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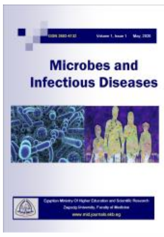

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Original article

Evaluation of ceftazidime/avibactam alone and in combination with amikacin, colistin and meropenem against carbapenemase-producing *Klebsiella pneumoniae*

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ABSTRACT

Background: Carbapenemase-producing *Klebsiella pneumoniae* (*K. pneumoniae)* poses a major threat to human health worldwide. Combination therapies of antibiotics with different mechanisms have been recommended in literatures. This study evaluated the in vitro antibacterial actions and synergistic actions of ceftazidime/avibactam alone and in combinations with other antibiotics. **Methods:** A total of 40 *K. pneumoniae* isolates were isolated from different clinical specimens. The revealing of carbapenemase production was performed using the modified carbapenem inactivation method. Antimicrobial susceptibility testing was conducted to determine the minimum inhibitory concentrations (MICs) of ceftazidime/ avibactam (CZA/AVI), amikacin (AK) meropenem (MEM), and colistin. The checkerboard method was used to assess the synergistic activity of these antibiotic combinations. **Results**: All (100%) isolates were susceptible to colistin, while only 2.5% were susceptible to CZA/AVI. All isolates were identified as carbapenemase producers, with 25% being serine carbapenemase producers and 75% being Metallo-β-lactamase producers. The fractional inhibitory concentration index (FICI) method revealed additive effect of CZA/AVI with AK in 42% of isolates, while combination of CZA/AVI with MEM was synergistic against 2.5% and additive in 55% of the isolates. Colistin displayed a synergistic effect against 7.5% of isolates and additive effect in 30% when was combined with CZA/AVI. The mean MIC value of CZA/AVI against the 40 *K. pneumoniae* strains decreased significantly when combined with AK, MEM and colistin and the greatest reduction was when combined with colistin (*P<0.001*). **Conclusion**: There is an emerging resistance developed against CZA/AVI. Thus, combination therapy including ceftazidime/avibactam may benefit more than monotherapy against carbapenemase-producing *K. pneumoniae*.

Introduction

The absence of effective antibiotic therapy alternatives has led to an increase in concern regarding gram-negative resistance in the medical field. The CDC has classified extended-spectrum lactamase (ESBL)-producing and carbapenem-resistant *Enterobacteriaceae* (CRE) as urgent hazards to public health. Therefore, swift action is needed to avoid the globalization of these organisms and develop new treatments [1].

The combination of a novel B-lactamase inhibitor and a third-generation cephalosporin,

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known as ceftazidime-avibactam (CZA/AVI), is relatively new. The *in vitro* activity of ceftazidime against Ambler class A, class C and some class D B-lactamase-producing bacteria is restored by avibactam (AVI). It exhibits inhibitory effects against *Klebsiella pneumoniae* carbapenemase (KPC) producing *K. pneumoniae*, ESBLs, AmpC-lactamases, and Gram-negative bacteria that produce B-lactamases [2].

Despite the broad range of efficacy of CZA/AVI, there have been instances of resistance to this treatment developing as a result of a mutation in the KPC-2 gene, which prevents avibactam from inhibiting KPC against –lactamases. This implies that resistance development could soon create a danger to the CZA's effectiveness. [3]. Likewise, mutations that produce variant KPC-3 enzymes that substantially lower CZA/AVI susceptibility and function essentially like ESBLs have also been reported. It is anticipated that resistance will grow stronger as CZA/AVI usage increases and that plasmids with mutant genes may spread through horizontal gene transfer [4].

To obtain the greatest antibacterial effect, combination therapy with antibiotics with distinct mechanisms has been shown to be helpful against a variety of resistant species. Regarding CZA/AVI's interaction with other antimicrobial agents against these pathogens, not much information is currently known.

Aim of the work

The aim of the work was to compare CZA/AVI alone and in combination with standard and novel antimicrobials against MDR strains of *K. pneumoniae* by using combination MIC testing to evaluate synergistic activity of these combinations for treatment of carbapenamase producer *K. pneumoniae.*

Materials and Methods

Bacterial isolates

A total of 40 *K. pneumoniae* isolates were obtained from different clinical samples (urine, pus, sputum, blood, and ascitic fluid) sent to the Diagnostic Microbiology Lab from patients admitted to Alexandria Main University Hospital from January 2023 to December 2023. Samples were directly plated onto blood agar (Oxoid, UK) and MacConkey agar (Oxoid, UK). The cultured plates were then incubated aerobically at 37 °C to be inspected for growth after 18–24 h. *K. pneumoniae* isolates were identified by colonial morphology, gram staining and biochemical reactions. Bacterial isolates were identified to species level by automated vitek-2 system (Bio-Mérieux, France).

Identification of carbapenemase producing *K. pneumoniae*

Modified Carbapenem inactivation method for detection of carbapenemase production was performed using meropenem disk inactivation method, eCIM (EDETA-CIM) was done for positive strains to detect metallobetalactamases in *Enterobacterales* following Clinical and Laboratory Standards Institute [5].

Antimicrobial susceptibility test

Determination of minimum inhibitory concentrations (MICs) for CZA/AVI, meropenem (MEM), amikacin (AK) and colistin were determined for the 40 isolates using cation adjusted Mueller- Hinton broth (CAMHB) (Oxoid, UK), by using the broth microdilution method. MICs of CZA/AVI, AK and MEM were determined according to Clinical and Laboratory Standards Institute guidelines [5]. Minimal inhibitory concentration (MIC) was defined as the lowest concentration that produced no visible growth of bacterial isolates. The breakpoints for susceptibility and resistance of isolates for colistin, AK, MEM and CZA/AVI were interpreted as described in CLSI in which isolates were reported resistant to colistin, CZA/AVI, MEM and AK if MIC was ≥4 µg/ml, ≥16 µg/ml, ≥4 µg/ml and, ≥64 µg/ml respectively [5].

Checkerboard of antibiotic combination

The checkerboard method was used in this study according to previous study [6]. Fractional inhibitory concentration index (FICI) indicated interactions of drug combinations was assessed according to previous study [7]. FICI values were indicated the following: synergism, FICI≤0.5; Additive 0.5<FICI≤ 1, indifference 1<FICI <4; and antagonism, FICI >4 [8].

Statistical analysis

All statistical analyses were performed by using the SPSS statistical software (version 22.0), and qualitative variables were expressed as percentages. All resistance characteristics were compared by Fisher's exact test for categorical variables. P value of <0.05 was considered statistically significant. Quantitative data were described using mean with standard deviation and median (Min. –Max.).

Results

The *in vitro* activity of antibiotics was compared between different isolates. The susceptibility testing results showed that all isolates (100%) were susceptible to colistin and only 2.5% (1/40) of all tested isolates were susceptible to CZA/AVI. None of the isolates were susceptible to amikacin or meropenem.

All isolates were carbapenemase producers, according to the modified Carbapenem inactivation method (mCIM) and (eCIM), 25% (10/40) were serine carbapenemase and 75% (30/40) were metalobetalactamase producers.

The fold reductions in baseline CZA/AVI MICs as a result of the combination with the used antibiotics are listed in **Table 1**. The mean MIC value of CZA/AVI against the 40 *K. pneumoniae* strains decreased significantly from 318.5 ± 234.2 µg/ml to 190.7 ± 171.0 µg/ml when combined with AK (P= 0.031). Furthermore, the mean CZA/AVI MIC value decreased to 174.4 ± 156.9 µg/ml when combined with MEM(P=0.012). While, the greatest reduction of the CZA/AVI MIC (36.9 ± 65.7 µg/ml) was when combined with colistin (P<0.001).

The results of the FICI of synergy testing of combined CZA/AVI with amikacin, meropenem and colistin are shown in **Table2**. A detailed analysis of in vitro synergy results showed that the combination of CZA/AVI with amikacin was additive in 42% (17/40) of isolates, while combination of CZA/AVI with MEM was synergistic in 2.5% (1/40) and additive in 55% (22/40). In addition, CAZ/AVI in combination with colistin displayed a synergistic effect against 7.5% (3/40) of isolates and additive effect in 30% (12/40) (**Figure 1).**

Table 1. Comparison of MIC values between the different studied groups**.**

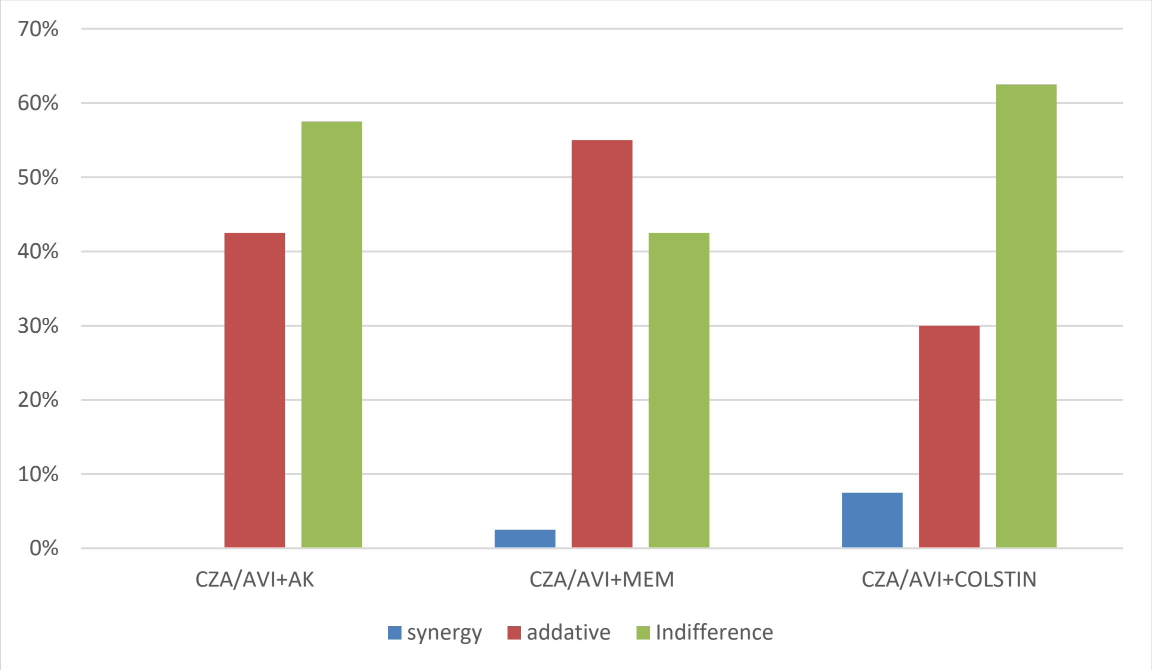
	CZA/AVI (n= 40)	**CZA/AVI+Ak (n = 40)**	**CZA/AVI + MEM (n = 40)**	**CZA/AVI + colistin (n = 40)**	**H**	**P**
Mean ± SD.	318.5 ± 234.2	190.7 ± 171.0	174.4 ± 156.9	36.9 ± 65.7	52.436*	<0.001*
Median (Min. –Max.)	512 (4 – 512)	192 (4 – 512)	192 (2 – 512)	8 (2 – 256)		
p_0		0.031*	0.012*	<0.001*		

SD: Standard deviation
H: H for Kruskal Wallis test, Pairwise comparison bet. each 2 groups was done using Post Hoc Test (Dunn's for multiple comparisons test)
p: p value for comparing between the studied groups
p0: p value for comparing between CZA/AVI and each other group.
*: Statistically significant at $p \leq 0.05$

Table 2. FICI distribution of ceftazidime/avibactam combined with amikacin, meropenem and colistin (n = 40).

	CZA/AVI + Ak (n=40)	CZA/AVI + MEM (n=40)	CZA/AVI + Colistin (n=40)
Synergy (FICI≤0.5)	0 (0%)	1 (2.5%)	3 (7.5%)
Additive (0.5<FICI≤ 1)	17 (42.5%)	22 (55%)	12 (30%)
Indifferent (1<FICI <4)	23(57.5%)	17 (42.5%)	25(62.5%)
Antagonist (FICI >4)	0 (0%)	0 (0%)	0 (0%)
Mean ± SD.	1.40 ± 0.45	1.24 ± 0.45	1.05 ± 0.38
Median (Min. –Max.)	1.50 (0.75 – 2)	1 (0.25 – 2.50)	1.01 (0.25 – 2)

Figure 1. FICI distribution of ceftazidime/avibactam combined with amikacin, meropenem and colistin (n = 40).



Discussion

Ceftazidime-avibactam is a novel antibiotic combination that is effective against a wide range of bacterial strains [9]. But a growing trend of bacterial resistance has been observed since this combination was first used in clinical settings. Our results showed low susceptibility to CZA/AVI (2.5%). This is consistent with Campogiani *et al.* [10] who reported a growing resistance to CZA/AVI, particularly among MBL-producing strains, with 81.3% of *Klebsiella pneumoniae* isolates showing resistance, and also Bella *et al.* [11] has reported similar findings with high resistance to CZA/AVI.

On the other hand, among *K. pneumoniae* isolates from Ain shams, they reported that *K. pneumoniae* showed the highest susceptibility to ceftazidime-avibactam (87.9%) and colistin (93.9%) [12]. This discrepancy is attributed to the emergence of resistance that developed since the application of CZA/AVI in the clinic [13, 14]. *K. pneumoniae* isolates acquire resistance via beta-lactamase related amino acid substitutions, porin deficiencies and efflux pumps [15]. Moreover, with increased use of CZA, resistance is predicted to emerge, and plasmids harboring mutant genes may spread via horizontal gene transfer [4]. In the current study *K. pneumoniae* strains were isolated mainly from critically ill patients in intensive care units (ICU) where there is a higher antibiotic exposure. Also, these patients were exposed to many invasive procedures which increase the risk of contracting drug-resistant bacterial infections. Resistance against CZA in patients who had not been exposed to CZA but had previously been treated with meropenem and ceftazidime was reported by Gaibani, *et al.* [16] which was related to enhanced K. pneumoniae carbapenemase-3 (KPC-3) expression. The D179Y mutation of KPC-3 may lead to evolution of resistance to CZA which could be transmitted to other bacteria via plasmids.

Ceftazidime-avibactam resistance has also been detected in patients not exposed to the antibiotic previously with long hospitalization duration due to ability of the CAZ/AVI resistance genes to horizontally transfer between strains and patients, highlighting the need for important surveillance programs and strict infection control measures [17].

Colistin was the only antibiotic to which 100% of the isolates were susceptible, confirming previous studies showing the consistent efficacy of colistin against carbapenemase-producing *K. pneumoniae.* [18]. Despite its efficacy, colistin's use is often limited due to nephrotoxicity, making it crucial to explore combinations that enhance its activity.

In the present study, mCIM detected carbapenemase production in all (100%) of isolated

K. pneumoniae strains which correlated with Li *et al.*, (96%) and Tsai *et al.*, (100%) [19,20]. While Koul *et al*. and Alemayehu *et al.* reported 48.48% and 30% respectively, carbapenemase production in isolated isolates [21,22]. Our results showed 30 isolates (75%) were Metallo-β-lactamase producers and 25% were Serine-β-lactamase producers which is comparable to Koul *et al.* [21] who reported 75% of *klebsiella* isolates were MBL, while Aboulela *et al.*[23] reported 52.8% were MBL and 30.2% were serine carbapenemase producers.

Ceftazidime-avibactam is ineffective against MBL-positive isolates due to hydrolysis of ceftazidime and avibactam by the MBL class B of β-lactamases [24]. The current study makes this abundantly evident, explaining the high prevalence of CZA/AVI resistance among *K. pneumoniae* isolates.

Minimal inhibitory concentration**Error! Bookmark not defined.** study of CZA/AVI in combination with AK, MEM, and colistin revealed a significant reduction in the MICs of the isolated isolates. Combining CZA/AVI with colistin resulted in the largest ($P<0.001$) MIC reduction of CZA/AVI for *K. pneumoniae*, followed by combination with MEM (*P=0.012*) and with AK (*P=0.031*). However, Mikhail *et al.*, reported that MEM resulted in the largest MIC reduction for CZA/AVI when administered in conjunction with it for *K. pneumoniae*, followed by AK and colistin. [9]. This discrepancy could be attributed to the fact that all of the isolated *K. pneumoniae* in the current investigation produced carbapenemase [9].

CZA/AVI combined with meropenem led to a significant reduction in MIC values (to 174.4 µg/ml, P=0.012), despite the lack of susceptibility to meropenem alone. This finding aligns with shields *et al.*,(2017), demonstrating that carbapenem combinations can restore some activity in carbapenem-resistant strains, particularly when combined with beta-lactamase inhibitors [25].

Furthermore, FICIs of the combination of CZA/AVI with MEM and colistin were <0.5, indicating synergistic impact on 2.5% and 7.5% of strains, respectively. FICIs of $0.5<FICI\leq 1$ indicated additive effects of CZA/AVI with AK, MEM, and colistin in 42.5%, 55%, and 30% of the strains, respectively. However, Chen *et al*., found that CZA/AVI coupled with amikacin had a synergistic impact against all tested *K. pneumoniae* (4/4) [26].

Conclusion

Although CZA/AVI is a new alternative combination therapy, there is increasing resistance to it, and CZA/AVI monotherapy is frequently ineffective in infection treatment. Thus, our investigation demonstrated that combination therapy with ceftazidime/avibactam may be more effective than monotherapy against carbapenemase-producing *K. pneumoniae*.

Ethical approval:

The study was approved by the Research Ethics Committee of Faculty of Medicine, Alexandria University (Federal Wide serial number: 0305948). It was approved and conducted in accordance with the Ethics Committee of the Faculty of Medicine, Alexandria University, Egypt with the number: IRB NO: 00012098- FWA NO: 00018699. Signed informed consent was obtained from all patients before the study.

Availability of data and materials:

The datasets used and/or analyzed during the current study are available in the manuscript.

Competing interests:

The authors have no competing interests, or other interests that might be perceived to influence the results and/or discussion reported in this paper.

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All authors have agreed on the content of the manuscript. S.A.E. has put the conception and study design. A.S.B has performed the Data collection, acquisition. N.A.H has performed Data analysis and interpretation. All authors have participated in manuscript writing and revision.

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