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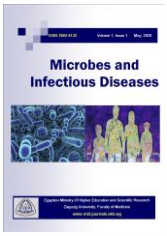

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Original article

New promising antibiotics for treatment of carbapenem resistant *Enterobacteriaceae*

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ABSTRACT

Background: Carbapenem resistance has become a significant public health threat, leading to rapid spread, major outbreaks, and treatment failures associated with clinically important carbapenem-resistant *Enterobacteriaceae* (CRE).The aim of this work was to isolate CRE from patients with hospital acquired infections (HAIs), determination of the type of carbapenemase genes phenotypically and evaluation of in vitro sensitivity of: Imipenem/relebactam (I/R), Meropenem/vaborbactam (M/V), Ceftazidime/avibactam (CZA) and Cefiderocol against different classes of CRE. **Methods:** This cross-sectional study was carried out on 100 *Enterobacteriaceae* isolates obtained from 100 patients of all age groups showing criteria of HAIs admitted in ICU. *Enterobacteriaceae* isolates were tested for carbapenem sensitivity. CRE isolates underwent carbapenemase detection using the Combi Carba Plus test. Confirmed CPE were further tested for susceptibility to imipenem/relebactam, meropenem/vaborbactam, and ceftazidime/avibactam via E-test, and cefiderocol by disc diffusion. **Results:** The study showed that (70/100) of the *Enterobacteriaceae* isolates were carbapenem resistant. Most CRE isolates (52/70) had the Metallo-B-Lactamase (MBL) gene. All seventy CRE isolates had a sensitive response against cefiderocol, on the contrary, all seventy CRE isolates were resistant to I/R. Regarding CZA and M/V they had a sensitive response to (9/70, 17/70) of the CRE isolates studied respectively. MBL was significantly resistant to M/V ($P< 0.001$) and CZA ($P =0.007$). **Conclusions:** *Klebsiella pneumoniae* was the most common type of isolated CRE. Most of the studied CRE isolates had MBL genes. Cefiderocol is a reasonable option and may serve as a last-resort therapy for infections due to MBL-producing CRE supporting its recommendation in guidelines.

Introduction

Carbapenem antibiotics are the most potent group of antibiotics with proven efficacy in the treatment of patients with severe bacterial infections, including those caused by antibiotic resistant (AR) strains [1].

There are three major mechanisms by which *Enterobacteriaceae* become resistant to carbapenems: production of carbapenemases, efflux pumps and porin mutations or loss depriving the bacterial cell of the usual carriers that allow carbapenem entry through their outer membrane [2]. Carbapenemase producing *Enterobacteriaceae*

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(CPE) are considered to be a more significant concern since carbapenemase genes are carried on plasmids that are transferred between bacterial species, so they tend to spread among patients also, outbreaks due to CPE are commonly reported and associated with difficult treatment of active infection and high mortality [3].

Globally, the prevalence of CRE has been escalating, with significant variations in the distribution of carbapenemase enzymes. *Klebsiella pneumoniae* carbapenemase (KPC) enzymes are predominant in the United States and parts of Europe, while metallo-β-lactamases (MBLs) like New Delhi metallo-β-lactamase (NDM), Verona integron-encoded metallo-β-lactamase (VIM), and imipenemase (IMP) are more prevalent in South Asia, the Middle East, and certain European regions. The rapid global dissemination of these enzymes underscores the urgent need for effective therapeutic options [4].

There are different approaches to treat infections caused by these bacteria, which include the repurposing of already existing antibiotics, dual therapies with these antibiotics, and the development of new ß-lactamase inhibitors and antibiotics [5].

Imipenem/relebactam (I/R) is a newly approved antibiotic combination of β-lactam and a new β-lactamase inhibitor [6]. Relebactam is structurally related to avibactam, but it differs from it in that it does not inhibit class D carbapenemases but does possess inhibitory activity (in the combination I/R) against clinical isolates of *Klebsiella pneumoniae* carrying variant KPC-3 enzymes that are resistant to CZA [7].

Vaborbactam is a cyclic boronic acid β-lactamase inhibitor with a broad-spectrum activity, including class A and class C enzymes while inhibition of class D enzymes was rather poor [8].

CZA is an intravenously administered combination of the third-generation cephalosporin ceftazidime and the novel, non-β-lactam β-lactamase inhibitor avibactam. It has an excellent in vitro activity against many extended spectrum beta-lactamase-(ESBLs-), class C ampicillinase- (AmpC-), KPC- and OXA-48- producing *Enterobacteriaceae* [9].

Cefiderocol is an injectable formerly S-649266, is a first in its class, an injectable siderophore cephalosporin that combines a catechol-type siderophore and cephalosporin core with side chains similar to cefepime and ceftazidime. This structure and its unique mechanism of action confer enhanced stability against hydrolysis by many β-lactamases, including ESBLs such as CTX-M, and carbapenemases such as KPC, NDM, VIM, IMP [10].

Unlike traditional β-lactam antibiotics, cefiderocol exploits bacterial iron transport systems to enter the periplasmic space, a “Trojan horse” strategy that not only enhances uptake but also evades some resistance mechanisms. This novel mode of entry allows cefiderocol to remain effective against carbapenem-resistant organisms, including those harboring MBLs, which are typically resistant to nearly all available β-lactams. Therefore, cefiderocol offers a promising therapeutic option, particularly in regions where MBLs such as NDM and VIM are endemic [11, 12].

The aim of this work was to isolate CRE from patients with HAI, determine the type of carbapenemase genes phenotypically and evaluate the in vitro sensitivity of I/R, M/V, CZA and Cefiderocol against different classes of CRE isolates.

Methods

This cross-sectional study was carried out on 100 *Enterobacteriaceae i*solates obtained from 100 patients of all age groups showing criteria of HAIs admitted in ICU. The study was done from January 2023 to December 2023 after approval from the Ethical Committee (approval code: 34116/9/20). This study was done according to the Declaration of Helsinki.

Informed consent: An informed written consent was obtained from the patient or relatives of the patients.

All patients were subjected to complete history taking with reference to name, age, history of prior antibiotic therapy, cause and duration of hospital stay.

Sample collection

The 100 samples including blood, sputum, urine, wound and bed sore swabs collected under aseptic condition were clearly labelled with the patient's name, number, date, and time of collection then transported as rapidly as possible to Microbiology and Immunology department laboratory then cultured on MacConkey, chocolate and blood agar (Oxoid, England) aerobically at 37°C for 24 hours [13].

Identification of the *Enterobacteriaceae* isolates

Enterobacteriaceae colonies isolated on MacConkey agar were further identified using citrate test, motility indole ornithine (MIO) test, lysine iron agar (LIA) test, triple sugar iron (TSI) test, urease test and carbohydrate fermentation tests [13]. The yielded *Enterobacteriaceae* isolates were screened for CR using Kirby-Bauer disc diffusion method on Muller–Hinton agar (MHA) (Hi-Media, India) [14]. A set of discs of meropenem, imipenem and ertapenem (10 µg each, Oxoid, England) was applied to the surface of MHA, plates were incubated for 24h at 37°C, and diameters of inhibition zones were recorded , and the result was interpreted according to the clinical and laboratory standards institute (CLSI,2023) instructions [14].

Interpretative breakpoints used were as follows (CLSI, 2023): imipenem – susceptible ≥23 mm, intermediate 20–22 mm, resistant ≤19 mm; meropenem – susceptible ≥23 mm, intermediate 20–22 mm, resistant ≤19 mm; ertapenem – susceptible ≥22 mm, intermediate 19–21 mm, resistant ≤18 mm.

Internal quality control strains *Escherichia coli* ATCC 25922 and *Klebsiella pneumoniae* ATCC 700603 were used to ensure the accuracy and reliability of susceptibility testing throughout the study.

Isolates identified as CRE were further tested phenotypically for carbapenemase production using the Combi Carba Plus test (MASTDISCS, England).

Susceptibility testing of new antibiotics

CPE isolates underwent antibiotic susceptibility test for new antibiotics. After the inoculation of MHA with 0.5-McFarland CRE suspension, I/R (0.002/4-32/4 µg/mL), M/V (0.016/8-256/8µg/mL), CZA (0.016/4-256/4µg/ml) E-tests and cefiderocol 30 µg discs, (Lioflichem, Italy) were placed on the inoculated MHA and the result were interpreted according to (CLSI,2023) [14].

Statistical analysis

Statistical analysis was done by SPSS v26 (IBM Inc., Chicago, IL, USA). Quantitative variables were presented as mean and standard deviation (SD) and compared between the three groups utilizing ANOVA (F) test with post hoc test (Tukey). Qualitative variables were presented as frequency and percentage (%) and were analyzed utilizing the Chi-square test. A two tailed P value < 0.05 was considered statistically significant.

Results

Baseline characteristics and in-hospital stay data of the studied patients were insignificantly different between carbapenem resistant patients' group and carbapenem sensitive patients' group. **Table 1**

The most common type of carbapenemases produced by CRE isolates was MBL. **Figure 1**

There was a significance difference between type of carbapenemase gene and type of CRE isolates (P<0.05). *Klebsiella pneumoniae* isolates were the most common MBL producing CRE. **Table 2**

CRE isolates had a sensitive response against cefiderocol, on the contrary, all CRE isolates were resistant to I/R. Regarding M/V and CZA antibiotics, they had a sensitive response to 17 (24.29%) and 9 (12.86%) of the studied CRE isolates, respectively. **Figure 2**

CRE isolates including mainly MBL producing isolates had a sensitive response against cefiderocol but had a resistant response against I/R. MBL was significantly resistant to M/V and CZA. **Table 3**

The studied patients had a sensitive response against cefiderocol but had a resistant response against I/R. CRE isolated from sputum samples were significantly sensitive to M/V (P<0.05). CRE isolated from blood samples were significantly sensitive to CZA (P<0.05). **Table 4**

The relationship between the type of isolated CRE and different used antibiotics was insignificant. **Table 5**

Table 1. Baseline characteristics and in-hospital stay data of the studied patients.

Age (years)		**CR patients (n=70)**	**CS patients (n=30)**	**P**
		41.86±21.22	37.67±21.37	0.369
Sample	**Blood**	23(23.0%)	11(11.0%)	0.932
	Sputum	24(24.0%)	8(8.0%)	
	Wound	9(9.0%)	5(5.0%)	
	Urine	8(8.0%)	4(4.0%)	
	Bed sore	6(6.0%)	2(2.0%)	
Duration of hospital stay (days)		21.71±8.78	21.1±8.71	0.749
The cause of hospital stay	**Pneumonia**	18(25.71%)	5(16.67%)	0.087
	Respiratory distress	14(20.0%)	6(20.0%)	
	Stroke	9(12.86%)	4(13.33%)	
	Pulmonary embolism	6(8.57%)	3(10.0%)	
	Hepatic encephalopathy	7(10.0%)	1(3.33%)	
	Appendectomy	5(7.14%)	2(6.67%)	
	UT infection	7(10.0%)	2(6.67%)	
	Diabetic coma	4(5.71%)	1(3.33%)	
	Intracerebral hemorrhage	0(0.0%)	4(13.33%)	
	COPD	0(0.0%)	1(3.33%)	
	Cerebral infarction	0(0.0%)	1(3.33%)	
Previous antibiotics	**Levofloxacin**	35(50.0%)	15(50.0%)	0.999
	Amikin	7(10.0%)	3(10.0%)	
	Ciprofloxacin	39(55.71%)	17(56.67%)	
	Meropenem	24(34.29%)	9(30.0%)	
	Ceftazidime	7(10.0%)	3(10.0%)	
Type of organism	***Klebsiella pneumoniae***	40(40.0%)	17(17.0%)	0.999
	E. coli	9(9.0%)	4(4.0%)	
	Enterobacter	14(14.0%)	6(6.0%)	
	Proteus	7(7.0%)	3(3.0%)	

Data is presented as mean ± SD or frequency (%). CR: Carbapenem resistance, CS: Carbapenem sensitive, COPD: Chronic obstructive pulmonary disease, UT: Urinary tract.

Table 2. Relationship between the type of carbapenemase and the types of CRE isolates.

	MBL (n=52)	**MBL and KPC (n=18)**	**P**
***Klebsiella pneumoniae* (n=40)**	23(44.23%)	17(94.44%)	**0.002***
***Enterobacter* (n=14)**	14(26.92%)	0(0.0%)	
***E.coli* (n=9)**	8(15.09%)	1(5.26%)	
***Proteus* (n=7)**	7(13.46%)	0(0.0%)	

Data is presented as frequency (%). * Significant P value <0.05. MBL: Metallo-B-Lactamase, KPC: *Klebsiella pneumoniae* carrying variant.

Table 3. Relationship between types of carbapenemase and different antibiotics used against CRE.

		MBL (n=52)	**MBL and KPC (n=18)**	**P**
Meropenem/ Vaborbactam	**Sensitive**	5(9.62%)	12(66.67%)	**<0.001***
	Resistant	47(90.38%)	6(33.33%)	
Ceftazidime/ Avibactam	**Sensitive**	3(5.77%)	6(33.33%)	**0.007***
	Resistant	49(94.23%)	12(66.67%)	
Imipenem/ Relebactam	**Sensitive**	0(0.0%)	0(0.0%)	--
	Resistant	52(100.0%)	18(100.0%)	
Cefiderocol	**Sensitive**	52(100.0%)	18(100.0%)	--
	Resistant	0(0.0%)	0(0.0%)	

Data is presented as frequency (%). * Significant P value <0.05. MBL: Metallo-B-Lactamase, KPC: *Klebsiella pneumoniae* carrying variant.

Table 4. Relationship between the type of sample and different antibiotics used against CRE isolates.

		Blood (n=23)	Sputum (n=24)	Wound (n=9)	Urine (n=8)	Bed sore (n=6)	P
Meropenem/ vaborbactam	**Sensitive**	4(17.39%)	11(45.83%)	0(0.0%)	2(25.0%)	0(0.0%)	**0.022***
	Resistant	19(82.61%)	13(54.17%)	9(100.0%)	6(75.0%)	6(100.0%)	
Ceftazidime/ avibactam	**Sensitive**	8(34.78%)	0(0.0%)	1(11.11%)	0(0.0%)	0(0.0%)	**0.003***
	Resistant	15(65.22%)	24(100.0%)	8(88.89%)	8(100.0%)	6(100.0%)	
Imipenem/ relebactam	**Sensitive**	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	--
	Resistant	23(100.0%)	24(100.0%)	9(100.0%)	8(100.0%)	6(100.0%)	
Cefiderocol	**Sensitive**	23(100.0%)	24(100.0%)	9(100.0%)	8(100.0%)	6(100.0%)	--
	Resistant	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	

Data is presented as frequency (%). * Significant P value <0.05.

Table 5. Relationship between type of CRE isolates and different used**.**

		Meropenem/ Vaborbactam	Ceftazidime/ Avibactam	Imipenem/ Relebactam	Cefiderocol
Klebsiella pneumoniae (n=40)	**Sensitive**	10(25.0%)	9(22.5%)	0(0.0%)	40(100.0%)
	Resistant	30(75.0%)	31(77.5%)	40(100.0%)	0(0.0%)
E. coli (n=9)	**Sensitive**	4(44.44%)	0(0.0%)	0(0.0%)	9(100.0%)
	Resistant	5(55.56%)	9(100.0%)	9(100.0%)	0(0.0%)
Enterobacter (n=14)	**Sensitive**	1(7.14%)	0(0.0%)	0(0.0%)	14(100.0%)
	Resistant	13 (92.86%)	14(100.0%)	14(100.0%)	0(0.0%)
Proteus (n=7)	**Sensitive**	2 (28.57%)	0(0.0%)	0(0.0%)	7(100.0%)
	Resistant	5 (71.43%)	7(100.0%)	7(100.0%)	0(0.0%)
P		0.230	0.051	--	--

Data is presented as frequency (%).

Figure 1. Type of carbapenemases in the studied CRE isolates.

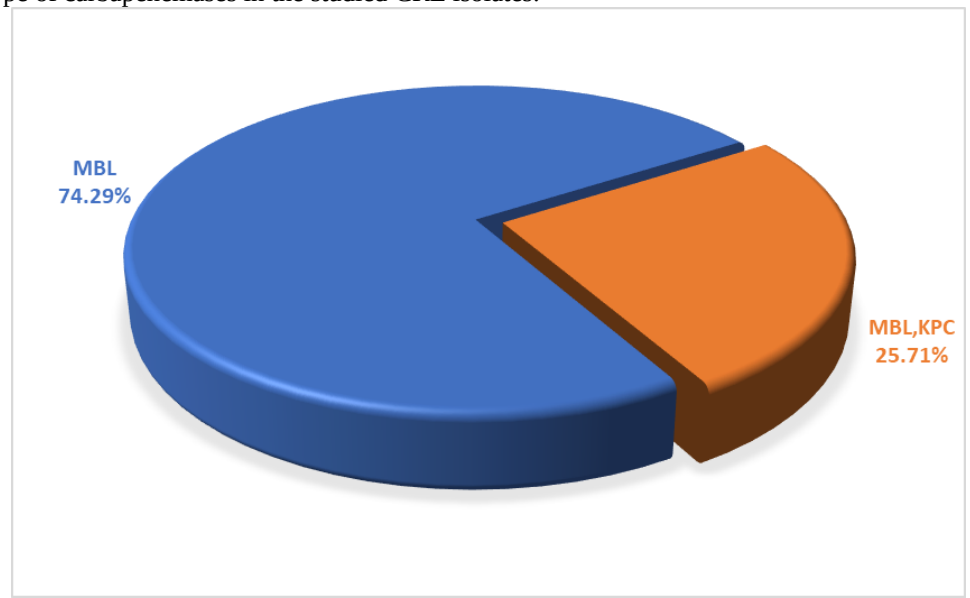
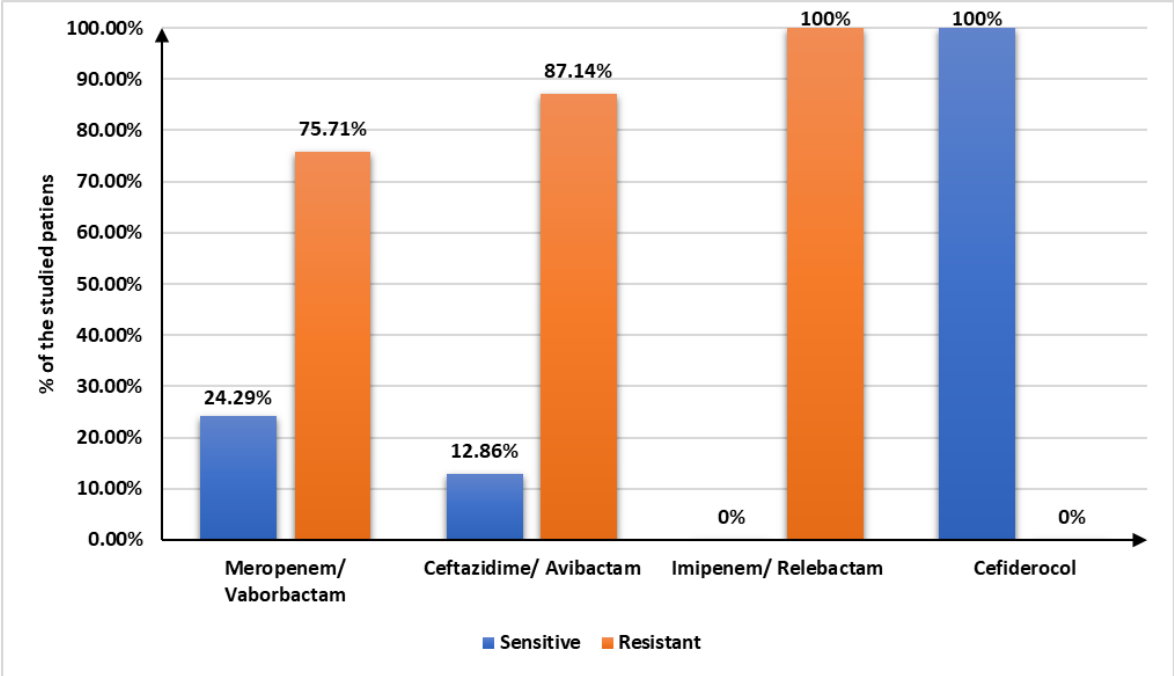


Figure 2: In-vitro sensitivity of different antibiotics used against the studied CRE isolates.



Discussion

The capacity of *Enterobacteriaceae* to produce ESBLs, which enable them to develop AR, initially presented a threat to the general public's health [15].The medical profession used first-line empirical therapies like carbapenems to combat this menace [16].

The present study showed that 70% (70/100) of the studied *Enterobacteriaceae* isolates were CR, while 30% (30/100) were CS. In the same line, Shanmugam *et al.* [17] illustrated that 93% of *Enterobacteriaceae* isolates were carbapenem resistant *Enterobacteriaceae* (CRE).

The present study showed that relationship between CRE and carbapenem sensitive *Enterobacteriaceae* (CSE) patients regarding the age, type of sample and type of isolated organism was insignificant. These results are in agreement with Zhen *et al.* [18] showed no significant difference between CRE group and CSE group regarding age of the patients, type of the sample and type of the isolated organism. On the other hand, Wesam *et al.* [19] stated that there was a significant difference between CRE and CSE patients regarding the age.

In this study we used carba plus test for detection of the type of carbapenemases among CRE isolates and we concluded that, more than half of CRE isolates 74.29% produced MBL and the rest 35.71% produced MBL and KPC genes. In agreement with this result, Iman *et al*. [20] found that 70% of CRE isolates were MBL producers. However, Wei *et al*. [21] found that blaKPC gene was the most often discovered carbapenemase gene (73.8%) followed by the blaNDM gene (24.8%) as well as (0.7%) both blaKPC and blaNDM.

The current study demonstrated that 100%, 88.8% and 57.5% of *Enterobacter, Klebsiella pneumoniae* and *E. coli* isolates produced MBL respectively. In the same line, Rashedi *et al*. [22] reported that 74% of CP *E. coli* isolates produced MBL. In contrast, Malik *et al*. [23] showed that 22% of *Klebsiella pneumoniae* isolates were MBL producers.

Concerning the present study, all CRE isolates including mainly those producing MBLs had a sensitive response against cefiderocol. In the same line with our result, Wang et al. [24] demonstrated that cefiderocol inhibited 100% of CRE isolates which was explained by the addition of a catechol siderophore moiety on the C-3 side-chain which allow cefiderocol to hijack bacterial iron transport systems, facilitating entry into cells, and therefore achieving high periplasmic concentrations [25]. In addition, cefiderocol has high affinity for penicillin-binding protein 3 and is less susceptible to β-lactamases, including *Klebsiella pneumoniae* carbapenemase (KPC), New Delhi metallo-β-lactamase (NDM) [26].

On the other hand, Timsit *et al*. [27] demonstrated that 70.8 %of CRE isolates were sensitive to cefiderocol respectively.

Concerning the current study, all CRE including mainly those producing MBLs were resistant to I/R. In the same line, Mashaly and Mashaly, [28] showed that there is no demonstrable activity of I/R against *Klebsiella pneumoniae* harboring MBLs. On contrary, Johnston *et al*. [29] illustrated that among the 203 total carbapenem resistant *E. coli* isolates, the sensitivity was high for I/R (89%).

In the current study, M/V had a sensitive response from (24.29%) of the studied CRE isolates. MBL isolates were significantly resistant to M/V, as 90.3% (47/52) of total MBL isolates showed resistance to M/V. Supporting our results, Supporting our results, Castanheira et al. [30] and Shortridge et al. [31] demonstrated that 83%, 80% of MBL isolates were resistant to M/V respectively . In contrary with our result Nordmann et al. [32] and, Gaibani et al. [33] showed that 77%, 87% of CRE isolates were susceptible to M/V this variation is explained by that KPC was the most common carbapenemase in their studies while MBL was the most predominant carbapenemase in our study respectively.

In this study, CZA had a sensitive response against 12.86% of total CRE isolates. MBL was significantly resistant to CZA as 5.8% of total MBL isolates were sensitive to CZA. This is supported by Aamir *et al*. [34] showed that 22.2% of CRE isolates were sensitive to CZA. In contrast, Lemos-Luengas *et al*. [35] stated that 63% of the total CRE isolates were susceptible to CZA and it was noted that most or even all of CZA sensitive isolates were none MBL producers.

In the current study, all samples including blood and sputum collected from the studied CRE patients had a sensitive response against cefiderocol. Also, all different types of CRE isolates had a sensitive response against cefiderocol. In agreement with the current results, Wang *et al*. [24] observed that cefiderocol inhibited 100% of CR-KP isolates. The current study revealed that CRE isolated from blood samples were significantly sensitive to CZA. In addition, all CZA sensitive CRE isolates were *Klebsiella pneumoniae.* Supporting our results, Shields *et al*. [36] revealed that 74% of patients with bacteremia showed a sensitive response to CZA and Clinical success was 85%. In the same line with our result, Bakthavatchalam et al. [37] and Zhang et al. [38] showed that 51% and 84% of the studied carbapenem resistant *Klebsiella Pneumoniae* isolates were sensitive to CZA respectively. In contrast to our result, Fontana *et al*. [39] showed that all CZA resistant isolates from CRE were *Klebsiella pneumoniae*.

The current study revealed that CRE isolated from sputum samples were significantly sensitive to M/V. Also, we stated that *Klebsiella pneumoniae* followed by *Ecoli* were the most common M/V sensitive CRE isolates. In the same line, Wenzler *et al*. [40] demonstrated ELF concentrations ranging from one-half to two times the simultaneous plasma concentrations, with ratios of ELF-to-plasma concentrations of meropenem and vaborbactam 65%.

In this study, we stated that all different CRE isolates showed resistant response against I/R.

Contrary to our results, Mashaly and Mashaly, [28] demonstrated that I/R showed resistance in 54.3% of CRKP isolates.

Limitations of the study included single centre study which may result in different findings than elsewhere, small sample size that may produce insignificant results, also phenotypic methods used. Further, we did not evaluate resistance mechanisms such as porin mutations or efflux pump upregulation, which might have contributed to CR in *Enterobacteriaceae,* and consequently to outcomes.

Conclusions:

As highlighted by the Global Priority List published by WHO, CRE pose an exponentially increasing threat for public health worldwide. These bacteria possess diverse and versatile mechanisms of drug resistance, which makes control and early detection of infections caused by CRE difficult. As a result, a joint effort must be made between the scientific and medical community to slow down the appearance of resistance. *Klebsiella pneumoniae* was the most common type of isolated CRE. The most common antibiotics previously abused by CRE patients were ciprofloxacin, levofloxacin and vancomycin respectively. The most common carbapenemase produced by CRE isolates was MBL. All CRE isolates had a sensitive response against cefiderocol, on the contrary, all CRE isolates were resistant to I/R. New β-lactam/β-lactamase inhibitor combinations (I/R, CZA and M/V) were of limited effictiveness against CRE isolates which mainly produced MBLs, causing the emergence of

resistance under therapy. MBLs were significantly resistant to M/V and CZA. The most effective used antibiotic on MBL producing CRE isolates was cefiderocol.

Declaration of interest and Funding information:

The authors report no conflicts of interest.

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