibactam susceptibility according to sample types (n)

Sample type	CR-KP	CR-EC	CR-PA	Total
Urine	101	27	13	141
ETA	38	2	22	62
Blood	33	8	9	50
Sputum	14	4	6	24
Abscess	9	5	1	15
Wound	5	2	2	9
Tissue	2	-	4	6
Bile	3	2	-	5
Thoracentesis fluid	2	2	1	5
Catheter	2	1	-	3
Total	**209**	**53**	**58**	**320**

ETA: Endotracheal aspirate, CR-KP: Carbapenem-resistant *K. pneumoniae*, CR-EC: Carbapenem-resistant *E. coli,* CR-PA: Carbapenem-resistant *P. aeruginosa*

Table 2 Ceftazidime-avibactam susceptibility rates of carbapenem-resistant isolates by bacterial species, testing method, and study year [number of CZA susceptible isolates/number of tested isolates (%)]

Date	Bacterial Species	BD Phoenix	Disk Diffusion Method
2021-2022	CR-KP	59/77 (76.6)	36/40 (90)
	CR-EC	12/18 (66.7)	7/7 (100)
	CR-PA	14/14 (100)	5/6 (83.3)
	Total	**85/109 (77.9)**	**48/53 (90.6)**
2022-2023	CR-KP	41/58 (70.7)	102/117 (81.2)
	CR-EC	8/13 (61.5)	27/29 (93.1)
	CR-PA	16/19 (84.2)	30/37 (81.1)
	Total	**65/90 (72.2)**	**159/183 (86.8)**
Total	CR-KP	100/135 (74.1)	138/157 (87.8)
	CR-EC	20/31 (64.5)	34/36 (94.4)
	CR-PA	30/33 (90.9)	35/43 (81.3)
	Total	**150/199 (75.3)**	**207/236 (87.7)**

S: Susceptible, CR-KP: Carbapenem-resistant K. pneumoniae,
CR-EC: Carbapenem-resistant *E. coli,* CR-PA: Carbapenem-resistant *P. aeruginosa*

Table 3 Comparison of the CZA susceptibility test results obtained by the disk diffusion method and the BD Phoenix automated system according to bacterial species [n (%)]

Bacterial Strains			Methods		
			BD Phoenix		
			S	R	Total
CR-KP	Disk Diffusion Method	S	61 (73.4)	10 (12.1)	71 (85.5)
		R	1 (1.2)	11 (13.3)	12 (14.5)
		Total	62 (74.6)	21 (25.4)	83 (100)
			BD Phoenix		
			S	R	Total
CR-EC	Disk Diffusion Method	S	10 (71.4)	3 (21.5)	13 (92.9)
		R	0 (0)	1 (7.1)	1 (7.1)
		Total	10 (71.4)	4 (28.6)	14 (100)
			BD Phoenix		
			S	R	Total
CR-PA	Disk Diffusion Method	S	16 (88.8)	0 (0)	16 (88.8)
		R	1 (5.6)	1 (5.6)	2 (1.2)
		Total	17 (94.4)	1 (5.6)	18 (100)
			BD Phoenix		
			S	R	Total
All strains	Disk Diffusion Method	S	87 (75.6)	13 (11.3)	100 (86.9)
		R	2 (1.8)	13 (11.3)	15 (13.1)
		Total	89 (77.4)	26 (22.6)	115 (100)

CR-KP: Carbapenem-resistant *K. pneumoniae*,
CR-EC: Carbapenem-resistant E. coli, CR-PA: Carbapenem-resistant *P. aeruginosa*

While the CZA susceptibility rate was determined as 77.9% by the automated system between 2021 and 2022, 72.2% of the isolates tested between 2022 and 2023 were found to be susceptible to CZA. Of the 236 isolates tested for CZA susceptibility by DDM, 207 (87.7%) were found to be susceptible and 29 (12.3%) were found to be resistant. While the CZA susceptibility rate determined by DDM was 90.6% between 2021-2022, 86.8% of the isolates tested by DDM between 2022-2023 were found as susceptible to CZA (Table 2).

When the susceptibility test results were evaluated considering the bacterial species, CZA susceptibility rate was found to be 74.1% for CR-KP, 64.5% for CR-EC, and 90.9% for CR-PA using the automated system, while it was 87.8% for CR-KP, 94.4% for CR-EC, and 81.3% for CR-PA using DDM. Ceftazidime-avibactam susceptibility rates of carbapenem-resistant isolates according to bacterial species, testing method, and study year are given in Table 2. While a decrease in susceptibility rates was observed over the years with both methods, there was no statistically significant difference between CZA susceptibility rates determined by BD Phoenix (p=0.35) and DDM (p=0.47) between 2021-2022 and 2022-2023 (Table 2).

Of the 115 isolates that were tested using both methods, the CZA susceptibility rate was detected as 77.4% by the automated system and 86.9% by DDM, while 75.6% of the isolates were detected as susceptible by both methods. The overall categorical agreement rate of the CZA susceptibility test results obtained by the DDM and automated system was 86.9% (100/115). On the other hand, when bacterial species were taken into account, categorical agreement rates were 86.7% (72/83) for CR-KP, 78.6% (11/14) for CR-EC, and 94.4% (17/18) for CR-PA (Table 3). While moderate agreement was observed between the DDM and automated system results for all isolates (κ=0.56), substantial agreement for CR-PA (κ=0.64), moderate agreement for CR-KP (κ=0.59), and fair agreement for CR-EC (κ=0.32) was observed. Among the isolates with discordant test results, 9 were urine, 4 were endotracheal aspirates, and 2 were blood isolates. These included 11 CR-KP, 3 CR-EC, and 1 CR-PA isolates.

Discussion

Infections caused by MDR gram-negative bacteria are a significant cause of morbidity and mortality. Due to high resistance rates to existing antibiotics, new antibiotics are essential for effective treatment (12, 13). Determining the susceptibility of CZA, approved specifically for treating resistant infections, is crucial for managing and controlling these challenging pathogens (5). This study investigated the susceptibility of CR-KP, CR-EC, and CR-PA isolates to CZA, which is a prominent option in the treatment of serious infections caused by these isolates. Moreover, annual variations in susceptibility rates and the outcomes of different testing methods were compared. It was observed that the CZA susceptibility rates determined by both the automated system (from 77.9% to 72.2%) and DDM (from 90.6% to 86.8%) for all isolate types decreased in 2022-2023 compared to 2021-2022. Although a statistically significant difference was not observed between the two periods, the observed trend toward decreased susceptibility to CZA may indicate an early warning sign of emerging resistance.

Several international programs have been conducted to determine CZA susceptibility and perform surveillance. These studies are important for evaluating the global situation, analyzing potential resistance problems, and developing appropriate solutions. According to the International Network for Optimal Resistance Monitoring (INFORM) Surveillance Program, CZA susceptibility was found to be 88.3% for CR-KP, 76.2% for CR-EC, and 81.5% for CR-PA. CZA susceptibility in isolates included in this surveillance program from Turkey was reported as 89.5% for CR-KP and 85.7% for CR-EC (14, 15). According to the Antimicrobial Testing Leadership and Surveillance (ATLAS) data network, CZA susceptibility was 52.1% for CR-KP, 8.8% for CR-EC, and 41.1% for CR-PA. In this data network, the susceptibility rate for isolates originating from Turkey was found to be 85.8% for CR-KP, 75% for CR-EC, and 46.67% for CR-PA (16). Additionally, although the CZA susceptibility determined by both the DDM and the automated system in our study was higher than the ATLAS data overall, the results for isolates from our country in the ATLAS program were similar to those in our study.

Among the methods used to determine CZA susceptibility, BMD is considered the gold standard; however, it is costly and requires specialized laboratory equipment. The DDM is practical and cost-effective. Automated systems are practical for routine laboratory use and help minimize operator errors; however, inaccurate results may still occur (17). For these reasons, numerous studies have been conducted to determine CZA susceptibility using different methods. In studies conducted in Turkey between 2022 and 2024 involving CR-KP, CR-EC, and CR-PA isolates, varying susceptibility rates were reported using the DDM, ranging from 64% to 85% for CR-KP, 44% to 100% for CR-EC, and 24% to 83% for CR-PA (18-24). In our study, CZA susceptibility determined by the DDM was 87.9% for CR-KP, 94.4% for CR-EC, and 81.4% for CR-PA. These rates are comparable to those reported by Cetinkol et al., Koca et al., and Bilgin et al., and notably higher than those reported by Oztas et al., Arici et al., Akbas et al, and Yakut et al. (18-24). In our study, CZA susceptibility determined by DDM was similar to that reported in the INFORM study for all isolates, while susceptibility determined by the automated system was lower for CR-KP and CR-EC and higher for CR-PA compared to INFORM. Arici et al. attributed the lower susceptibility observed in their study to a higher prevalence of extensively drug-resistant (XDR) isolates in their study whereas Akbas et al. suggested that the reduced susceptibility in their setting might be associated with the presence of specific resistance genes (22, 23). The higher CZA susceptibility rates determined in our study compared to previous reports may be attributed to the lower proportion of MDR isolates. Additionally, the lower prevalence of isolates harboring carbapenemase genes associated with intrinsic resistance to CZA may also have contributed to this finding.

Using the CPO test panel of the BD Phoenix 100 automated system, Ugurlu et al. reported CZA susceptibility rates of 97.6% for CR-KP and 50% for CR-EC (25). Mermutluoglu et al. reported rates of 57% and 66% for CR-KP and CR-EC, respectively, while Albichr et al. documented a CZA susceptibility rate of 31.1% for CR-PA (26, 27). In our study, the CZA susceptibility rates determined by the automated system were 74.1% for CR-KP, 64.5% for CR-EC, and 90.9% for CR-PA. In comparison to the findings of Mermutluoglu et al., in our study CZA susceptibility rate for CR-KP isolates was higher, while the CR-EC result was similar. Compared to Albichr et al., our CR-PA result was higher. Albichr et al. reported that 60% of the isolates in their study contained Ambler class B carbapenemase, and therefore their CZA susceptibility for CR-PA isolates remained low (26). Hosbul et al. determined the susceptibility of CZA using BMD as 92.7% for CR-KP and 100% for CR-PA (28, 29). These rates were higher than those we observed with both methods in all isolates. In the study conducted at our hospital by Kole et al. between 2018 and 2020, CZA susceptibility among CR-KP isolates, as determined by the BMD method, was reported to be 91.4% (30). In our study conducted between 2021 and 2023, CZA susceptibility among CR-KP isolates was found to be 74.1% using the automated system and 87.9% using DDM, indicating a decrease in CZA susceptibility rates in our hospital over the years. This decrease may be associated with the increased use of CZA, which can contribute to the development of resistance. Additionally, this difference in susceptibility rates compared to those reported by Kole et al. may also be attributed to the use of different testing methods to determine CZA susceptibility. The inability to perform BMD testing in our study represents a limitation that may have influenced the comparability of the results.

Numerous studies have been conducted to compare different methods for determining CZA susceptibility and to evaluate their accuracy in order to identify the most appropriate, cost-effective, and practical option. Shields et al. reported a categorical agreement of 76% between DDM and BMD among CRE isolates, while emphasizing that 28% of CZA susceptible CRE isolates were misclassified as resistant by DDM. The cause remained unclear, possibly related to the antibiotic disks used or the distribution of the antibiotic on the agar. Based on these findings, the authors concluded that BMD could overestimate CZA resistance and emphasized the need for further studies to evaluate the suitability of DDM for routine clinical use in CZA susceptibility testing (7). In contrast, Park et al. found the categorical agreement between BMD and the BD Phoenix 100 automated system to be 97.6% for *Enterobacterales* and 100% for P. aeruginosa (8). Schaumburg et al. reported categorical agreement between DDM and BMD in MDR *P. aeruginosa* and XDR *P. aeruginosa* strains as 79.7% and 88%. The authors also found very major errors (VME) as 1.4% and major errors (ME) as 17.8-30.9%, and accordingly, it was concluded that DDM was not a suitable alternative to BMD (31). Wenzler et al. found that the categorical agreement between DDM and BMD for CR-KP was 98.5% when using a 10/4 µg CZA disk and 82.6% with a 30/20 µg CZA disk. The authors reported that although 10/4 µg CZA disks performed better in determining CZA susceptibility in CR-KP, DDM was not considered a valid alternative to BMD due to the relatively high ME compared to BMD (32). In contrast, Wang et al. reported categorical agreement values of 98.5% and 93.5% between DDM and BMD for *Enterobacterales* and *P. aeruginosa*, respectively, and concluded that the DDM could be considered as an alternative to the BMD method for Enterobacterales and *P. aeruginosa* (33). Similarly, Daragon et al. compared DDM and the Vitek2 automated system using BMD as the reference and concluded that DDM was a reliable method for determining CZA susceptibility in *P. aeruginosa*, recommending its validation with BMD due to high VME rates observed with the Vitek2 system (34). Zhang et al. found categorical agreement between BMD and DDM to be 100% for *Enterobacterales* and 95.9% for P. aeruginosa, indicating that DDM met the laboratory requirements for CZA susceptibility (35). Sharma et al. also reported a high categorical agreement (94.6%) between DDM and BMD in CRE isolates and suggested DDM as a potential alternative to BMD for determining CZA susceptibility in these isolates (36).

In our study, we aimed to compare DDM and the BD Phoenix automated system, which are considered practical and cost-effective methods for the determination of CZA susceptibility. Among 115 isolates tested by both methods, the categorical agreement was found to be 86.9%. These findings are consistent with those reported by Park et al., Wenzler et al., Wang et al., Daragon et al., Zhang et al., and Sharma et al., who supported the applicability of DDM (8,32-36). The categorical agreement rate in our study was higher than that reported by Shields et al. and Schaumburg et al., who did not accept DDM as a viable alternative (7,31). Additionally, when the categorical agreement rates of both methods were examined at the species level, they were determined as 86.7% for CR-KP, 78.6% for CR-EC, and 94.4% for CR-PA. These findings reveal that agreement rates between methods may vary by species and emphasize the importance of determining species-specific susceptibility tests. Further studies using BMD as the reference standard are warranted to validate the accuracy and clinical reliability of both DDM and automated systems for CZA susceptibility testing. In our hospital, CZA susceptibility ranged from 75% to 88% with both the automated system and DDM, and a decline in susceptibility rates was observed over the years using both methods. The decrease in CZA susceptibility over the years may be associated with widespread use of CZA, highlighting the need to investigate the potential resistance mechanisms to prevent further development and dissemination of CZA resistance. Additionally, further studies are needed to evaluate and compare different methods to identify methodological issues that may affect CZA susceptibility.

In conclusion, clinical laboratories must report CZA susceptibility results to healthcare providers using at least one validated method, such as DDM or an automated antimicrobial susceptibility testing system, to support the consideration of CZA as a therapeutic alternative for infections caused by carbapenem-resistant bacteria. In our study, it was observed that the automated system and DDM did not always give consistent results in terms of CZA susceptibility results. Therefore, we emphasize the need for additional studies to determine a reliable susceptibility testing method for CZA and to assess its effectiveness in antimicrobial management.

Conflict of Interest Statement

There is no financial conflict of interest with any organization, institution, or person related to our article, and there is no conflict of interest between the authors.

Ethical Approval

This study was Ethical approval was obtained from the Ethics Committee of Suleyman Demirel Faculty of Medicine (Decision no:38, date May 12, 2025). The study was conducted in accordance with the principles outlined in the Declaration of Helsinki.

Consent to Participate and Publish

Written informed consent to participate and publish was obtained from all individual participants included in the study.

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Availability of Data and Materials

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Artificial Intelligence Statement

The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

Authors' Contributions

TAR: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Visualization; Writing-original draft; Validation

YS: Data curation; Formal analysis; Supervision; Visualization; Validation

MTE: Investigation; Data curation; Validation

GB: Investigation; Data curation; Validation

ESC: Project administration; Supervision; Visualization; Writing-original draft; Writing-review and editing; Validation

MCS: Supervision; Writing-review and editing; Validation.

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