

Emerging ceftazidime-avibactam resistance against carbapenem resistant *Escherichia coli* and *Klebsiella pneumoniae* in Lebanon

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Abstract

Introduction: Ceftazidime-avibactam (CZA) has been introduced as a novel therapy to essentially combat the rising trends of carbapenem resistant *Enterobacteriaceae*. In the absence of *in vitro* data about the activity of this drug against carbapenem resistant (CR) *Escherichia coli* and *Klebsiella pneumoniae* in Lebanon, this study was warranted.

Method: A total of 150 isolates, identified using the MALDI-TOF, encompassing 50 CR *E. coli*, 60 CR *K. pneumoniae*, and 10 isolates each of extended-spectrum Beta-lactamases (ESBLs), and non-CR multidrug-resistant (MDR) of each species were analyzed. The minimum inhibitory concentration (MIC) for CZA was determined by the E-test (Liofilchem, Roseto degliAbruzzi, Italy). In addition, the disk diffusion (DD) test was used to determine the activity of CZA and of the antimicrobials routinely used to test for such pathogens.

Results: The CZA activity against the 50 CR *E. coli* showed an MIC₅₀ ≥ 256 µg/mL, MIC₉₀ ≥ 256 µg/mL, and an MIC range of 0.023 to ≥ 256 µg/mL, reflecting a susceptibility of 40%. As For the 60 CR *K. pneumoniae* isolates, the MIC₅₀ was ≥ 256 µg/mL, MIC₉₀ ≥ 256 µg/mL, and the MIC range was 0.094 to ≥ 256 µg/mL, reflecting a susceptibility of 35%. However, uniform CZA susceptibility (100%) was detected against ESBL and MDR isolates of both species, being comparable or higher to the routinely used antimicrobials.

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Conclusion: Although CZA was recently introduced into Lebanon, it was surprising to note this low activity of CZA against CR *E. coli* and CR *K. pneumoniae*. To explain such findings, it is worth pursuing investigations related to antimicrobial utilization in clinical practice and antimicrobial stewardship. Moreover, genotypic determination is needed to be revealed to help explain the observed phenotypic resistance.

Keywords

Antimicrobial Resistance; Ceftazidime Avibactam; Carbapenem Resistance, CR *E. Coli*; CR *K. Pneumoniae*; Lebanon.

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Introduction

The surging encounter of resistant Gram-negative bacteria is imposing a great global public threat, as well as increased mortality, morbidity, hospital stay, and not to forget the economic burden [1]. This is essentially attributed to the increasing rates of ESBL, failure in their treatment which led to subsequent increase in CRE, and the deprivation of effective antimicrobial agents to treat such highly resistant isolates [2] [<https://www.who.int/news/item/27-02-2017-who-publishes-list-of-bacteria-for-which-new-antibiotics-are-urgently-needed>].

Ceftazidime-avibactam has been introduced as one of the therapeutic options to treat such resistant isolates. It received FDA approval for the treatment of complicated urinary tract infections including pyelonephritis, complicated intra-abdominal infections and hospital acquired pneumonia/ventilator associated pneumonia [3, 4]. This drug is a novel antibiotic combination consisting of a third-generation cephalosporin (ceftazidime) combined with a non- β -lactam β -lactamase inhibitor (avibactam). The latter is a synthetic non- β -Lactam molecule that protects β -lactams from Extended spectrum β -lactamases and carbapenem resistant Gram-negative bacteria by inhibiting Class A, C and

some Class D β -lactamases enzymes, by covalently acetylating the β -lactamases targets mainly the serine domain, but not the metallo β -lactamases [5].

Although ceftazidime-avibactam is relatively new in the market, bacterial resistance to this drug has been reported worldwide, especially among *Pseudomonas* spp., *Acinetobacter* spp. and carbapenem resistant *Enterobacteriaceae* (CRE) isolates [6]. In Lebanon, ceftazidime-avibactam has been available for a few years now. However, no data is available about the prevalence of its resistance, thus prompted us to assess the *in vitro* activity of CZA against multi-resistant *E. coli* and *K. pneumoniae* pathogens in this country.

Method

Bacterial isolates and their identification

Non-duplicate isolates consisting of 70 *E. coli* (10 ESBLs, 10 MDR, and 50 CRE isolates) and 80 *K. pneumoniae* (10 ESBLs, 10 MDR, and 60 CRE isolates) recovered from different clinical specimens that were submitted for investigation at the Clinical Microbiology Laboratory, Department of Pathology and Laboratory Medicine, American University of Beirut Medical Center (AUBMC) during the period

between May 2019 and March 2021. Identification of the isolates was done using the matrix-assisted laser desorption/ionization time of flight (MALDI-TOF) system (Bruker Daltonik, GmbH, Bremen, Germany).

Antimicrobial susceptibility testing

Antimicrobial susceptibility testing was performed using the E-test for minimal inhibitory concentration (MIC) determination and the disk diffusion (DD) test as reported in a previous study done at our center [7]. Both the CZA MIC strips (concentration range ≤ 0.016 and ≥ 256 $\mu\text{g}/\text{mL}$) and the CZA disks (50 μg) were obtained from Liofilchem, Scozia, Italy. The 2020 Clinical and Laboratory Standards Institute (CLSI) CZA MICs' breakpoints ($\mu\text{g}/\text{mL}$) were used to interpret the CZA susceptibility category for *Enterobacteriaceae* as susceptible (≤ 8 $\mu\text{g}/\text{mL}$) and resistant (≥ 16 $\mu\text{g}/\text{mL}$), and for the CZA (50 μg) DD, the susceptible and resistant zone of inhibition (mm), were ≥ 21 , and ≤ 20 , respectively. The other antimicrobial agents tested by DD are the ones routinely used for testing these pathogens, and their results were also interpreted according to the 2020 CLSI guidelines.

The categorization of bacterial resistance to antimicrobial agents was based on the definition created by a group of international experts initiated by the European Center for Disease Prevention and Control and the Centers for Disease Control and Prevention. They defined MDR as acquired non-susceptibility to at least one agent in three or more antimicrobial categories [8]. In our study, resistance to ceftazidime was also included in categorizing *E. coli* and *K. pneumoniae* isolates as MDR. The characterization of *E. coli* and *K. pneumoniae* isolates as ESBL producers was carried out as previously reported in a study done at our center [9]. Carbapenem resistance was determined based on resistance to one of the carbapenem agents: ertapenem, imipenem, or meropenem.

Quality Control

The quality of testing with E-test and DD test was ensured using the American Type Culture Collection (ATCC) quality control strain of *E. coli* (ATCC 25922).

Results

The clinical sources for the CR isolates of *E. coli* and *K. pneumoniae*, respectively, were urinary 34% and 23%; DTA 8% and 25%; skin screenings 16% and 18%; blood 22% and 20%. Other sources with very low isolate recovery (20% and 14%) included tissues, fluids, catheters, and wounds.

The distribution of the tested isolates according to their CZA MICs range, MIC₅₀, and MIC₉₀ among the ESBL, MDR and CR *E. coli*, and *K. pneumoniae* is presented in **Table 1**.

The CZA MICs activity against the 50 CR *E. coli* reflected a susceptibility of 40%, while the CZA activity against the 60 CR *K. pneumoniae* isolates showed a susceptibility of 35%. However, uniform CZA susceptibility (100%) was detected against the ESBL and MDR isolates of both species, being comparable and higher to the routinely used antimicrobials.

Figure 1 shows the scatter of CZA MICs for both CR isolates of *E. coli* and *K. pneumoniae*, ranging between 0.016 and ≥ 256 $\mu\text{g}/\text{mL}$.

The disk diffusion results of the different bacterial types of resistance against CZA and other routinely tested antimicrobial agents used for these pathogens in a clinical setting are shown in **Table 2**.

Although CZA susceptibility rates were lower than those shown for aminoglycosides for *E. coli* and close to those shown for these drugs in *K. pneumoniae*, they were higher than those reported for the other tested antimicrobial agents for both species.

Comparing the DD results with those of the MICs results, no discrepant findings were shown among the tested CR *K. pneumoniae* isolates. However, among the tested CR *E. coli* isolates, 2 discrepancies

Table 1. Minimum inhibitory concentration (MIC µg/mL) of resistant *E. coli* and *K. pneumoniae* isolates against CZA and carbapenems.

MICs (µg/mL) results against resistant <i>E. coli</i> and <i>K. pneumoniae</i>						
Antimicrobial	Organism	Resistance Characteristic	MIC 50	MIC 90	Range	% Susceptible in Category
CZA	<i>E. coli</i>	ESBL (n=10)	0.19	0.5	0.094 - 0.75	100
		MDR (n=10)	0.38	2	0.125 - 3	100
		CR (n=50)	≥256	≥256	0.023 - ≥256	40
	<i>K. pneumoniae</i>	ESBL (n=10)	0.38	1.5	0.25 - 3	100
		MDR (n=10)	0.5	2	0.25 - 2	100
		CR (n=60)	≥256	≥256	0.094 - ≥256	35
ERT	<i>E. coli</i>	CR (n=50)	≥32	≥32	2 - ≥32	0
	<i>K. pneumoniae</i>	CR (n=60)	≥32	≥32	1.5 - ≥32	0
IMP	<i>E. coli</i>	CR (n=50)	≥32	≥32	0.064 - ≥32	10
	<i>K. pneumoniae</i>	CR (n=60)	≥32	≥32	0.25 - ≥32	7
MERO	<i>E. coli</i>	CR (n=50)	≥32	≥32	0.25 - ≥32	8
	<i>K. pneumoniae</i>	CR (n=60)	≥32	≥32	0.25 - ≥32	8

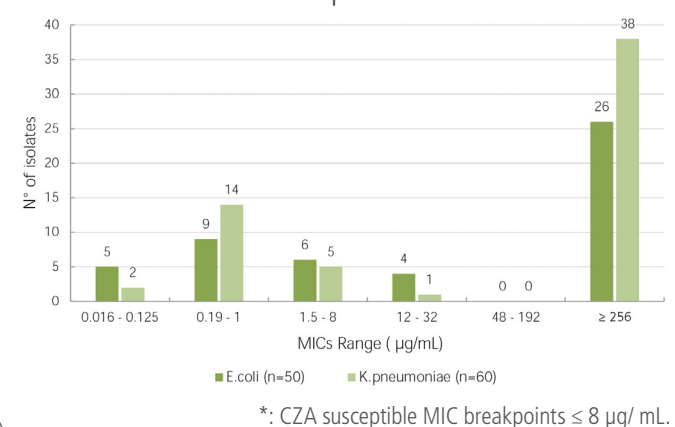
CR= Carbapenem resistant, CZA: Ceftazidime-Avibactam, ERT: Ertapenem, IMP: Imipenem, MERO: Meropenem.

Table 2. Disk diffusion susceptibility of resistant *E. coli* and *K. pneumoniae* isolates to CZA and other antimicrobial agents.

Antimicrobial agents	Percent (%) susceptibility among					
	E. coli			K. pneumoniae		
	ESBL	MDR	CRE	ESBL	MDR	CRE
	n=10	n=50	n=10	n=60		
Ceftazidime-Avibactam*	100	100	32	100	100	35
Amikacin	100	100	86	100	100	40
Ciprofloxacin	0	0	2	0	10	3
Gentamicin	60	50	70	100	70	33
Tazocin	90	50	6	40	70	0
Tetracycline	60	20	16	40	80	8
Trimethoprim-Sulfamethoxazole	40	0	14	40	30	20
Tigecycline	-	-	91	50	100	67
Colistin	-	-	10	∅	∅	11
Fosfomycin	80	80	92	80	100	27

*: CZA susceptible MIC breakpoints ≤ 8 µg/ mL.

Figure 1: Results of CZA MICs* Scatter among CR *E. coli* and *K. pneumoniae*.



were encountered whereby the DD results showed 18 mm (indicating resistant) for both isolates, while the MICs were 6 µg/ mL and 2 µg/ mL (indicating susceptible).

Discussion

This is the first study that reports on the in vitro CZA activity against the most commonly encountered Gram-negative bacteria from Lebanon. An unanticipated high rates of resistance, as

determined by MICs levels, were revealed against CR *K. pneumoniae* (65%) and CR *E. coli* (60%), despite the fact that this antimicrobial agent was only introduced in Lebanon in the second quarter of 2019 and procured at our medical center in July 2019. However, its activity remained uniformly high (100%) against ESBL and MDR strains of both species, a similar finding to what was reported from regional and other countries [10-15].

Also in our study, the CZA activity by disk diffusion versus other antimicrobial agents routinely tested in our laboratory against CR *E. coli* and CR *K. pneumoniae* pathogens were compared. The findings revealed higher CZA activity compared to ciprofloxacin, piperacillin/tazobactam, tetracycline, SXT and colistin against both species. However, the activities of aminoglycosides and fosfomycin were higher than CZA among CR *E. coli* isolates but were closer to those among CR *K. pneumoniae* isolates (**Table 2**).

To make relevance, the activity of CZA against CR isolates in our study is compared to those reported internationally and regionally and indicated variable findings. Internationally for example, the 60% resistance rate detected among our CR *E. coli* isolates was lower than reported from China (71%) [16]. However, the 65% resistant rate detected among our CR *K. pneumoniae* isolates was far higher than those reported from USA (0-21%) [17, 11, 12], China (15%) [16] and Brazil (3%) [18].

Nevertheless, regionally no published data on integrate on species per se were reported, rather they were lump summed under Enterobacteriaceae. Among the latter, for example high rates of CZA resistance were reported from UAE (55%) [23] and Arabian Peninsula (47%) [24]. These were higher than rates reported from USA (range between 0.3% and 3.6%) [19, 20, 21] and China (25%) [16, 22].

The mechanisms of resistance in Gram-negative bacteria generally fall under three main types: enzymatic resistance, expression of an alternative target or chemical modification of the antibiotic target, and expression of efflux pumps or changes in

cell permeability [27]. The resistance to CZA was mainly ascribed to the enzymatic type of resistance, although combination with the two other mechanisms was also reported to further increase MIC levels [28]. In *Enterobacteriaceae*, the reported bacterial genes involved in CZA resistance included mutations among the following genes: KPC-2, KPC-3, CTX-M-14, CTX-M-15, SHV, AmpC, OXA-2, OXA-48 and NDM [6]. In this context, studies indicated that the high CZA resistance rates against CRE were correlated with specific resistance genes existing in the pathogen. For example, in a global collection of *K. pneumoniae* isolates positive and negative for MBL gene, the resistance rate to CZA showed 98% and 0.2%, respectively [15]. Similar findings were also reported among tested isolates from Arabian Peninsula and Europe [24, 25]. A study from UAE also noted increased CZA resistance rates associated with specific genes as follows: 20% in OXA-48, 71% in NDM-1, and 95% in isolates containing dual genes OXA-48 and NDM-1 [23]. Moreover, a study done at a major cancer center in USA showed increased resistance to CZA among isolates harboring the NDM-1 gene [26].

At our Medical Center, the determination of genes involved in CZA resistance against the CR *E. coli* and CR *K. pneumoniae* isolates in the current study are being pursued. Unfortunately, this analysis was delayed due to the multifaceted problems inflicting Lebanon. However, earlier molecular studies from our institution revealed that CR genes in both species were: bla-OXA-1, bla-CTXM-15, bla-TEM-1, bla-CMY-2, bla-OX-48 and NDM-1. In addition, *E. coli* isolates were found to harbor outer membrane porin encoding genes (OmpC and OmpF) isolates while *K. pneumoniae* lacked these genes [29, 30, 31]. Whether these genes or newly emerged ones have been contributing to the CZA high rates of resistance encountered among the CRE isolates in our study remains to be determined.

Conclusion

Although CZA was recently introduced in Lebanon, it was surprising and unexpected to note its low activity against CR *E. coli* and CR *K. pneumoniae*, thus posing a challenging issue concerning the treatment of carbapenem resistant *Enterobacteriaceae*. It is important to note that the findings in this study relate to investigation at a major tertiary care center and does not necessarily represent what is going on at the country level, as the latter would require a nationwide study. Minimizing the drug resistance necessitates pursuing investigations related to proper antimicrobial utilization in clinical practice and antimicrobial stewardship. Moreover, genotypic determination is needed to help explain the observed phenotypic resistance.

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