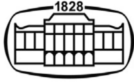

AKADÉMIAI KIADÓ

Ceftazidime – Avibactam susceptibility among carbapenem-resistant Enterobacterales in a pilot study in Turkey

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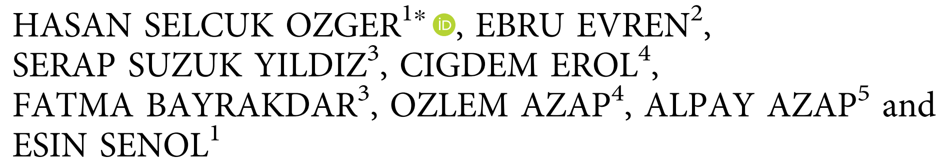

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RESEARCH ARTICLE

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ABSTRACT

This study aimed to detect carbapenemase genes and to determine the *in vitro* susceptibility of Ceftazidime-Avibactam (CZA) in *Enterobacterales* isolates. Carbapenemase genes were detected by polymerase chain reaction. CZA sensitivity of isolates was evaluated with broth microdilution (BMD) and disk diffusion methods. A total of 318 carbapenem-resistant *Enterobacterales* isolates were included. Most of the isolates ($n = 290$, 91.2%) were identified as *Klebsiella pneumoniae*. The most common carbapenemase type was OXA-48 ($n = 82$, 27.6%). CZA susceptibility was evaluated in 84 isolates with OXA-48 and KPC carbapenemase activity. Both BMD and disk diffusion methods revealed that 95.2% of the isolates were sensitive to CZA; whereas, 4 (4.76%) isolates were resistant to CZA. Among colistin resistant isolates, 96.5% ($n = 80$) of them were susceptible to CZA. Our study demonstrated high *in vitro* efficacy of CZA in *Enterobacterales* isolates producing OXA-48 carbapenemase. High susceptibility rates against colistin resistant isolates which generally are also pan drug resistant, makes CZA a promising therapeutic choice for difficult-to-treat infections. Due to its high correlation with the BMD, disk diffusion method is a suitable and more practical method in detecting CZA *in vitro* activity.

KEYWORDS

carbapenemase, ceftazidime-avibactam, colistin, *Enterobacterales*

INTRODUCTION

Carbapenem-resistant (CR) gram-negative bacterial infections are becoming an important public health concern [1]. Increased resistance to carbapenem among *Enterobacterales* has led to these microorganisms being included in the World Health Organization (WHO) priority list of resistant pathogens [2]. According to 2019 Central Asian and European Surveillance of Antimicrobial Resistance (CAESAR) data, the frequency of carbapenem resistance in *Klebsiella* isolates was ranged between 34% and 50% in Turkey [3]. In addition to carbapenem resistance, it is necessary to include new antimicrobial agents for therapy of infections due to increasing resistance to last resort treatment options, such as colistin or fosfomycin [4]. Therefore, the

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search for new antibiotics or new combinations has accelerated. Ceftazidime-Avibactam (CZA), a combination of ceftazidime and a diazabiocyclo-octane beta-lactamase inhibitor, is one of these treatment alternatives [5]. CZA has increased activity against gram-negatives due to avibactam, a potent inhibitor of ambler class A, C and group D beta-lactamases [5]. However, avibactam is ineffective against class B beta-lactamases which is the most common resistance mechanism against CZA [5]. For this reason, it is important to specify the general definition of CR, to clearly define resistance mechanisms, and to determine their *in vitro* activities to use new therapeutic agents effectively such as CZA [1].

CZA is approved for clinical use by the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) for the treatment of complicated intra-abdominal infections, complicated urinary tract infections, nosocomial pneumonia, including ventilator-associated pneumonia, and gram-negative bacterial infections for which treatment options are limited [6, 7]. However, CZA has been recently approved in Turkey with a limited indication for use. This study aims to evaluate the local carbapenemase activity in *Enterobacterales* isolates and to determine the *in vitro* susceptibility of CZA in these isolates.

MATERIALS AND METHODS

Bacterial strains

Isolates were obtained from clinical samples (blood and lower respiratory tract samples) between 2016 and 2018 at Ankara University (Ankara, Turkey), Baskent University (Ankara, Turkey), and Gazi University (Ankara, Turkey) medical faculty hospitals were included in the study. Only one isolate from each patient was included. Isolates that might have been associated with an outbreak were excluded from the study based on local surveillance data. Isolates were stored passaged in brain heart infusion broth at −80 °C till the study.

Identification of isolates

Pure bacterial colonies obtained from fresh culture passages after 18–20 h of incubation at 37° C in an aerobic environment, ambinet atmosphere, were used in the study. The identification of bacteria was done by MALDI-TOF MS (Bruker, Germany).

Investigation of carbapenem resistance

Meropenem susceptibilities of all samples included in our study were evaluated by broth microdilution (BMD) method and isolates with minimum inhibitory concentration (MIC) value >8 mg/L were considered meropenem resistant according to the EUCAST criteria [3]. Carbapenemase genes were detected by polymerase chain reaction (PCR) for the 8 most common carbapenemase genes (*bla*$_{OXA-23}$, *bla*$_{OXA-48}$, *bla*$_{OXA-51}$, *bla*$_{OXA-58}$, *bla*$_{NDM}$, *bla*$_{IMP}$, *bla*$_{VIM}$, and *bla*$_{KPC}$) (Table 1) [8–13].

Table 1. Oligos used for amplification

Oligos	5′ → 3′	Amplicon Size (bp)
OXA-23	GATCGGATTGGAGAACCAGA ATTTCTGACCGCATTTCCAT	501
OXA-48	TTGGTGGCATCGATTATCGG GAGCACTTCTTTTGTGATGGC	733
OXA-51	TAATGCTTTGATCGGCCTTG TGGATTGCACTTCATCTTGG	353
OXA-58	AAGTATTGGGGCTTGTGCTG CCCCTCTGCGCTCTACATAC	599
NDM	GTAGTGCTCAGTGTCGGCAT GGGCAGTCGCTTCCAACGGT	476
VIM	GTGTTTGGTCGCATATCGC CGCAGCACCAGGATAGAAG	380
IMP	GGAATAGAGTGGCTTAATTCTC CCAAACCACTACGTTATC	624
KPC	ATGTCACTGTATCGCCGTC TTTTCAGAGCCTTACTGCCC	893

OXA, Oxacillinase; NDM, New Delhi metallo-lactamase; VIM, Verona integron-encoded metallo-β-lactamase; IMP, Imipenem-hydrolyzing β-lactamase; KPC, *Klebsiella pneumoniae* carbapenemase.

Determination of CZA and colistin susceptibility of isolates

CZA *in vitro* activity was evaluated in OXA-48 and KPC carbapenemase positive isolates by 2 different phenotypic methods. BMD was used as a reference method for determining *in vitro* activity of CZA. BMD was performed using cation-adjusted Mueller-Hinton broth (Becton Dickinson, NJ, USA) according to the recommendations of ISO 20776-1 and Clinical and Laboratory Standards Institute (CLSI) guidelines [14, 15]. Ceftazidime was purchased from Biosynth Carbosynth (UK), avibactam was obtained from MedChemExpress (NJ, USA). According to EUCAST and CLSI recommendations, ceftazidime was tested at double dilution concentrations of 0.016–256 mg/L, while avibactam concentration was fixed at 4 mg/L [3, 16]. According to the EUCAST criteria, isolates with an MIC value ≤8 mg/L were considered CZA susceptible, and isolates >8 mg/L were considered CZA resistant [2].

Disk diffusion was used as a comparison method to evaluate the *in vitro* activity of CZA. Disk diffusion tests were performed according to the manufacturer's instructions (Mueller – Hinton agar, 0.5 McFarland suspension of test organism, incubated at 35° C, read after 16–18 h of incubation) using 10/4 µg (Oxoid, UK) CZA discs. According to the EUCAST criteria, isolates with a zone diameter of ≥13 mm were considered CZA susceptible, and isolates <13 mm were considered resistant [3].

Multidrug resistance is defined as combined resistance to at least one representative of three antimicrobial groups: fluoroquinolones (levofloxacin and/or moxifloxacin), carbapenems (ertapenem, imiponem and/or meropenem) and aminoglycosides (gentamicin and/or amicacin). Isolates with

missing data on one or more of the groups are excluded from the analysis of multidrug resistance. Colistin susceptibility in these isolates was also evaluated by BMD method and isolates with MIC values >2 mg/L according to EUCAST criteria were accepted as colistin-resistant [3].

Statistical analysis

PASW 18.0 for Windows program was used for statistical analysis. Descriptive statistics were presented as mean, standard deviation, median, percentile 25 (Q1), percentile 75 (Q3), minimum and maximum for numerical variables. Spearman's rho test statistics were used for correlation between continuous data that did not show normal distribution. Statistical significance level was accepted as a *P*-value less than 0.05.

RESULTS

A total of 318 isolates were included in the study. 194 (61%) of the isolates were isolated from lower respiratory tract samples and 124 (39%) from blood samples. MALDI-TOF MS (Bruker, Germany) identification and carbapenemase resistance gene analysis results of the isolates were evaluated. The most frequently isolated bacteria were identified as *Klebsiella pneumoniae* with 290 (91.2%) of the isolates (Table 2). Carbapenemase activity was evaluated in 297 isolates (21 isolates were not reproduced). No carbapenemase activity was detected in 85 (28.6%) of the isolates. The most common type of carbapenemase was OXA-48 ($n = 82$, 27.6%). More than one carbapenemase gene positivity was detected in 89 (29.9%) of the isolates (Fig. 1).

CZA susceptibility was evaluated by disk diffusion and BMD methods in 84 isolates with OXA-48 and KPC carbapenemase activity. Eighty (95.2%) of the isolates were susceptible to CZA by BMD. According to the disc diffusion result using CZA 10/4 µg disk, 80 (95.2%) of the isolates were detected as susceptible to CZA (Table 3). The distribution of MIC values according to the zone diameters of disk diffusion results was presented in Fig. 2. A high level of correlation was found between BMD and disk diffusion methods in determining the *in vitro* activity of CZA (Spearman correlation coefficient = −0.72, $P < 0.001$). CZA resistance was detected in 4 (4.76%) of the 84 isolates. All of the resistant isolates were identified as *K.pneumoniae*. One of the four CZA resistant isolates were KPC positive and 3 were OXA-48 positive. Two of these isolates were also resistant to colistin. Other antibiotic susceptibilities were evaluated retrospectively in 62 of 84 isolates and 77.4% (48/62) of these strains were evaluated as MDR. 93.8% (45/48) of MDR isolates were susceptible to CZA. Among 84 isolates, 58 (69.0%) of them were found resistant to colistin by BMD method (Table 3). Of these 58 isolates, 56 (96.5%) were susceptible to CZA (Table 4).

Table 2. MALDI-TOF MS Identification of *Enterobacterales* isolates ($N = 318$)

Enterobacterales	n (%)
Klebsiella pneumoniae	290 (91.2)
Escherichia coli	20 (6.3)
Enterobacter cloacae	6 (1.9)
Klebsiella variicola	1 (0.3)
Proteus mirabilis	1 (0.3)

Table 3. In vitro activity of CZA and Colistin in OXA-48 and KPC positive *Enterobacterales* isolates

$N = 84$*		n (%)	%95 CI
Co MIC	R (>2 mg/L)	58 (69.0)	0.58–0.79
	S (≤2 mg/L)	26 (31.0)	0.21–0.42
CZA DD (10/4 µg)	R (<13 mm)	4 (4.8)	0.01–0.12
	S (≥13 mm)	80 (95.2)	0.88–0.99
CZA MIC	R (>8 mg/L)	4 (4.8)	0.01–0.12
	S (≤8 mg/L)	80 (95.2)	0.88–0.99

*Reproduction was not achieved in 1 isolate.
Abbreviations: CZA, Ceftazidime-Avibactam; Co, Colistin; R, Resistant; S, Sensitive; MIC; Minimum inhibitory concentration; DD; Disc diffusion.

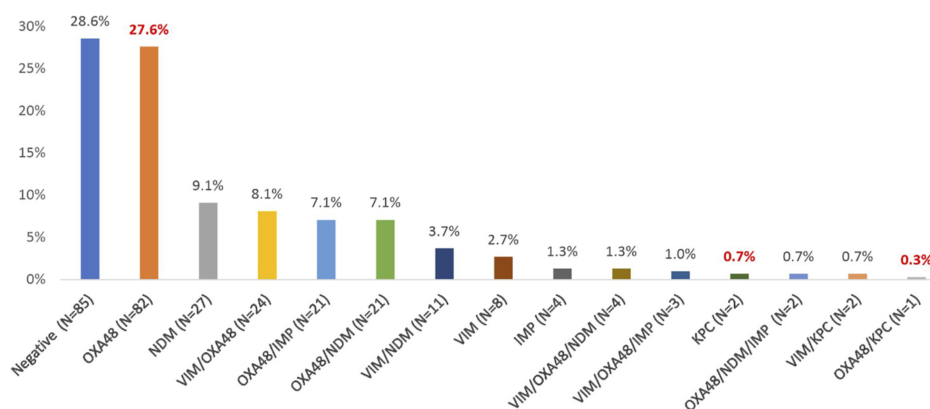

Fig. 1. Carbapenemase distribution of *Enterobaterales* isolates

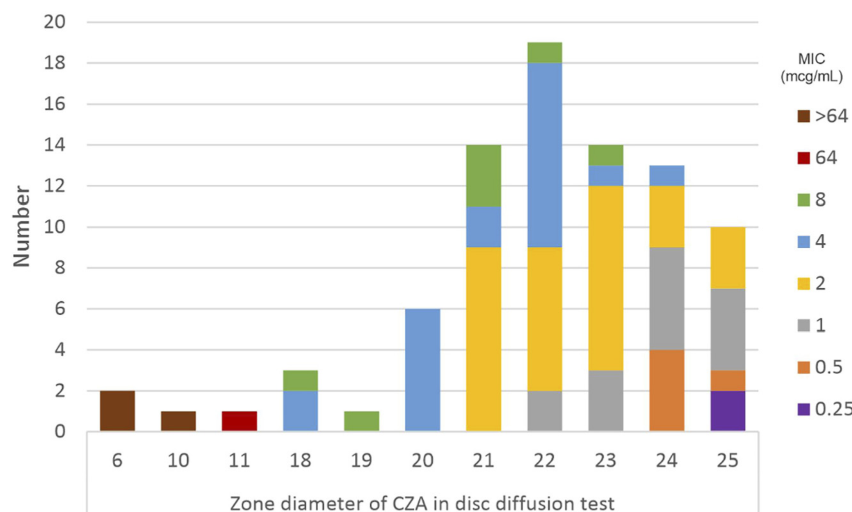

Fig. 2. Distribution of isolates MIC values according to zone diameter in disk diffusion method

Table 4. In vitro activity of CZA among Co resistant isolates, *N* = 84

		CZA MIC (mg/L)	
		R	S
Co (mg/L)	R	2 (50.0)	56 (70.0)
	S	2 (50.0)	24 (30.0)

CZA, Ceftazidime-Avibactam; MIC, Minimum inhibitory concentrations; R, Resistant; S, sensitive; Co, Colistin

DISCUSSION

Our study demonstrated high *in vitro* efficacy of CZA, especially in *Enterobacterales* isolates producing OXA-48 carbapenemase. This *in vitro* activity was also demonstrated in colistin-resistant isolates. Due to its high correlation with the BDM, disk diffusion is a suitable method in detecting CZA *in vitro* activity.

CZA *in vitro* activity in *Enterobacterales* isolates is above 99% and this *in vitro* activity also continues over 95% against ceftazidime resistant, multi-drug resistant, and colistin resistant isolates [6, 7, 17]. On the other hand, the *in vitro* activity of CZA in carbapenemase-producing *Enterobacterales* varies according to the carbapenemase type. Due to the *in vitro* ineffectiveness of avibactam against Ambler class B beta-lactamases, CZA does not show *in vitro* activity against MBL-positive isolates, and its *in vitro* activity is found to be low in countries with high MBL activity [17–19]. In contrast, *in vitro* efficacy in MBL-negative (KPC, OXA-48, GES producing *Enterobacterales*) CREs is very high and varies between 95% and 99% [6, 7, 17]. In-vitro susceptibility of CZA against OXA-48 and OXA-48-like enzyme producing *Enterobacterales* is 99.2% and 100%, respectively [17]. Based on these *in vitro* data, in our study, CZA activity was evaluated only in OXA-48 and KPC positive isolates and 95.2% *in vitro* activity was found. OXA-48 carbapenemases most prevalent in Turkey, is also the most common type of carbapenemases in our study [20–23]. According to a recent study evaluating the carbapenemases epidemiology in Turkey, the most common carbapenemases are OXA-48 and KPC with 52.2% and 16.1% frequency, respectively [24]. When our study is evaluated together with these *in vitro* results, it supports that the potential effectiveness of CZA in clinical use may be high in Turkey. On the other hand, the high number of MBL positive isolates in our study indicates the importance of carbapenemase local epidemiology before the widespread clinical use of CZA. It was shown that, frequency of MBL producing *Enterobacterales* increases in Turkey, especially in certain regions or centers [24–27]. Also, in our study, more than one carbapenemase gene positivity was detected, one of which was MBL type carbapenemases in a significant portion of the isolates. It is stated that as a result of the selective pressure of beta-lactams, pathogens carrying multiple carbapenemase genes will become more common [20]. The *in vitro* reports from Turkey about *Enterobacterales*, carrying multiple carbapenemase genes, are also increasing [24]. Although the most important cause of carbapenem resistance in *Enterobacterales* is the production of plasmid-derived carbapenemase, the role of different mechanisms other than carbapenemase production such as intrinsic resistance, porin loss in the development of carbapenem resistance should not be ignored [1]. Carbapenemase production was not detected in a significant amount of the CR isolates in our study. This indicates the importance of reliable *in vitro* susceptibility tests, as well as the epidemiology of carbapenemase before the clinical use of CZA.

In our study, CZA sensitivity was evaluated by BMD, which is the recommended reference method, and disk diffusion (10/4 μg CZA disk) as a comparison method. In both methods, 95.2% of the isolates are susceptible to CZA according to the cut-off values [2]. It is thought that the high correlation between both methods will facilitate the phenotypic determination of CZA *in vitro* sensitivity in

OXA-48 positive *Enterobacterales* isolates in practice. The test results of the quality for CZA 10/4 µg disc by EUCAST showed that the 13 mm cut-off value correlates well with BMD MIC values and the frequency of major error (false detection) for *Enterobacterales* is 1.6% [28]. However, it is stated that type of microorganism and resistance pattern (MDR, ceftazidime and carbapenem-resistant) may affect the sensitivity of phenotypic methods and resistance can be detected higher than it is with the disc diffusion method [29, 30]. Therefore, with our study results, it is thought to be important to detect similar disk diffusion efficiency in *Enterobacterales* isolates, all of which are carbapenem-resistant.

In our study, CZA resistance was detected in 4 isolates (4.76%). According to the literature data, the overall CZA resistance in *Enterobacterales* is below 2.6% [31] CZA resistance has been reported in *Enterobacterales* with a frequency of <3.7% in North America, <5.3% in South America, <1.1% in Europe, and <1.7% in the Asia-Pacific region [31]. In isolates positive for KPC, OXA-1, OXA-48, CTX-M, ESBL, and AmpC genes, CZA resistance is generally ≤2.8% [31]. Compared with these data, the CZA resistance rate in our study was high. CZA resistance can develop with mutations and amino acid changes in the beta-lactamase critical site, chemical modifications in the antibiotic target region, and changes in cell permeability or efflux pump activations [31]. MIC elevations against CZA have often been reported as a result of KPC-2, KPC-3 mutations in class A carbapenemase positive isolates [30–33]. In OXA-48 positive *E.coli* isolates, the Ala68Pro-Ser211Tyr change, which was detected as a result of CZA exposure, caused CZA resistance together with the decrease in avibactam inhibitor activity [31, 34]. KPC and OXA-48 positivity were detected in *K.pneumoniae* isolates with CZA resistance in our study, but the possible resistance mechanisms mentioned above could not be evaluated. Despite this limitation, it is considered that this resistance data, which is not related to drug exposure, is important and should be supported by studies evaluating resistance mechanisms before the widespread use of CZA.

Our study has several limitations. First, our study was conducted on isolates collected from centers located in a certain region (Ankara, Turkey), as it was a pilot study. This situation caused the number of isolates to be limited and prevented the generalization of the results obtained. Second, the limited number of KPC positive isolates in which CZA was expected to be effective, made it difficult to evaluate CZA activity for KPC-producing isolates. Third, it was difficult to evaluate CZA activity for non-Klebsiella isolates as *K.pneumoniae* constituted the majority of isolates. Fourth, some of the phenotypic methods that can be used to detect CZA sensitivity could not be studied, and the effectiveness of other phenotypic methods could not be evaluated and compared.

In conclusion, CZA showed high *in vitro* efficacy in OXA-48-producing *Enterobacterales*, including isolates with colistin-resistant isolates. These *in vitro* results suggest that CZA may be a potential treatment alternative in Turkey. However, due to the increasing MBL producing *Enterobacterales* isolates, CZA should be integrated into clinical use, taking into account the carbapenemase epidemiology or *in vitro* susceptibility results. The disk diffusion (10/4 µg) method can be used effectively in the evaluation of CZA *in vitro* activity due to its high level of correlation with BMD. This first multicenter pilot study, evaluating the *in vitro* efficacy of CZA in Turkey, is expected to pave the way for large-scale studies having the number and distribution of isolates that can represent the general of Turkey.

Conflict of interest: This work obtained grants from Pfizer A.S.

Ethical approval: The study was approved by the Ankara University Medical School Human Studies Ethical Committee (Date: 12Sep2019, decision number: I3-114-19).

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Author contributions: Study design: EE, SS, OA, AA, ES; Data collection and testing: HSO, CE, EE, SS, FB; Data analysis: EE, SS, HSO; Data interpretation: ES, OA, AA, SS, EE, HSO, CE; Writing: HSO, SS, EE.

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