Pomeranian J Life Sci 2024;70(1):7-14 doi: 10.21164/pomjlifesci.973

Beta-lactam antibiotics in combination with novel β-lactamase inhibitors – an alternative therapy for infections caused by multidrug-resistant bacteria

Małgorzata Brauncajs[1, 2, A], Filip Bielec[1, 2, B] ✉, Anna Macieja[1, C], Dorota Pastuszak-Lewandoska[1, D]

[1] Medical University of Lodz, Department of Microbiology and Laboratory Medical Immunology, Pomorska 251, 92-213, Łódź, Poland
[2] Central Teaching Hospital of the Medical University of Łódź, Medical Microbiology Laboratory, Pomorska 251, 92-213, Łódź, Poland

[A] ORCID: 0000-0002-6529-8886; [B] ORCID: 0000-0003-4446-0802; [C] ORCID: 0000-0001-6056-7808; [D] ORCID: 0000-0001-7602-9203

✉ filip.bielec@umed.lodz.pl

ABSTRACT

Introduction: New combinations of old β-lactam drugs with novel β-lactamase inhibitors, approved in recent years by the US Food and Drug Administration and the European Medicines Agency, are a promising alternative for the treatment of infections caused by multidrug-resistant strains. Due to limited availability and increasing resistance to antibacterial drugs, they should be used with caution, especially in patients with limited treatment options. It should be noted that both diazobicycloctane and boron inhibitors are inactive against metallo-β-lactamase (MBL) producing strains. The aim of this study was to evaluate the in vitro susceptibility of carbapenemase-producing Gram-negative bacilli to meropenem/vaborbactam, imipenem/relebactam and ceftazidime/avibactam in clinical samples from hospitalized patients.

Materials and methods: The analysis included 102 clinical strains of carbapenemase-producing Enterobacterales and non-fermenters from hospital centers in Łódź, Poland. A minimum inhibitory concentration test strip method was used to determine antimicrobial susceptibility.

Results: Seventy-one percent of *Escherichia coli*, 40% of *Klebsiella pneumoniae*, and 67% of *Pseudomonas aeruginosa* were resistant to meropenem/vaborbactam, 57%, 66%, and 60% to imipenem/relebactam, and 71%, 74%, and 60% to ceftazidime/avibactam, respectively. Considering carbapenemase resistance mechanisms, the highest efficacy was observed in *Klebsiella pneumoniae* carbapenemases (KPC) strains for each drug combination tested.

Conclusions: The results of our study confirm the conclusions of the studies evaluating the susceptibility of Gram-negative, fermenting, and non-fermenting bacilli to ceftazidime/avibactam, meropenem/vaborbactam and imipenem/relebactam and indicate that there are reasonable grounds for using these antibiotics in the treatment of patients hospitalized with serious infections. However, limitations in their use against MBL-producing strains are highlighted.

Keywords: antimicrobials; meropenem/vaborbactam; imipenem/relebactam; ceftazidime/avibactam; multi-drug resistance; antimicrobial susceptibility testing; epidemiology.

INTRODUCTION

Drug resistance, which has grown rapidly in recent years, poses a challenge to the development of new antimicrobial drugs. Increasingly, we are dealing with pathogens that are resistant to all available antibiotics and for which there are no alternative therapeutic options. Therefore, the development of new antimicrobial drugs, especially those that block β-lactamases, is essential. The existing ones (clavulanic acid, sulbactam, tazobactam), which have been used for years in combination with aminopenicillins or piperacillin, are beginning to lose their efficacy because bacteria modify the enzymes they produce, making them more effective. More and more interesting new β-lactamase inhibitors have been developed, including carbapenemases. These inhibitors are combined with well-known antibiotics [1, 2].

One example is meropenem/vaborbactam, which is approved for the treatment of complicated urinary tract infections (including pyelonephritis), abdominal infections, nosocomial pneumonia (including ventilator-associated pneumonia), and the treatment of patients with bloodstream infections associated with any of the aforementioned conditions. This antibiotic is indicated for the treatment of infections caused by aerobic Gram-negative organisms in adult patients with limited treatment options. Vaborbactam is a non-β-lactam inhibitor of class A and class C serine β-lactamases, including *Klebsiella pneumoniae* carbapenemases (KPC). It forms a covalent adduct with β-lactamases and is stable to hydrolysis by β-lactams. Vaborbactam does not inhibit class B enzymes (metallo-β-lactamases – MBL) or class D carbapenemases [3, 4].

Another new drug is imipenem/relebactam (also in combination with cilastatin, which reduces the renal metabolism of imipenem but has no antibacterial activity), which is indicated for the treatment of nosocomial pneumonia, including ventilator-associated pneumonia; for the treatment of bacteremia known or suspected to be associated with pneumonia; and for the treatment of infections caused by aerobic Gram-negative bacteria in adult patients with limited treatment

options [5]. Relebactam is a non-β-lactam inhibitor of Ambler class A and C β-lactamases, including KPC and extended-spectrum β-lactamases (ESBL), and class C β-lactamases (type AmpC), including cephalosporinase produced by *Pseudomonas* spp. Relebactam does not inhibit class B enzymes (MBL) or class D carbapenemases. Similar to imipenem and meropenem, both relebactam and vaborbactam are primarily excreted by the kidneys and their clearance correlates with creatinine clearance [6, 7, 8].

Another compound of note is ceftazidime/avibactam, which is indicated for use in adults and children 3 months of age and older for the treatment of the following types of infections: complicated intra-abdominal infections, urinary tract infections (including pyelonephritis), nosocomial pneumonia (including ventilator-associated pneumonia and bacteremia). Avibactam is a non-β-lactam β-lactamase inhibitor that forms a covalent complex with the enzyme molecule that is stable and resistant to hydrolysis. This binding results in the inhibition of both class A and C β-lactamases and some Ambler class D enzymes, including ESBL, KPC, and OXA-serine carbapenemases 48 (oxacillinase-48 – OXA-48) and AmpC enzymes. Avibactam does not inhibit class B enzymes (MBL) and cannot inhibit many class D enzymes [9, 10].

Meropenem/vaborbactam, imipenem/relebactam, and ceftazidime/avibactam have not been available in Polish hospitals for a long time, and their use in critical cases of multidrug-resistant infections was linked to the implementation of the target import procedure. Due to the lack of susceptibility testing for these drugs in routine microbiological diagnostics, we need insight into the susceptibility profiles of clinical isolates. The aim of this study was to evaluate the susceptibility of novel β-lactam/β-lactamase inhibitor combinations against multidrug-resistant Gram-negative bacilli strains isolated in recent years from hospitalized patients in Łódź, Poland.

MATERIALS AND METHODS

A total of 102 strains producing KPC, MBL, and OXA-48 carbapenemases were evaluated. All strains were isolated from clinical specimens: bronchial alveolar lavage (BAL), blood, urine, rectal swabs (carbapenemase producing organisms screening), lower respiratory tract specimens (other than BAL), intraoperative swabs, nasal swabs, wound swabs, and pressure ulcer swabs.

All bacteria were stored in Viabank™ storage beads (Medical Wire and Equipment, UK) at a max. of –80°C for 6 months and regenerated on Columbia Agar with 5% sheep blood (Thermo Fisher Scientific, USA) at 37°C for 18–24 h. Isolates were tested for susceptibility to meropenem/vaborbactam, imipenem/relebactam, and ceftazidime/avibactam using minimum inhibitory concentration (MIC) test strips (Liofilchem, Italy) with the same standardized inoculum. Drug susceptibility was determined on standard Mueller-Hinton Agar (Thermo Fisher Scientific, USA), incubated for 18 ±2 h at 35 ±1°C, according to the guidelines of the European Committee on Antimicrobial Susceptibility Testing (EUCAST) [11]. The ability of all strains tested to produce carbapenemases was evaluated and confirmed as previously described [12].

Descriptive statistics were performed using Microsoft Excel 2019 software (Microsoft Corporation, USA).

RESULTS

The raw results of the susceptibility testing are presented in the Supplementary file. The strains tested were from the same collection described in the authors' previous publication [12]. The group of tested bacteria consisted of 50 *Klebsiella pneumoniae*, 7 *Escherichia coli*, 15 *Pseudomonas aeruginosa*, and 26 *Acinetobacter baumannii*. The remaining 4 isolates were single strains of *Aeromonas sobria*, *Klebsiella varicola*, *Pseudomonas alcaligenes*, and *Pseudomonas putida*. The distribution of resistance mechanisms detected is shown in Tables 1, 2, 3.

TABLE 1. Antimicrobial *in vitro* activity of meropenem/vaborbactam against the carbapenemase-producing species

Resistance mechanism	n	MIC50 (mg/L)	MIC90 (mg/L)	MIC range (mg/L)
CIM	26	192	>256	0.032–>256
MBL	58	12	>256	0.023–>256
OXA-48	6	96	>256	0.023–>256
KPC	11	0.125	1	0,016–>256
GES	35	12	>256	1.5–>256

MIC – minimum inhibitory concentration; MIC50 – MIC required to inhibit the growth of 50% of bacteria; MIC90 – MIC required to inhibit the growth of 90% of bacteria; CIM – carbapenem inactivation method; MBL – metallo-β-lactamase; OXA-48 – oxacillinase-48; KPC – ***Klebsiella pneumoniae*** carbapenemase; GES – Guiana extended-spectrum

TABLE 2. Antimicrobial *in vitro* activity of imipenem/relebactam against the carbapenemase-producing species

Resistance mechanism	n	MIC50 (mg/L)	MIC90 (mg/L)	MIC range (mg/L)
CIM	26	32	>32	0.125–>32
MBL	58	4	>32	0.064–>32
OXA-48	6	24	>32	0.25–>32
KPC	11	0.5	1	0.19–>32
GES	35	12	>32	0.38–>32

MIC – minimum inhibitory concentration; MIC50 – MIC required to inhibit the growth of 50% of bacteria; MIC90 – MIC required to inhibit the growth of 90% of bacteria; CIM – carbapenem inactivation method; MBL – metallo-β-lactamase; OXA-48 – oxacillinase-48; KPC – ***Klebsiella pneumoniae*** carbapenemase; GES – Guiana extended-spectrum

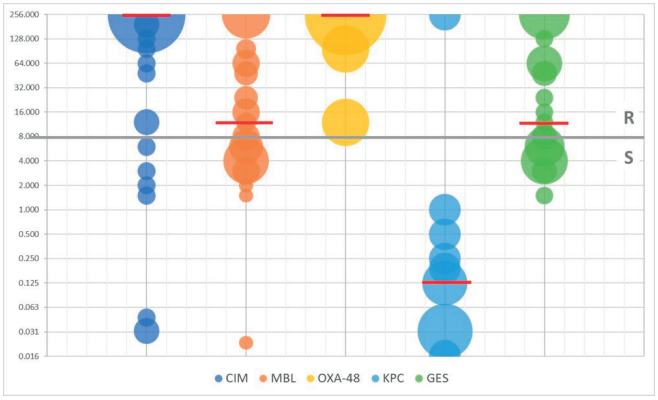
TABLE 3. Antimicrobial *in vitro* activity of ceftazidime/avibactam against the carbapenemase-producing species

Resistance mechanism	n	MIC50 (mg/L)	MIC90 (mg/L)	MIC range (mg/L)
CIM	26	8	16	0.016–32
MBL	58	>256	>256	≤0.016–>256
OXA-48	6	>256	>256	0.094–>256
KPC	11	1	3	0.25–32
GES	35	>256	>256	≤0.016–>256

MIC – minimum inhibitory concentration; MIC50 – MIC required to inhibit the growth of 50% of bacteria; MIC90 – MIC required to inhibit the growth of 90% of bacteria; CIM – carbapenem inactivation method; MBL – metallo-β-lactamase; OXA-48 – oxacillinase-48; KPC – ***Klebsiella pneumoniae*** carbapenemase; GES – Guiana extended-spectrum

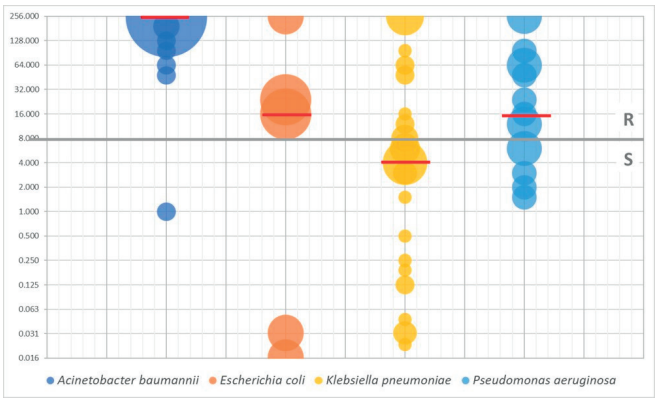
Among Gram-negative rods of the order Enterobacterales, 71% of *E. coli* and 40% of *K. pneumoniae* showed resistance to meropenem/vaborbactam. When isolates of non-fermenting Gram-negative bacilli were analyzed, 67% of *P. aeruginosa* strains showed no susceptibility to this drug; 96% of *A. baumannii* strains had a MIC above 8 (EUCAST did not provide a breakpoint for this species).

Table 1 shows the values of the growth inhibition zone range, MIC range, MIC50 and MIC90 for meropenem/vaborbactam. Figures 1 and 2 show the *in vitro* antimicrobial activity of meropenem/vaborbactam against the species analyzed in this study and in relation to their resistance mechanism.



MIC – minimum inhibitory concentration; CIM – carbapenem inactivation method; MBL – metallo-β-lactamase; OXA-48 – oxacillinase-48; KPC – ***Klebsiella pneumoniae*** carbapenemase; GES – Guiana extended-spectrum; R – resistant; S – susceptible

FIGURE 1. *In vitro* antimicrobial activity of meropenem/vaborbactam against carbapenemase-producing bacteria depending on the resistance mechanism – MIC test strip method. The size of the bubble depends on the percentage of strains with a given MIC value. The gray line indicates the breakpoint between susceptible and resistant, and the red lines indicate the average MIC values



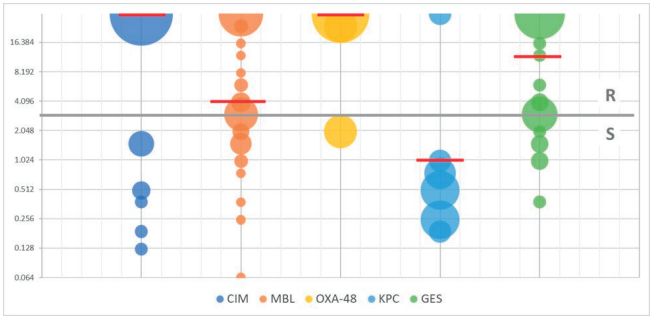
MIC – minimum inhibitory concentration; R – resistant; S – susceptible

FIGURE 2. *In vitro* antimicrobial activity of meropenem/vaborbactam against carbapenemase-producing bacteria depending on the species – MIC test strip method. Bubble size depends on the percentage of strains with a given MIC value. The gray line indicates the breakpoint between susceptible and resistant, and the red lines indicate the average MIC values

Similar data were observed for imipenem/relebactam susceptibility. Among Gram-negative rods of the order Enterobacterales, 57% of *E. coli* and 66% of *K. pneumoniae* strains were resistant to this antibiotic. Analysis of Gram-negative non-fermenting rod isolates showed no susceptibility to this drug in 60% of *P. aeruginosa* strains, while 96% of *A. baumannii* strains had an MIC above 2 mg/L.

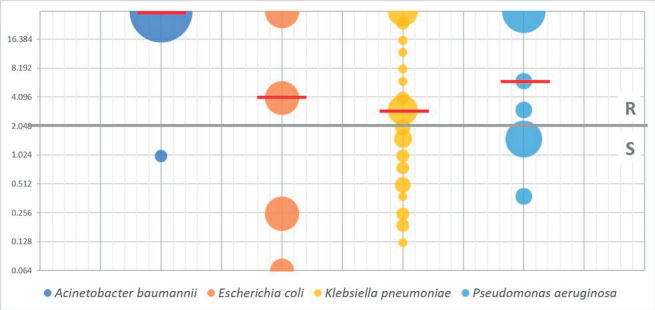
For both combinations of carbapenems with novel inhibitors, the highest efficacy was observed in the treatment of infections caused by KPC strains.

Table 2 shows the values of the inhibition zone range, MIC range, MIC50 and MIC90 for imipenem/relebactam. Figures 3 and 4 show the *in vitro* antimicrobial activity of imipenem/relebactam against the species analyzed in this study and in relation to their resistance mechanism.



MIC – minimum inhibitory concentration; CIM – carbapenem inactivation method; MBL – metallo-β-lactamase; OXA-48 – oxacillinase-48; KPC – ***Klebsiella pneumoniae*** carbapenemase; GES – Guiana extended-spectrum; R – resistant; S – susceptible

FIGURE 3. *In vitro* antimicrobial activity of imipenem/relebactam against carbapenemase-producing bacteria as a function of resistance mechanism – MIC test strip method. The size of the bubble depends on the percentage of strains with a given MIC value. The gray line indicates the breakpoint between susceptible and resistant, and the red lines indicate the average MIC values

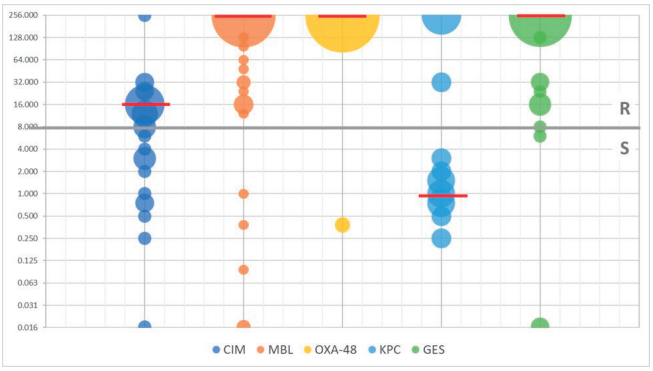


MIC – minimum inhibitory concentration; R – resistant; S – susceptible

FIGURE 4. *In vitro* antimicrobial activity of imipenem/relebactam against carbapenemase producing bacteria as a function of species – MIC test strip method. The size of the bubble depends on the percentage of strains with a given MIC value. The gray line indicates the breakpoint between susceptible and resistant, and the red lines indicate the average MIC values

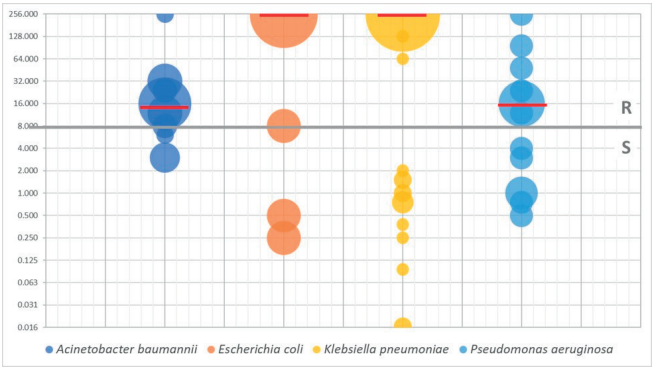
Evaluation of the susceptibility of Enterobacterales Gram-negative rods to ceftazidime/avibactam showed that 71% of *E. coli* and 74% of *K. pneumoniae* strains are resistant to this antibiotic. Among Gram-negative non-fermenting bacilli, 60% of *P. aeruginosa* strains showed no susceptibility to this drug; 85% of *A. baumannii* strains had a MIC above 8 mg/L.

Table 3 shows the values of the growth inhibition zone range, MIC range, MIC_{50} and MIC_{90} for ceftazidime/avibactam. Figures 5 and 6 show the *in vitro* antimicrobial activity of ceftazidime/avibactam against the species analyzed in this study and in relation to their resistance mechanism.



MIC – minimum inhibitory concentration; CIM – carbapenem inactivation method; MBL – metallo-β-lactamase; OXA-48 – oxacillinase-48; KPC – ***Klebsiella pneumoniae*** carbapenemase; GES – Guiana extended-spectrum; R – resistant; S – susceptible

FIGURE 5. *In vitro* antimicrobial activity of ceftazidime/avibactam against carbapenemase-producing bacteria according to resistance mechanism – MIC test strip method. The size of the bubble depends on the percentage of strains with a given MIC value. The gray line indicates the breakpoint between susceptible and resistant, and the red lines indicate the average MIC values



MIC – minimum inhibitory concentration; kiR – resistant; S – susceptible

FIGURE 6. *In vitro* antimicrobial activity of ceftazidime/avibactam against carbapenemase-producing bacteria as a function of species – MIC test strip method. The size of the bubble depends on the percentage of strains with a given MIC value. The gray line indicates the breakpoint between susceptible and resistant, and the red lines indicate the average MIC values

DISCUSSION

In recent years, the lack of drugs available to treat patients with infections caused by multidrug-resistant bacteria has become a serious problem. In particular, resistance to carbapenems continues to grow. Beta-lactamases are the enzymes responsible for bacterial resistance to these antibiotics. By inhibiting the action of β-lactamases, the novel inhibitors vaborbactam, relebactam and avibactam protect the β-lactam antibiotics they are combined with from inactivation and restore their activity against many, but not all, carbapenem-resistant pathogens.

In a systematic literature review, Soriano et al. analyzed 73 relevant publications, including 1926 cases of patients treated with ceftazidime/avibactam (as monotherapy or in combination with other antimicrobials) and 1114 patients in the control group. All patients were hospitalized for serious illnesses, mainly pneumonia, bacteremia or skin and urinary tract infections. Most of these publications reported positive effects of ceftazidime/avibactam: clinical success rates ranged 45–100%, and 30-day mortality ranged 0–63% [9].

Our *in vitro* studies showed that 67% of KPC-positive strains were susceptible to the combination of ceftazidime/avibactam. The efficacy of this drug in the production of class A carbapenemases was demonstrated by Gaibani et al. [13]. The authors characterized 105 KPC producers out of 120 carbapenemase-producing strains. Resistance to ceftazidime/avibactam was identified in 3 (2.9%) KPC strains isolated from ceftazidime/avibactam-naive patients. Also, Swaminathan et al. [14], similar to Zalas-Więcek et al. [15], demonstrated that the combination of a third-generation cephalosporin and a non-β-lactam β-lactamase inhibitor was clinically effective in the treatment of multidrug resistant (MDR) infections and reduced mortality. On the other hand, Bonnin et al. showed that in the group of 33 carbapenem-resistant Enterobacterales isolates they tested that were classified as resistant to ceftazidime/avibactam, other novel combinations – imipenem/relebactam and

meropenem/vaborbactam – still showed susceptibilities of 54.5% and 48.5%, respectively [16].

The Achilles' heel, however, is that MBL-positive bacteria are inherently resistant to ceftazidime in combination with avibactam. Ceftazidime/avibactam retains good activity against Gram-negative bacteria, especially *Enterobacteriaceae*. *Pseudomonas aeruginosa* is less susceptible to ceftazidime/avibactam than *Enterobacteriaceae*, with a resistance rate of 2.9–18% [17]. In our study, the resistance rate for *P. aeruginosa* was 60%. Resistance to ceftazidime/avibactam exceeds 50% in *A. baumannii*. Such values were obtained by Wang et al. in their research [17]. In our work, the resistance rate for *A. baumannii* was 85%. Of these isolates, 35% had a MIC value of 16 mg/L. Ceftazidime/avibactam should not be used against pathogens that are naturally resistant to it. For strains resistant to ceftazidime/avibactam, other effective antibacterial agents or ceftazidime/avibactam in combination with other antibacterial agents should be considered [17].

Similar to ceftazidime/avibactam, meropenem/vaborbactam has been shown to be effective in the treatment of infections caused by KPC strains. Gaibani et al. showed that only 8% of KPC-positive strains were resistant to this antibiotic due to mutations in porin proteins [18]. In our study, the percentage of resistance was almost identical (9%), and all of these isolates had a MIC >256 mg/L. In contrast, the most susceptible KPC-positive strains (27%) had a MIC of 0.032 mg/L. The MIC_{90} for isolates producing only KPC was 1 mg/L. Hackel et al. found the same value in their investigation of the exact resistance mechanisms [19]. Nordmann et al. studied 150 carbapenemase producers, among which *K. pneumoniae* and *E. coli* predominated, as in our study [20]. Their research showed, similar to our research results, that all combinations of β-lactams with novel inhibitors showed the greatest efficacy against KPC-positive strains compared to other carbapenemase genetic mechanisms. Sader et al. also came to similar conclusions. Ceftazidime/avibactam, meropenem/vaborbactam, and imipenem/relebactam were highly active against KPC-producing carbapenem-resistant Enterobacterales isolates, with susceptibility rates ranging 97.8–98.8% [21].

Similar to our findings, Castanheira et al. demonstrated that meropenem with vaborbactam was ineffective in the treatment of infections caused by OXA-48 strains. They analyzed susceptibility data for another antibiotic, a combination of an old drug with a new inhibitor, imipenem/relebactam [22]. Our studies showed only 9% resistance among KPC strains: all of these isolates had a MIC >32 mh/L. In addition, the most susceptible KPC-positive strains, which accounted for 64% in our study, had MICs <0.5 mg/L. The resistance rate among the Enterobacterales Gram-negative rods was over 60%, and among *A. baumannii* isolates it was 96%. Unfortunately, like the previously described drugs, it does not affect MBL-positive strains [5].

CONCLUSIONS

The results of our study confirm the conclusions of the studies evaluating the susceptibility of Gram-negative, fermenting, and non-fermenting bacilli to ceftazidime/avibactam, meropenem/vaborbactam and imipenem/relebactam and indicate that there are reasonable grounds for using these antibiotics in the treatment of patients hospitalized with serious infections. However, limitations in their use against MBL-producing strains are highlighted.

Supplementary file. The data presented in the study

No.	Organism	Carbapenemase					Antibiotic susceptibility					
							MER/VAB		IMI/REL		CAZ/AVI	
		CIM	MBL	OXA-48	KPC	GES	MIC (mg/L)	interpretation	MIC (mg/L)	interpretation	MIC (mg/L)	interpretation
1	*A. baumannii*	+					192	–	>32	R	32	–
2	*A. baumannii*	+					>256	–	>32	R	16	–
3	*A. baumannii*	+					256	–	32	R	16	–
4	*A. baumannii*	+					>256	–	>32	R	24	–
5	*A. baumannii*	+					>256	–	>32	R	16	–
6	*A. baumannii*	+					>256	–	>32	R	12	–
7	*A. baumannii*	+				+	>256	–	>32	R	24	–
8	*A. baumannii*				+	+	>256	–	>32	R	32	–
9	*A. baumannii*				+		1	–	1	S	3	–
10	*A. baumannii*	+					192	–	>32	R	3	–
11	*A. baumannii*	+				+	256	–	32	R	8	–
12	*A. baumannii*	+				+	>256	–	32	R	16	–

No.	Organism	Carbapenemase					Antibiotic susceptibility					
							MER/VAB		IMI/REL		CAZ/AVI	
		CIM	MBL	OXA-48	KPC	GES	MIC (mg/L)	interpre-tation	MIC (mg/L)	interpre-tation	MIC (mg/L)	interpre-tation
13	*A. baumannii*	+				+	>256	–	32	R	16	–
14	*A. baumannii*	+				+	64	–	32	R	256	–
15	*A. baumannii*	+				+	256	–	32	R	32	–
16	*A. baumannii*		+				256	–	32	R	32	–
17	*A. baumannii*	+					256	–	32	R	8	–
18	*A. baumannii*	+					256	–	32	R	12	–
19	*A. baumannii*	+					48	–	32	R	3	–
20	*A. baumannii*	+					256	–	32	R	16	–
21	*A. baumannii*	+					96	–	32	R	12	–
22	*A. baumannii*	+					256	–	32	R	12	–
23	*A. baumannii*	+					256	–	32	R	16	–
24	*A. baumannii*	+					256	–	32	R	16	–
25	*A. baumannii*	+					>256	–	>32	R	16	–
26	*A. baumannii*	+				+	128	–	>32	R	6	–
27	*A. sobria*	+					0.032	S	0.5	S	0.016	S
28	*E. coli*	+					256	R	>32	R	8	S
29	*E. coli*				+		0.016	S	0.25	S	0.25	S
30	*E. coli*				+		0.032	S	0.25	S	0.5	S
31	*E. coli*		+				24	R	0.064	S	256	R
32	*E. coli*		+				16	R	4	R	256	R
33	*E. coli*		+			+	24	R	32	R	>256	R
34	*E. coli*		+				16	R	4	R	>256	R
35	*K. pneumoniae*		+			+	>256	R	>32	R	>256	R
36	*K. pneumoniae*		+	+			>256	R	>32	R	>256	R
37	*K. pneumoniae*		+			+	6	S	1.5	S	>256	R
38	*K. pneumoniae*		+			+	3	S	1	S	128	R
39	*K. pneumoniae*		+			+	64	R	32	R	>256	R
40	*K. pneumoniae*	+					0.047	S	0.125	S	0.25	S
41	*K. pneumoniae*		+			+	6	S	12	R	>256	R
42	*K. pneumoniae*		+			+	12	R	3	R	>256	R
43	*K. pneumoniae*		+			+	4	S	2	S	256	R
44	*K. pneumoniae*		+			+	3	S	0.38	S	256	R
45	*K. pneumoniae*		+				4	S	3	R	256	R
46	*K. pneumoniae*		+	+			12	R	2	S	0.38	S
47	*K. pneumoniae*		+				>256	R	>32	R	256	R
48	*K. pneumoniae*	+					0.032	S	0.19	S	0.75	S
49	*K. pneumoniae*		+				3	S	2	S	256	R
50	*K. pneumoniae*				+		0.5	S	0.75	S	1.5	S
51	*K. pneumoniae*		+				8	S	8	R	>256	R
52	*K. pneumoniae*		+				4	S	1.5	S	256	R
53	*K. pneumoniae*		+				0.023	S	0.25	S	0.094	S

No.	Organism	Carbapenemase					Antibiotic susceptibility					
							MER/VAB		IMI/REL		CAZ/AVI	
		CIM	MBL	OXA-48	KPC	GES	MIC (mg/L)	interpre-tation	MIC (mg/L)	interpre-tation	MIC (mg/L)	interpre-tation
54	*K. pneumoniae*		+				4	S	3	R	>256	R
55	*K. pneumoniae*		+				8	S	1,5	S	256	R
56	*K. pneumoniae*		+			+	16	R	32	R	256	R
57	*K. pneumoniae*		+			+	4	S	1	S	0.016	S
58	*K. pneumoniae*		+			+	4	S	3	R	>256	R
59	*K. pneumoniae*				+		0.19	S	0.5	S	0.75	S
60	*K. pneumoniae*				+		0.125	S	0.5	S	1	S
61	*K. pneumoniae*				+		0.032	S	0.25	S	0.75	S
62	*K. pneumoniae*		+			+	8	S	6	R	>256	R
63	*K. pneumoniae*		+	+			>256	R	>32	R	>256	R
64	*K. pneumoniae*		+			+	6	S	4	R	>256	R
65	*K. pneumoniae*		+	+			>256	R	>32	R	>256	R
66	*K. pneumoniae*		+	+			96	R	24	R	>256	R
67	*K. pneumoniae*		+				256	R	24	R	>256	R
68	*K. pneumoniae*				+		0.032	S	0.19	S	1	S
69	*K. pneumoniae*				+		0,125	S	0.75	S	1,5	S
70	*K. pneumoniae*		+			+	4	S	3	R	>256	R
71	*K. pneumoniae*		+			+	64	R	16	R	>256	R
72	*K. pneumoniae*		+				>256	R	>32	R	64	R
73	*K. pneumoniae*		+				4	S	3	R	>256	R
74	*K. pneumoniae*		+			+	6	S	3	R	>256	R
75	*K. pneumoniae*		+				>256	R	>32	R	>256	R
76	*K. pneumoniae*		+			+	4	S	3	R	>256	R
77	*K. pneumoniae*		+			+	48	R	3	R	0,016	S
78	*K. pneumoniae*		+			+	1.5	S	1.5	S	>256	R
79	*K. pneumoniae*		+			+	48	R	>32	R	>256	R
80	*K. pneumoniae*				+		0.25	S	0.5	S	2	S
81	*K. pneumoniae*		+			+	6	S	4	R	>256	R
82	*K. pneumoniae*		+			+	8	S	>32	R	>256	R
83	*K. pneumoniae*		+			+	4	S	3	R	>256	R
84	*K. pneumoniae*		+			+	4	S	3	R	>256	R
85	*K. varicola*		+				256	R	32	R	256	R
86	*P. aeruginosa*	+					1.5	S	0.38	S	0.75	S
87	*P. aeruginosa*		+				16	R	3	R	16	R
88	*P. aeruginosa*		+				>256	R	>32	R	24	R
89	*P. aeruginosa*		+				48	R	6	R	16	R
90	*P. aeruginosa*		+				6	S	1.5	S	1	S
91	*P. aeruginosa*	+					12	R	1.5	S	1	S
92	*P. aeruginosa*	+					2	S	1.5	S	0.5	S
93	*P. aeruginosa*	+					6	S	1.5	S	4	S
94	*P. aeruginosa*		+				24	R	32	R	48	R

No.	Organism	Carbapenemase					Antibiotic susceptibility					
							MER/VAB		IMI/REL		CAZ/AVI	
		CIM	MBL	OXA-48	KPC	GES	MIC (mg/L)	interpre-tation	MIC (mg/L)	interpre-tation	MIC (mg/L)	interpre-tation
95	*P. aeruginosa*	+					12	R	1.5	S	3	S
96	*P. aeruginosa*		+				3	S	>32	R	12	R
97	*P. aeruginosa*		+				96	R	32	R	96	R
98	*P. aeruginosa*		+			+	>256	R	>32	R	>256	R
99	*P. aeruginosa*		+				64	R	>32	R	16	R
100	*P. aeruginosa*		+			+	64	R	>32	R	16	R
101	*P. alcaligenes*		+				2	S	0.75	S	32	R
102	*P. putida*	+					3	S	0.5	S	2	S

CIM – carbapenem inactivation method; MBL – metallo-β-lactamase; OXA-48 – oxacillinase-48; KPC – ***Klebsiella pneumoniae*** carbapenemase; GES – Guiana extended-spectrum; MIC – minimum inhibitory concentration; MER/VAB – meropenem/vaborbactam; IMI/REL – imipenem/relebactam; CAZ/AVI – ceftazidime/avibactam; S – susceptible; R – resistant

REFERENCES

1. Yahav D, Giske CG, Grāmatniece A, Abodakpi H, Tam VH, Leibovici L. New β-lactam-β-lactamase inhibitor combinations. Clin Microbiol Rev 2020;34(1):e00115-20.
2. Yahav D, Giske CG, Gramatniece A, Abodakpi H, Tam VH, Leibovici L. Erratum for Yahav et al., "New β-lactam-β-lactamase inhibitor combinations". Clin Microbiol Rev 2021;34(2):e00021-21.
3. Novelli A, Del Giacomo P, Rossolini GM, Tumbarello M. Meropenem/vaborbactam: a next generation β-lactam β-lactamase inhibitor combination. Expert Rev Anti Infect Ther 2020;18(7):643-55.
4. Patel TS, Pogue JM, Mills JP, Kaye KS. Meropenem-vaborbactam: a new weapon in the war against infections due to resistant Gram-negative bacteria. Future Microbiol 2018;13(9):971-83.
5. Mansour H, Ouweini AEL, Chahine EB, Karaoui LR. Imipenem/cilastatin/relebactam: A new carbapenem β-lactamase inhibitor combination. Am J Health Syst Pharm 2021;78(8):674-83.
6. Zhanel GG, Lawrence CK, Adam H, Schweizer F, Zelenitsky S, Zhanel M, et al. Imipenem-relebactam and meropenem-vaborbactam: two novel carbapenem-β-lactamase inhibitor combinations. Drugs 2018;78(1):65-98.
7. Bhagunde P, Zhang Z, Racine F, Carr D, Wu J, Young K, et al. A translational pharmacokinetic/pharmacodynamic model to characterize bacterial kill in the presence of imipenem-relebactam. Int J Infect Dis 2019;89:55-61.
8. Ghazi IM, El Nekidy WS, Sood A, Dulku A, Patel R, Patel K, et al. Y-site administration of imipenem/cilastatin/relebactam with common intravenous medications. Clin Ther 2020;42(3):475-85.
9. Soriano A, Carmeli Y, Omrani AS, Moore LSP, Tawadrous M, Irani P. Ceftazidime-avibactam for the treatment of serious gram-negative infections with limited treatment options: a systematic literature review. Infect Dis Ther 2021;10(4):1989-2034.
10. Hayden DA, White BP, Bennett KK. Review of ceftazidime-avibactam, meropenem-vaborbactam, and imipenem/cilastatin-relebactam to target *Klebsiella pneumoniae* carbapenemase-producing Enterobacterales. J Pharm Technol 2020;36(5):202-10.
11. European Committee on Antimicrobial Susceptibility Testing. Breakpoint Tables for Interpretation of MICs and Zone Diameters, ver. 13.0. Vaxjo, Sweden: EUCAST; 2023. https://www.eucast.org/fileadmin/src/media/PDFs/EUCAST _files/Breakpoint_tables/v_13.0_Breakpoint_Tables.pdf (1.10.2023).
12. Brauncajs M, Bielec F, Macieja A, Pastuszak-Lewandoska D. Carbapenem-resistant Gram-negative fermenting and non-fermenting rods isolated from hospital patients in Poland – what are they susceptible to? Biomedicines 2022;10(12):3049.
13. Gaibani P, Re MC, Campoli C, Viale PL, Ambretti S. Bloodstream infection caused by KPC-producing *Klebsiella pneumoniae* resistant to ceftazidime/avibactam: epidemiology and genomic characterization. Clin Microbiol Infect 2020;26(4):516.e1-4.
14. Swaminathan S, Routray A, Mane A. Early and appropriate use of ceftazidime-avibactam in the management of multidrug-resistant Gram-negative bacterial infections in the Indian scenario. Cureus 2022;14(8):e28283.
15. Zalas-Więcek P, Prażyńska M, Pojnar Ł, Pałka A, Żabicka D, Orczykowska-Kotyna M, et al. Ceftazidime/avibactam and other commonly used antibiotics activity against Enterobacterales and *Pseudomonas aeruginosa* isolated in Poland in 2015–2019. Infect Drug Resist 2022;15:1289-304.
16. Bonnin RA, Bernabeu S, Emeraud C, Naas T, Girlich D, Jousset AB, et al. *In vitro* activity of imipenem-relebactam, meropenem-vaborbactam, ceftazidime-avibactam and comparators on carbapenem-resistant non-carbapenemase-producing Enterobacterales. Antibiotics (Basel) 2023;12(1):102.
17. Wang Y, Wang J, Wang R, Cai Y. Resistance to ceftazidime-avibactam and underlying mechanisms. J Glob Antimicrob Resist 2020;22:18-27.
18. Gaibani P, Lombardo D, Bussini L, Bovo F, Munari B, Giannella M, et al. Epidemiology of meropenem/vaborbactam resistance in KPC-producing *Klebsiella pneumoniae* causing bloodstream infections in northern Italy, 2018. Antibiotics (Basel) 2021;10(5):536.
19. Hackel MA, Lomovskaya O, Dudley MN, Karlowsky JA, Sahm DF. *In vitro* activity of meropenem-vaborbactam against clinical isolates of KPC-positive *Enterobacteriaceae*. Antimicrob Agents Chemother 2017;62(1):e01904-17.
20. Nordmann P, Bouvier M, Poirel L. Efficacy of ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-relebactam combinations against carbapenemase-producing Enterobacterales in Switzerland. Eur J Clin Microbiol Infect Dis 2023;42(9):1145-52.
21. Sader HS, Mendes RE, Duncan L, Kimbrough JH, Carvalhaes CG, Castanheira M. Ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-relebactam activities against multidrug-resistant Enterobacterales from United States Medical Centers (2018–2022). Diagn Microbiol Infect Dis. 2023;106(2):115945.
22. Castanheira M, Huband MD, Mendes RE, Flamm RK. Meropenem-vaborbactam tested against contemporary gram-negative isolates collected worldwide during 2014, including carbapenem-resistant, KPC-producing, multidrug-resistant, and extensively drug-resistant *Enterobacteriaceae*. Antimicrob Agents Chemother 2017;61(9):e00567-17.