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REVIEW

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Meropenem/vaborbactam: a next generation β-lactam β-lactamase inhibitor combination

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ABSTRACT

Introduction: infections due to carbapenem-resistant *Enterobacterales* (CRE) constitute a worldwide threat and are associated with significant mortality, especially in fragile patients, and costs. Meropenem-vaborbactam (M/V) is a combination of a group 2 carbapenem with a novel cyclic boronic acid-based β-lactamase inhibitor which has shown good efficacy against KPC carbapenemase-producing *Klebsiella pneumoniae*, which are amongst the most prevalent types of CRE.

Areas covered: This article reviews the microbiological and pharmacological profile and current clinical experience and safety of M/V in the treatment of infections caused by CRE.

Expert opinion: M/V is a promising drug for the treatment of infections due to KPC-producing CRE (KPC-CRE). It exhibited an almost complete coverage of KPC-CRE isolates from large surveillance studies and a low propensity for resistance selection, retaining activity also against strains producing KPC mutants resistant to ceftazidime-avibactam. Both meropenem and vaborbactam have a favorable pharmacokinetic profile, with similar kinetic properties, a good intrapulmonary penetration, and are efficiently cleared during continuous venovenous hemofiltration (CVVH). According to available data, M/V monotherapy is associated with higher clinical cure rates and lower rates of adverse events, especially in terms of nephrotoxicity, if compared to 'older' combination therapies.

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1. Introduction

Infections with carbapenem-resistant *Enterobacterales* (CRE) is an urgent health threat since they have spread worldwide. The carbapenem resistance is usually caused by the production of carbapenemases (KPC enzymes, MBLs, and OXA enzymes). Less often, it stems from deficient outer-membrane protein expression.

Even if data on CRE epidemiology are not available everywhere, alarming rates emerge from reports from several countries [1,2]. According to the last European Centre for Disease Prevention and Control (ECDC) report for the year 2018, data concerning carbapenem-resistance in *Klebsiella pneumoniae* isolates in Europe showed a population-weighted mean of 7.2%, with resistance rates that reached 27% to 64% in Italy and Greece, respectively [1]. In the United States of America (USA), 7.9% of *K. pneumoniae* and 0.6% of *Escherichia coli* invasive isolates submitted to the National Healthcare Safety Network were resistant to carbapenems in 2014 [2]. CRE infections are still associated with a high risk of clinical failure and a mortality averaging 20–40% [3–6]. Furthermore, until the advent of new drugs the use of high dose combination therapies has led to an excess of toxicity, especially nephrotoxicity (up to 50% in some reports) associated with the use of polymyxins [7].

The development of new combinations based on an old β-lactam molecule with a novel β-lactamase inhibitor active on carbapenemases is actually one of the most promising strategies for the treatment of CRE infections. Recently meropenem-vaborbactam (M/V) joined ceftazidime-avibactam (C/A) in the group of novel β-lactamase inhibitor combinations (BLICs) available for the treatment of CRE infections.

M/V is a combination of meropenem and a novel β-lactamase inhibitor with a broad spectrum of enzyme inhibition covering also several CRE strains. *In vitro* data are available for many Gram-negative species [8,9]. Clinical efficacy and safety have been evaluated in two randomized clinical trials, TANGO I and TANGO II, showing promising results vs. other comparators also in non-urinary source infections [10,11]. M/V has been approved by FDA in August 2017 as the first carbapenem β-lactamase inhibitor combination with activity against CRE and is indicated for complicated urinary tract infections (cUTI) including acute pyelonephritis (AP) in adults [12,13]. More recently it has been approved by European Medicines Agency (EMA) for cUTI and AP, complicated intra-abdominal infections (cIAI), hospital-acquired pneumonia (HAP), ventilator-acquired pneumonia (VAP) and infections due to aerobic Gram-negative organisms in adults with limited treatment options.

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Article highlights

- Meropenem–vaborbactam (M/V) is a fixed-dose combination product of a carbapenem and a cyclic boronic acid β-lactamase inhibitor.
- The addition of vaborbactam to meropenem restores the activity of meropenem against *Enterobacterales* producing Ambler class A carbapenemases (e. g. KPC).
- Vaborbactam does not inhibit Amber class B or D carbapenemases, nor does it improve the activity of meropenem against multidrug-resistant nonfermenting Gram-negative bacilli, notably *Acinetobacter* spp. and *Pseudomonas aeruginosa*.
- The potential for resistance selection appears to be overall lower than that observed with C/A and colistin.
- M/V has favorable pharmacokinetic and pharmacodynamics profiles compared with other older antibiotics with activity against CRE.
- M/V has a favorable toxicity profile and appeared to be safe and well-tolerated in clinical trials.
- The efficacy of M/V for the treatment of complicated urinary tract infections and acute pyelonephritis was demonstrated in a Phase 3 trial (TANGO I).
- Another Phase 3 study (TANGO II) supported the efficacy of M/V for the treatment of infections caused by CRE.
- More evidences derived from clinical studies are needed to confirm M/V as a major backbone agent for the treatment of KPC-CRE infections.

The purpose of this review is to explore in detail the microbiological and pharmacological aspects of M/V and to highlight the most updated evidence on efficacy and safety that emerged from clinical trials and from the first real-life experiences.

2. Methods

This article is a narrative review of the available information on the microbiological and pharmacological profiles, and of the clinical efficacy of M/V. Relevant publications were searched through the MEDLINE/PubMed database, using specific keywords for each topic. Subsequently, drafts were produced by different authors, each addressing one of the covered topics, and the drafts were assembled in a final manuscript, reviewed and edited by all authors.

3. Chemistry of M/V

M/V is a new fixed-dose (1:1) antimicrobial combination available for the treatment of infections due to MDR Gram-negative pathogens.

Meropenem ((4 R,5 S,6 S)-3-{[(3 S,5 S)-5-(dimethylcarbamoyl) pyrrolidin-3-yl]sulfanyl}-6-[(1 R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid) is a broad-spectrum group 2 carbapenem antibiotic, a synthetic derivative of thienamycin, active against Gram-positive and Gram-negative bacteria first approved in USA in 1996 [14,15].

The presence of a methyl group at the C_1 position confers the resistance to degradation by DHP-I. Therefore, meropenem does not require to be administered with cilastatin to be active in urine [16] (Figure 1).

Vaborbactam (formerly RPX7009) ({(3 *R*,6 *S*)-2-Hydroxy-3-[2-(thiophen-2-yl)acetamido]-1,2-oxaborinan-6-yl}acetic acid) has been discovered with research programs specifically targeted on KPC β-lactamases. The addition of a 2-thienyl acetyl group instead of an N-acetyl group in vaborbactam structure led to increased inhibitory potency against KPC, when compared to other promising synthetized boronic molecules [17]. This compound is the first cyclic boronic acid derivative which has been approved by the FDA in 2017 in combination with meropenem [17]. It is a non-suicidal inhibitor and lacks antibacterial activity [18].

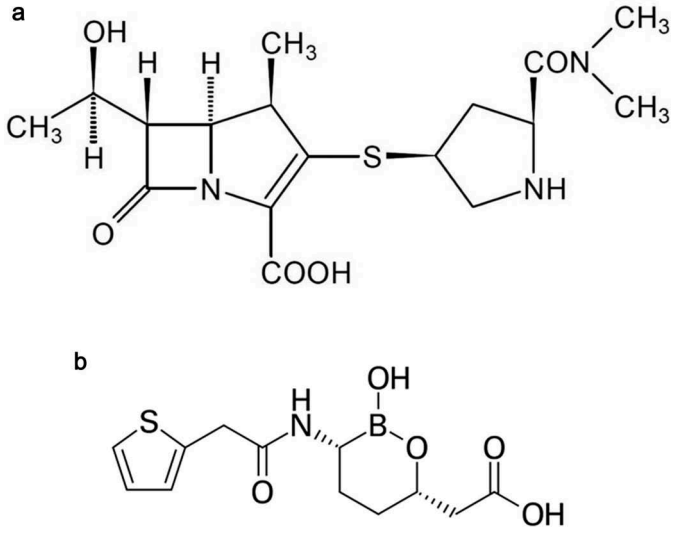

Figure 1. a)Meropenem ($C_{17}H_{25}N_3O_5S$ mol weight 383.463 b) Vaborbactam ($C_{12}H_{16}BNO_5S$ mol weight 297.13).

Vaborbactam is highly specific as a β-lactamase inhibitor and, hosting a boron heterocyclic structure, unlike other boronic derivatives such as the dipeptide derivative bortezomib (a proteasome inhibitor), has either no effect on various human proteases or affinity against all tested human serine hydrolases [17–19].

4. Microbiological profile of M/V

4.1. Spectrum of activity

Meropenem-vaborbactam (M/V) is a combination of a group 2 carbapenem with a novel cyclic boronic acid-based β-lactamase inhibitor. Given its β-lactamase inhibition profile (see below, pharmacodynamic properties), vaborbactam extends the spectrum of activity of meropenem to strains of *Enterobacterales* producing KPC-type and other class A serine carbapenemases. These strains are typically resistant to meropenem and other carbapenems, as well as to other older β-lactams, and are often also resistant to several non-β-lactam drugs due to the accretion of chromosomal mutations and mobile genetic elements carrying resistance determinants [20,21]. In fact, the rates of susceptibility to M/V against *Enterobacterales* producing KPC-type carbapenemases were shown to be >99% by several large surveillance studies (Table 1). M/V was also shown to be active against strains of *Enterobacterales* producing other types of class A serine carbapenemases such as SME and NMC-A enzymes [18]. Interestingly, M/V retains activity also against strains producing KPC mutants that confer resistance to ceftazidime-avibactam (C/A) (e. g. KPC-8, KPC-31) [22]. Moreover,

Table 1. Activity of Meropenem/Vaborbactam *vs.* various difficult-to-treat Gram-negative pathogens.

Pathogens and relevant resistance mechanisms (no. isolates)	Sources (years)	% susceptibility (CLSI)	% susceptibility (EUCAST)	References
Enterobacterales KPC+ (294)[a]	Global (2000–2013)	94.6	97.3	[69]
Enterobacterales KPC+ (135)[b]	Global (2014)	99.3	100	[25]
Enterobacterales KPC+ (991)[c]	Global (2014–2015)	99	99.6	[49]
Enterobacterales KPC+ (206)	Global (2015)	99.5	99.5	[33]
Enterobacterales KPC+ (124)	USA (2016–2018)	99.2	100	[23]
Enterobacterales KPC+ (128)[d]	China (2004–2014)	81.3	97.7	[24]
Achromobacter spp. (100)[e]	USA-Canada (2013–2018)	86	≥90	[30]
Burkholderia cepacia complex (150)[f]	USA-Canada (2013–2018)	97	≥97	[30]
Burkholderia gladioli [48]	USA-Canada (2013–2018)	100	100	[30]

[a]Including *Klebsiella pneumoniae, Klebsiella oxytoca, Escherichia coli, Enterobacter cloacae, Citrobacter freundii.*
[b]Including *K. pneumoniae, K. oxytoca, E. coli, E. cloacae, C. freundii, Serratia marcescens.*
[c]Including *K. pneumoniae, K. oxytoca, E. coli, Enterobacter* spp., *Citrobacter* spp., *Serratia marcescens.*
[d]Including 94 *K. pneumoniae* and 22 *E. coli.*
[e]Including *A. dolens, A. ruhlandii*, and *A. xylosoxydans.*
[f]Including *B. cenocepacia, B. cenocepacia, B. contaminans, B. multivorans, B. vietnamiensis.*

vaborbactam is also able to reduce meropenem MICs of enterobacterial strains that exhibit reduced meropenem susceptibility due to the production of ESBL or AmpC-type β-lactamases in the presence of permeability defects [18].

As previously mentioned, vaborbactam does not efficiently inhibit class D or class B carbapenemases, and CPE strains producing these enzymes are usually resistant to M/V [25]. The occasional susceptibilities observed to this drug reflect the residual activity that meropenem may retain against some of these strains and is not influenced by vaborbactam [26].

With *Pseudomonas aeruginosa* and *Acinetobacter spp*. the activity of M/V was found to be overall similar to that of meropenem alone [27,28]. This is apparently due to the fact that, in *P. aeruginosa* and *Acinetobacter spp*., meropenem resistance is largely mediated by mechanisms that are not antagonized by vaborbactam (e. g. outer-membrane impermeability, upregulation of efflux systems, and production of class B or class D β-lactamases). However, a recent work demonstrated that, with some *P. aeruginosa* strains, the addition of vaborbactam produced an increased bacterial killing in a thigh infection model even in the absence of modified MIC values, suggesting that some of these strains may contain an inducible β-lactamase that is inhibited by vaborbactam [19,29].

The activity of M/V against less common but difficult-to-treat Gram-negative pathogens is variable. With *Stenotrophomonas maltophilia* and *Pandoraea spp*., activity was found to be overall poor and comparable to that of meropenem alone [30], while with *Achromobacter spp.* and *Burkholderia spp*., the activity was found to be high (Table 1). However, some gain vs. the activity of meropenem alone was only observed with *Achromobacter spp.* and members of *Burkholderia cepacia* complex, while with *Burkholderia gladioli,* the activity of M/V was comparable to that of meropenem alone [30].

Against anaerobes, vaborbactam was not found to significantly potentiate the activity of biapenem [31] and, consequently, it is not expected to potentiate the activity of meropenem as well.

Interestingly, vaborbactam inhibits the broad-spectrum β-lactamase produced by *Mycobacterium abscessus* and was found to significantly reduce meropenem MICs vs. clinical isolates of this species, suggesting that M/V could become a β-lactam of choice for these difficult-to-treat infections [9].

4.2. Resistance mechanisms

In vitro experiments revealed that both meropenem and vaborbactam normally enter in *K. pneumoniae* through two major outer membrane porins, OmpK35 and OmpK36, the latter being the major entry channel for the inhibitor [18]. In fact, the inactivation of both porins or of OmpK36 had a higher effect in reducing the potency of M/V than inactivation of OmpK35 [18]. The major multidrug efflux pump AcrAB-TolC was also implicated in reduced carbapenem susceptibility of *Enterobacterales*. However, the upregulation of this pump only exhibited a minimal effect on M/V potency, even in the absence of major porins [18]. The highest reduction of M/V potency was observed in KPC-producing strains lacking both porins and overexpressing AcrAB. Nevertheless, with vaborbactam concentrations of 8 mg/L, meropenem MICs usually remained <8 mg/L (i. e. the susceptibility breakpoint for EUCAST) even with the most resistant strains containing multiple mutations [18,32]. Reduced susceptibility to M/V was also found to be associated with overexpression of KPC due to increased *bla*KPC gene copy number [32], while no mutations of the KPC enzyme resistant to vaborbactam have so far been reported.

Currently, there are few surveillance studies reporting M/V resistant isolates. In one recent surveillance study, there was only one *K. pneumoniae* isolate from Greece displaying an MIC of 32/8 mg/L out of 11,559 isolates. Sequencing revealed that there was a frameshift mutation in OmpK35 gene and an insertion into the OmpK36 gene [33].

No resistant isolates were identified in the patient population recruited in the TANGO II Clinical study [11]. The microbiological analysis revealed only one isolate with a fourfold MIC increase (from 0.25 to 1 mg/L) though still in the susceptibility range [11]. In a recent report on early clinical experience with M/V for treatment of CRE infections, one patient infected by an ST258 strain of KPC-Kp producing KPC-31 and treated with the drug exhibited a microbiological failure associated with the selection of a mutant with an M/V MIC of 8 mg/L [34]. The mutant

carried an insertion in the promoter of the OmpK36 gene, confirming the role of alterations in this porin in reducing susceptibility to the drug.

4.3. Susceptibility testing

M/V susceptibility can be tested by broth microdilution, with vaborbactam at a fixed concentration of 8 mg/L using the Clinical & Laboratory Standards Institute (CLSI)/International Organization for Standardization (ISO) methodology [35]. Clinical breakpoints are provided by EUCAST (recognized by EMA) and by CLSI (recognized by FDA). EUCAST has set the susceptibility and resistance breakpoints (given as 2 gM/2 gV every 8 h in 3 h infusion) at an MIC value ≤8 mg/L and >8 mg/L, respectively, for both *Enterobacterales* and *P. aeruginosa* [36]. CLSI has set the susceptibility and resistance breakpoints at an MIC value ≤4 mg/L and >8 mg/L, respectively, only for *Enterobacterales* [37].

M/V is currently available for testing in some semi-automated commercial systems (Microscan, Beckman Coulter; Sensititre, Thermo Fisher), and is under development in other such systems. Gradient diffusion tests for M/V are available (Etest, bioMérieux; MIC Test Strips, Liofilchem). Etest for M/V has recently been evaluated in a large multicenter trial: results showed an overall acceptable performance for susceptibility testing of *Enterobacterales* (except *Proteus mirabilis*) when using the CLSI breakpoints, while an unacceptable rate of very major errors (false susceptibilities) was observed with *Enterobacterales* when using the EUCAST breakpoints [38], reflecting the lack of an 'I' category with the latter breakpoints. Disk diffusion may also be used for susceptibility testing of M/V according to CLSI standard [37], while EUCAST has not yet released clinical breakpoints for disk diffusion testing of the drug [36].

5. Pharmacological properties of M/V

5.1. Pharmacodynamic aspects

The stability of the carbapenems to degradation by many β-lactamases (AmpC enzymes and ESBLs of the TEM, SHV, and CTX-M families) is mainly due to the *trans* orientation of the hydrogens at carbons 5 and 6 [15]. Meropenem has also a dimethyl-pyrrolidine side chain in position C_2 which, in combination with the *trans* orientation of the 6-hydroxyethyl moiety, enhances the activity against Gram-negative rods; thus, it shows MIC values for ESBL-positive *K. pneumoniae* strains generally 8- to 16-fold lower than imipenem [15,39–41].

Meropenem inhibits at least three penicillin-binding proteins (PBPs) in the bacterial cell wall. It preferentially binds PBPs 1, 2, and 4 of *Staphylococcus aureus* [39]. In *Enterobacterales* and *P. aeruginosa*, meropenem, similarly to imipenem has the highest affinity for PBP2, but it is also capable to bind effectively other PBPs (PBP1a and 1b, PBP3 and even PBP4), thus exerting a fast bactericidal activity [15,42]. Moreover, in *P. aeruginosa* meropenem has a higher affinity for PBP2 than imipenem [2,15]. Due to their capability of inhibiting more than two main PBPs, carbapenems generally show a minimal inoculum effect, no biomass increase, and a negligible endotoxin release [15,32,42,43].

Therefore, meropenem, having a fast bactericidal activity notwithstanding the inoculum size, and being stable to ESBL and AmpC enzymes may be preferable to cephalosporins for combination with non-β-lactam carbapenemase inhibitors [44].

Meropenem possesses a relatively consistent PAE (higher than the one observed with imipenem), both *in vitro* and *in vivo*, even on Gram-negative rods, including *P. aeruginosa*, which may represent the time required for the *de novo* synthesis of PBPs and to synthesize a new cell wall [45].

Vaborbactam was shown to inhibit various class A carbapenemases (e. g. KPC-2, KPC-3, KPC-4, BKC-1, FRI-1, and SME-2), class A ESBLs (e. g. CTX-M, SHV, and TEM), and class C cephalosporinases (e. g. CMY, P99). The inhibitor has a weaker activity (around fivefold less potent than versus class A and C enzymes) against some class D carbapenemases (OXA-48-like) while is practically inactive (10 to 100 fold lower potency) against metallo-β-lactamases (e. g. NDM, VIM, and IMP) [15,18,46].

The boron atom present in vaborbactam is highly electrophile and capable to reversibly form covalent bonds with the active catalytic site of serine, leading to a rapid enzyme inactivation [17,39,47,48]. The rate of dissociation of the enzyme–inhibitor complex can vary, according to the enzyme, from a few minutes (i.e. AmpC) to many hours (i.e. KPC-2) [17,39]. However, as a remarkable feature, the boronic inhibitor is not hydrolyzed during the course of the reaction and the bond is slowly reversible, even with an enzyme residence time of more than 16 hours [17,39,47,48]. This mechanism might explain, at least in part, why vaborbactam is a more potent inhibitor of KPC enzymes than of SHV or TEM enzymes, suggesting that the lower potency is related to a lower propensity to form stable inhibitory complexes [39]. The lower inhibitory activity is however not relevant when vaborbactam is given in combination with meropenem which is stable to these enzymes [49].

Conversely, diazobicyclooctanes, and, namely, avibactam, form as well-covalent bonds with the opening ring, which, however, is recycled rather than hydrolyzed and thus, in many cases, regenerated [50]. Yet, this is not true with KPC which slowly desulfated avibactam with the formation of inactive products [47,50]. Therefore, against KPC avibactam generally needs to maintain higher concentrations (at least 8 mg/L) during the time after the dose to be effective [47,50–52].

It may be observed that such a high concentration could not be maintained for a long time, at least in the epithelial lining fluid (ELF), where the average peak level of avibactam is almost 5 to 6 mg/L after a 500 mg dose [53]. This is not the case of vaborbactam, which is capable to inhibit KPC2 and KPC3 without significant differences [17,18,47,48].

5.2. Pharmacokinetic properties

Meropenem has a pharmacokinetic profile very similar to that of imipenem when given with cilastatin [54]. Notably, β-lactams are time-dependent antibiotics and, due to their short half-lives, they benefit from prolonged or continuous infusion dosing strategies to maintain concentrations higher than the MIC (T> MIC) for a long period of time after administration [55]. Therefore, there are preclinical and clinical

evidences that meropenem administered by prolonged 3-h infusion as a 2 g dose every 8 h (q8 h) is associated with improved bacterial killing and clinical response [56].

When administered q8 h as a 3-h infusion, this carbapenem displays an elimination half-life (t½) of approximately 1 h, a peak plasma concentration (C_{max}) and an area under the plasma concentration–time curve (AUC) with a dose-related linear increase, and a volume of distribution at steady state (Vd_{ss}) around 21–22 L, related to a main extracellular distribution [57]. The plasma protein binding is very low (~2%) and up to 80% of the antibiotics (45% to 60% as unchanged drug) are recovered in urine at 24–48 h. Meropenem has a good penetration in tissues and body fluids, including CSF [54]. There is a significant linear relationship between total body clearance and creatinine clearance, with a reduction in the renal excretion rate related to age or renal impairment [54,57,58].

Vaborbactam pharmacokinetics has been evaluated in a Phase 1 study in healthy volunteers receiving both single and multiple IV doses ranging from 250 to 2000 mg, administered in a 3 h infusion. The average protein binding is 33% and C_{max} and AUC values increase in a dose-proportional manner, with an average t½ and Vd_{ss} of 1.5 h and 21.5 L, respectively [19]. The inhibitor is predominantly recovered in urine (75% to 90% as unchanged drug) with no evident accumulation after multiple doses (19).

The PK properties of both vaborbactam and meropenem either administered alone or combined, following single and multiple ascending doses, were recently evaluated by Rubino and coworkers in healthy adult subjects in a randomized, placebo-controlled, double-blind study [59].

The Authors concluded that meropenem and vaborbactam, when given up to 2 g doses q8 h, have similar pharmacokinetic properties, with no plasma or urine PK drug–drug interactions, and are well tolerated. Both drugs have a renal clearance exceeding the normal range for glomerular filtration rate (GFR), related to active tubular secretion [59].

The combination has been studied also in subjects with chronic renal impairment receiving a single IV dose of 1 g of meropenem plus 1 g of vaborbactam by 3-h infusion in a Phase 1, open-label, study (Table 2) [60].

The plasma clearance of meropenem and vaborbactam decreased in a similar manner with decreasing renal function, indicating for both the need of a proportional dose reduction in subjects with renal impairment. This decrease was more pronounced with vaborbactam, since for meropenem there exists at least a 20–30% non-renal elimination mainly due to metabolism of the parent compound by dipeptidases, by nonspecific degradation or, in a less extent (2% of dose), by fecal elimination [54,57–60].

Both meropenem and vaborbactam are removed by hemodialysis with a recovery in the dialyzate of 38.3% and 52.9% of a dose, respectively [60].

The population pharmacokinetic results obtained during Phase 3 studies are almost similar to those observed in healthy volunteers [61,62]. However, in general, mean C_{max} and AUC values were higher and mean half-life values longer than those observed in healthy volunteers in relationship to age and renal function of the patients (Table 3) [61,62].

The effects of CRRT on the pharmacokinetics of M/V have been evaluated by Sime and coworkers using an ex-vivo model [63].

The percent loss of meropenem due to circuit sequestration has been estimated to be less than 10%, being clinically irrelevant, while for vaborbactam there was no appreciable adsorption to the continuous venovenous hemofiltration (CVVH) circuit/filter. In both cases there was no relationship with the plasma level, meaning that even at low concentrations there is no excessive loss during CVVH.

Both drugs are efficiently cleared during CVVH, even though vaborbactam filter clearance is lower than meropenem, probably related to the higher protein binding. Therefore, in these patients, vaborbactam ensures a suitable β-lactamase inhibition for the entire course of the dosing interval, even for infection

Table 3. Meropenem/vaborbactam – PK properties in healthy adults and in patient population (mean values) [61,62].

Population		C_{max} (mg/L)	AUC (mg·h/L)	t½(h)	CL (l/h)	Reference
Healthy adults [8]	**MEM**	43.4	414	1.22	15.1	Wei X et al. 2017
	VAB	55.6	588	1.68	10.9	
Patients* (295)	**MEM**	57.3	650	2.30	10.5	Dhillon S et al. 2018
	VAB	71.3	835	2.25	7.95	

* 3 -h infusion.

C_{max} = peak observed concentration; AUC = area under the concentration–time curve;

t½ = elimination half-life; CL = plasma clearance; MEM = meropenem; VAB = vaborbactam.

Table 2. Pharmacokinetic parameters of meropenem and vaborbactam (2 g + 2 g in 3 h infusion) in subjects with different renal function [60].

Drug and renal study group	C_{max} (mg/L)	t½(h)	$AUC_{0-\infty}$ (mg·h/L)	V_{ss} (L)	CL_T (L/h)	CL_R (L/h)
MEROPENEM						
Normal (n = 8)	27.5 ± 7.03	1.3 ± 0.254	87.1 ± 26.7	19.2 ± 2.69	12.5 ± 3.83	7.69 ± 2.33
Mild (n = 8)	32.7 ± 9.1	1.43 ± 0.18	112 ± 40.6	16.5 ± 3.22	9.66 ± 2.42	5.55 ± 2.06
Moderate (n = 8)	40.5 ± 6.27	2.2 ± 0.867	181 ± 59.4	16.6 ± 2.21	6.05 ± 1.83	3.34 ± 1.19
Severe (n = 8)	45.5 ± 13.0	6.1 ± 2.59	397 ± 98.0	21.6 ± 6.69	2.65 ± 0.606	0.964 ± 0.37
VABORBACTAM						
Normal (n = 8)	27.8 ± 6.34	1.65 ± 0.35	99.4 ± 33.0	20.5 ± 3.53	11.1 ± 3.6	10.5 ± 2.77
Mild (n = 8)	30.1 ± 8.31	1.88 ± 0.274	116 ± 35.9	20.8 ± 3.73	9.17 ± 1.98	7.51 ± 1.99
Moderate (n = 8)	42.4 ± 7.45	3.45 ± 1.714	238 ± 108	18.8 ± 3.02	4.89 ± 1.78	4.25 ± 1.66
Severe (n = 8)	46.4 ± 12.3	13.5 ± 8.71	781 ± 279	23.3 ± 7.24	14.2 ± 0.465	1.13 ± 0.505

Values are means ± standard deviations.

C_{max} = peak observed concentration; t½ = elimination half-life; AUC = area under the concentration–time curve; V_{ss} = volume of distribution at steady state; CL_T = total plasma clearance; CL_R = renal clearance.

caused by KPC-producing organisms [63]. This observation has been clinically confirmed in a 60-year-old, male patient in septic shock and requiring CVVHD treated for a susceptible CR *K. pneumoniae* with 1 g M/1 g V 3 h infusion q8 h [64]. Meropenem pre-filter concentrations were at least four times greater than 4 mg/L for nearly the entire dosing interval, while vaborbactam levels were at least three times greater than 8 mg/L [64].

The good extravascular penetration of meropenem in tissues and body fluids is well known after several decades of clinical use [54]. Although meropenem demonstrates adequate penetration into the cerebrospinal fluid, no data are currently available regarding vaborbactam [54].

For M/V, at present, there are only the results of the Phase 1, randomized, open-label, multiple-dose study on the penetration of the two molecules in the epithelial lining fluid (ELF) of healthy adult subjects [65]. Meropenem and vaborbactam achieved and maintained over time similar concentrations in plasma and ELF with an intrapulmonary penetration, based on AUC values of ELF and total plasma levels of 63–53%, respectively. After the third dose, the penetration ratios ranged from 59% to 51% (end of infusion) to 185% and 95% (8 h after dose) for meropenem and vaborbactam, respectively (Figure 2) (Table 4). Moreover, when unbound plasma concentrations were considered, the average penetration rate was 65% for meropenem and raised to 79% for vaborbactam [65]. Indeed, this penetration rate is in general particularly high for β-lactams and β-lactamase inhibitors, including the non-β-lactam compounds. For β-lactam combinations administered every 8 h, when considering the total plasma levels, we may observe average mean AUC_{ELF}/AUC_{plasma} ratios ranging from 31% (ceftazidime) to 60% (meropenem) and from 35% (avibactam) to 52% (vaborbactam) [53,65,66].

Meropenem has been widely used in pediatric infections, however, since at present M/V has been registered only in adults, there are no published dosing recommendations for the use of M/V in this setting and the results of the TANGOKIDS, a dose-finding pharmacokinetic study in children

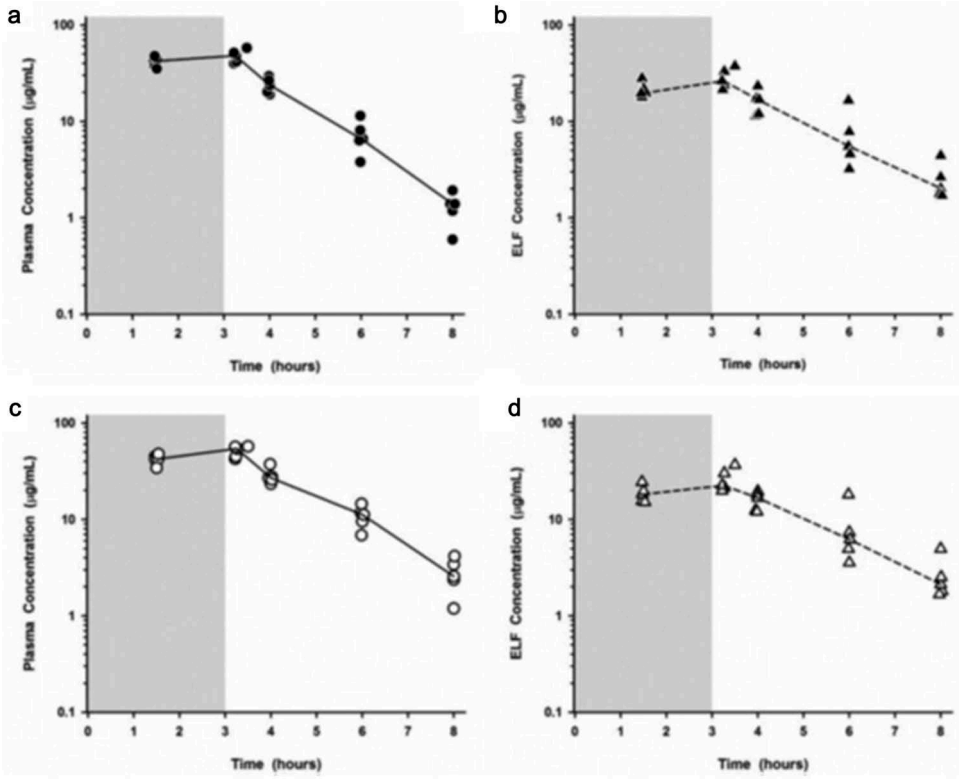

Figure 2. Meropenem 2 g + Vaborbactam 2 g in 3 h infusion* – Individual concentrations of meropenem in plasma (a; ●) and epithelial lining fluid (ELF) (b; ▲) and vaborbactam in plasma (c; ○) and ELF (d; △) Panels a,b,c,d are reproduced with permission from Antimicrob Agents and Chemother.Copyright © American Society for Microbiology [66].

Table 4. Meropenem/vaborbactam (2 g + 2 g in 3-h infusion) – Plasma and ELF concentrations in 25 healthy subjects (mean age 39.0 ± 10.6 yrs) [65].

	Mean conc. (mg/L) ±SD of meropenem in:			Mean conc. (mg/L) ±SD of vaborbactam in:		
BAL sampling time (h)	Total plasma	ELF	T/P (%)	Total plasma	ELF	T/P (%)
1.5	41.2 ± 5.02	21.4 ± 3.96	51.9	41.2 ± 5.00	18.6 ± 3.76	45.1
3.25	47.7 ± 7.28	28.3 ± 6.69	59.3	51.1 ± 6.78	26.1 ± 7.12	51.1
4	23.8 ± 4.30	16.1 ± 4.77	67.6	28.2 ± 5.32	15.7 ± 3.36	55.7
6	7.24 ± 2.79	7.51 ± 5.29	104	10.8 ± 2.82	8.04 ± 5.81	74.4
8	1.36 ± 0.51	2.51 ± 1.13	185	2.74 ± 1.12	2.61 ± 1.35	95.3

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with serious bacterial infections, are not yet available. At present, there is only a reference related to a case report on a 4-year-old male child with a central line for chronic total parenteral nutrition and hydration management and a KPC-producing *K. pneumonia*e bloodstream infection (BSI), successfully treated with M/V at a dosage of 40 mg/kg every 6 hours infused over 3 hours. Meropenem peak serum concentrations obtained on day 5 were 51.3 mg/L and the Authors adapted the optimized meropenem treatment schedule obtained in a previous PK-PD study in critically ill children in order to achieve a probability of target attainment (PTA) of 40% *f*T > MIC [67,68].

In summary, the main kinetic properties of vaborbactam highly match those of meropenem, thus satisfying one of the major requirements (i.e. kinetic equivalence), along with the mechanism of action, for antimicrobial fixed dose combinations [55]. It is noteworthy that the half-life of vaborbactam is slightly longer than that of meropenem, thus assuring the maintenance of effective concentrations for protecting the carbapenem throughout the administration interval. This feature is generally uncommon with the β-lactams and β-lactamase inhibitor combinations since the inhibitor usually has an almost shorter half-life than the combined active β-lactam [53,55,59,66].

5.3. Pharmacokinetic-pharmacodynamic (PK-PD) evaluation

Carbapenems, similarly to all β-lactams, show time-dependent activity, and the free drug concentrations should be maintained above the MIC for the specific pathogen at the infection site for a relatively prolonged time (a T> MIC of >20% of the dosing interval for stasis and >40% for killing) [55]. For vaborbactam, concentrations >4 mg/L consistently restore the activity of meropenem and, based on *in vitro* and *in vivo* results on experimental animal models, 8 mg/L may be considered as the optimal concentration for CRE treatment [69–71]. From data obtained in experimental animal models using a subset of clinical isolates with multiple resistance mechanisms, including KPC and mutation in outer membrane porins (OMP), the relationship between the exposure of the inhibitor and the microbiological response is given by the ratio between vaborbactam AUC and the combination MIC (constant vaborbactam concentration of 8 mg/L) (Figure 3) [72]. A possible explanation for this PK-PD efficacy determinant may be related to the mechanism of action of boronic acid derivative, since it exerts a rapid target binding which is slowly reversible [18,72]. The observation has been confirmed by a couple of recent PK-PD studies carried out by David Griffith and coworkers [73,74]. The first study was performed using the hollow-fiber infection model against a total of 17 *K. pneumoniae, Enterobacter cloacae* and *E. coli* strains, with a broad range of potential resistance mechanisms such as multiple β-lactamases in combination with KPC, as well as multiple OMP mutations, using a high inoculum (10^8 CFU/mL) over a 32 h time study and using concentrations up to those observed in patient PK data from Phase 1 and Phase 3 trials [73]. When the free 24-hAUC of vaborbactam was adjusted to ~500 mg/L.h (a value readily obtained in population pharmacokinetic studies, see Table 3), the combination was highly bactericidal against the tested strains even with a MIC of 16 mg/L and was capable of suppressing the development of resistance [73]. The second study was designed to evaluate the relationship between vaborbactam efficacy and AUC magnitude, against the same MDR strains of *Enterobacterales* of the first study. Using the hollow-fiber infection model the Authors concluded that a free 24-hAUC/MIC ratio of at least 18 produced a 1-Log kill while a ratio higher than 24 produced a 2-Log kill and suppressed the development of resistance (Figure 4) [74]. It is evident that the resistance amplification occurred for intermediate vaborbactam exposures, within the net-bacterial stasis zone in the exposure–response curve: higher exposures (producing >2-Log kill) avoided any resistance amplification [72,74]. The results obtained in these studies highlight the

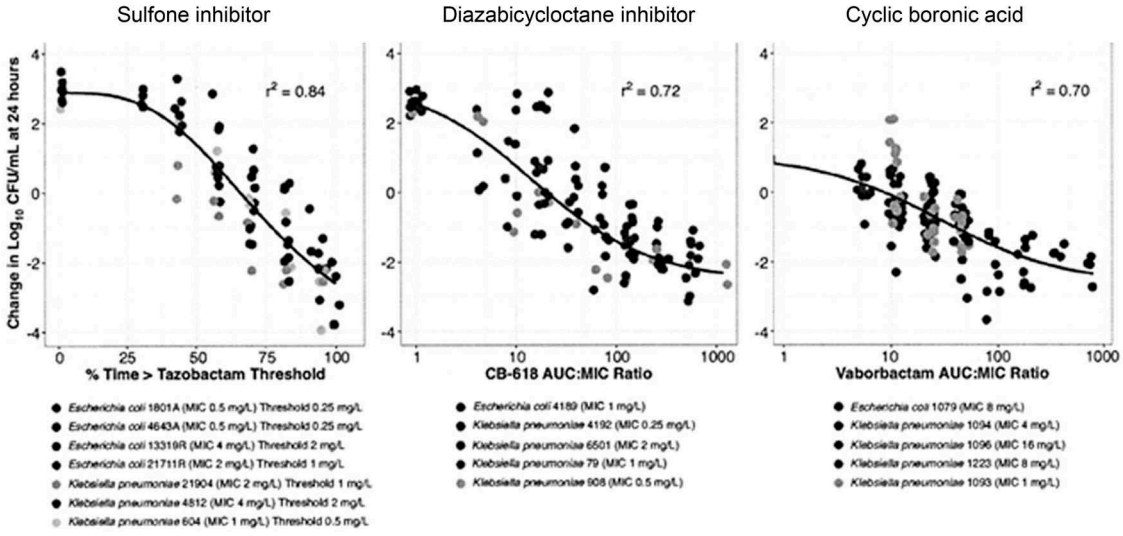

Figure 3. Relationship between exposure and response for three different β-lactamase inhibitor classes using either the neutropenic murine-thigh infection model, the lung infection model or the pyelonephritis model. Panels A,B,C, are reproduced with permission from Curr Opin Pharmacol. Copyright © Elsevier.[72].

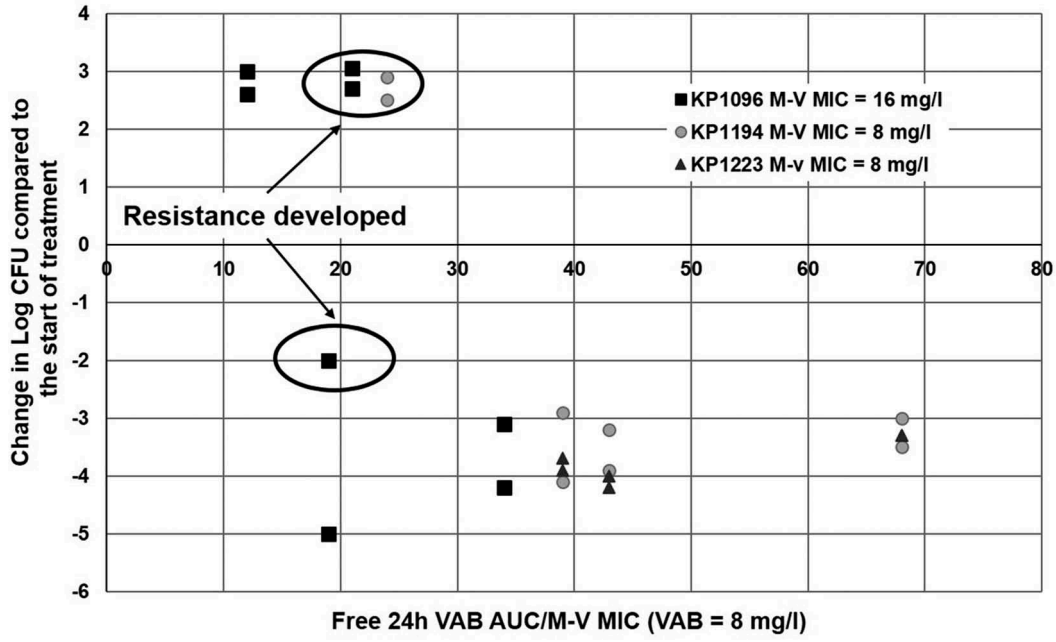

Figure 4. Meropenem/vaborbactam(2 g + 2 g in 3 h infusion) – Relationship between free 24 h AUC/MIC and resistance suppression in *Klebsiella pneumoniae* (KP) strains. Figure is reproduced with permission from Antimicrob Agents and Chemother. Copyright © American Society for Microbiology. [74]

role of the hollow-fiber infection model, since it is possible to simulate a wide range of clinically relevant concentration-time profiles, using a high inoculum (10^8CFU/mL), like in severe infections, thus overcoming some limitations associated with rodent PK/PD studies [55].

6. Clinical efficacy

6.1. Results of clinical trials

Two-Phase 3 studies have evaluated the clinical efficacy and safety of M/V. The first was an indication-focused trial to support regulatory approvals.

The Targeting Antibiotic Non-susceptible Gram-Negative Organisms (TANGO I) trial was a multicenter, double-blind, randomized, non-inferiority study comparing M/V (2 g/2g intravenously over 3 h every 8 h) to piperacillin/tazobactam (TZP, 4 g-0.5 g intravenously over 30 min every 8 h) in adult patients with cUTI (with and without removable focus) including acute pyelonephritis. Total treatment duration was 10 days (or 14 days for patients with bacteremia). If patients met clinical criteria for oral step down therapy, after a minimum of 15 doses of study drug, they switched to levofloxacin 500 mg oral tablets once daily or other antibiotics in case of fluoroquinolone-resistant isolates. Key exclusion criteria included baseline CrCl < 30 mL/min, more than one dose of antibiotics within 48 hours before randomization, concomitant use of other antibiotics or antifungals.

The primary end point for FDA was a clinical cure or overall success defined as improvement and microbiological eradication composite (or in some cases presumed eradication based on clinical response) at end of intravenous treatment time point (EOIVT) visit; for EMA primary end point was microbial eradication at test-to-cure visit (end of treatment + 7 days) in the microbiological modified intent to treat (mMITT) population (all patients who received at least one dose of study drug and had at least one baseline pathogen on urine culture) and microbiologic evaluable populations.

A total of 545 patients were randomized and received at least one dose of assigned antibiotic (272 M/V, 273 TZP), and 68% (n = 374) were included in the mMITT population. Fifty-nine percent had AP, the remaining patients had cUTI with (22%) or without (19%) a removable source. Bacteremia (BSI) occurred in 7% of the mMITT population. Overall success at the EOIVT was achieved in a high proportion of patients in both treatment groups (M/V 98.4% vs TZP 94%). The treatment difference met the established non-inferiority margin.

No failure at EOIVT in the M/V group was due to inefficacy but was secondary to adverse events (infusion-related reactions). In the TZP group, failures were mainly due to microbiological persistence or recurrence (n = 3) and to adverse events (n = 4). Overall response at the test of cure time-point (TOC; days 15–19) was considerably lower in both groups compared to the earlier assessment, but success remained numerically higher for M/V group (74.5% vs 70.3%). Lower overall success in both groups at TOC was driven by lower microbiological eradication rates (68.8% vs 62.1%). Lower microbiological eradication at later time points could likely reflect the high incidence of asymptomatic bacteriuria in patients with underlying urinary tract abnormalities. Only approximately half of patients with a nonremovable source of infection achieved microbial eradication at TOC underlying the importance of source control (M/V 51.4% vs TZP 53.5%).

M/V resistance was observed in only one case of *Enterobacterales* (*K. pneumoniae* carrying OXA-48) and in 43% of *P. aeruginosa* isolates. Among the carbapenemase-producing isolates, two out of three KPC-2 isolates had MICs of ≤0.06 mg/l, while one 2 mg/l. MIC increase was observed

during or following treatment with M/V in three patients. In all of them (n.3) the isolate was *K. pneumoniae*. They all got overall success at EOIVT but at TOC time point, two of them experienced microbiological recurrence.

The main potential limits of this trial are that 12% of *Enterobacterales* were resistant to TZP at baseline, thus suggesting that it may not have been an ideal comparator (even if despite *in vitro* resistance all patients achieved clinical cure); in addition, although not standardized for UTI, this study did not match extended infusion for both drugs (TZP was infused in 30 minutes while M/V in 3 hours). Further, the geographical distribution was not uniform: the majority of study sites were in the Eastern European region. It is of note that this trial was not focused on CRE, no *E. coli* and only one isolate of *K. pneumoniae* were resistant to meropenem in the mMITT population treated with M/V. This limits the evaluation of the contribution of vaborbactam to the effectiveness of the study drug M/V [8,10,28,75,76].

In 2017, another randomized open-label controlled trial, TANGO II evaluating efficacy/safety of M/V monotherapy was concluded. This study included patients with different CRE infections (UTI, HAP/VAP, cIAI, BSI) randomized 2:1 to receive M/V or best available therapy (BAT). BAT was confirmed by an unblinded investigator according to the standard of care and included polymixins, carbapenems, aminoglycosides, or tigecycline alone or in combination and C/A monotherapy. Patients were excluded if they were on continuous hemodialysis, if they had at the time of enrollment APACHE II score >30 or if they had a history of hypersensitivity to β-lactams, if they harbored an isolate producing oxacillinase-encoded- (OXA) β-lactamases or metallo β-lactamase: New Delhi Metallo (NDM)-, Verona integrin-encoded Metallo (VIM)-, imipenem-hydrolyzing (IMI)- β-lactamase [11].

Among the 75 patients who received the study drugs, 54 (35 M/V; 19 BAT) had a baseline Gram-negative pathogen (m-MITT population). Among these, 47 (32 M/V; 15 BAT) had a microbiologically confirmed infection with a CRE isolate (mCRE-MITT population). *K. pneumoniae* KPC was the most common pathogen (87.2% [41/47]) in the mCRE-MITT population. Other pathogens were *E. coli, E. cloacae, P. mirabilis,* and *Serratia marcescens*.

Five *K. pneumoniae* isolates showed resistance to M/V (MIC>4 μg/mL) (3 patients randomized to M/V; 2 to BAT): 4 produced metallo-β-lactamases or class D carbapenemases (NDM or OXA-48) and 1 produced KPC-3 (randomized to BAT). 1/32 isolates (3.1%) in the M/V group developed a ≥ fourfold increase in MIC during treatment vs. 1/15 (6.7%) in those in BAT group.

In the mCRE-MITT population, M/V was associated with higher rates of clinical cure than BAT at both EOT [65.6% (21/32) vs. 33.3% (5/15); difference, 32.3%, P = 0.03] and TOC [59,4% (19/32) vs. 26,7% (4/15); difference 32,7%; P = 0.02]. Microbiologic cure was reached at EOT more frequently in the M/V group compared to the BAT group [65.6% vs. 40.0%; difference, 25.6%; P = 0.09]; at TOC, this difference was 19.8% (53.1% vs. 33.3%; P = 0.19).

In the subgroup of patients with cUTI/AP, overall success rates at EOT were numerically higher among patients who received M/V than those who received BAT [75.0% (9/12) vs. 50.0% (2/4)]; overall success rates at TOC were 33.3% (4/12) for M/V and 50.0% (2/4) for BAT. Among the few patients with cIAI, the clinical cure rate at TOC was 100% (2/2) in the M/V group and 0% (0/2) in the BAT group. Among patients with HAP/VAP or bacteremia, the 28-day all-cause mortality rate was lower in the M/V group than the comparator group (22.2% (4/18) versus 44.4% (4/9), difference, −22.2%; P = 0.25)).

Among immunocompromised patients specifically M/V used in monotherapy showed substantially higher cure rates than BAT at TOC [63.6% (7/11) vs. 0.0% (0/8); P < 0.001] [11,77].

This trial was the first study with a direct comparison between M/V and BAT in patients with microbiologically confirmed CRE infections (not only UTI). Although it is the largest study at date specific for this topic, the small sample size may limit definitive conclusions. In addition, only one patient randomized to BAT group received C/A precluding a direct comparison with M/V.

6.2. Safety and tolerability data from clinical trials

In TANGO I trial among patients receiving M/V the percentages of any adverse events (AEs) experienced was 39% compared with 35% of TZP, study drug-related AEs were 15.1% with M/V vs 12.8% with TZP, severe AEs were 2.6% with M/V and 4.8% with TZP, life-threatening adverse events were 1.1% and 0%, respectively. 2.6% of patients in the M/V group discontinued treatment because of an AE compared to 5.1% with TZP. Headache was the most common AE reported with M/V in TANGO I trial (24/272, 8,8%) [10].

In TANGO II trial drug-related adverse events (TEAEs) occurred in a lower average of patients with M/V compared with BAT (24,4% vs. 44%). Those occurring in >10% of M/V included diarrhea, anemia, hypokalemia. A lower increase in serum creatinine was observed with M/V as well as fewer renal-related AEs [11]. This is not surprising because BAT regimens usually contained aminoglycosides and polymixins.

Clostridium difficile associated diarrhea has been observed with M/V in TANGO II in one patient [11].

There is a lack of data on the safety of M/V in pregnant and breastfeeding women because intravenous vaborbactam has been associated with fetal malformation in rabbits but this has not been demonstrated in humans. Interactions have been observed with probenecid competing for tubular secretion resulting in increased levels of meropenem plasma concentration and with valproic acid resulting in a decreased concentration of valproic acid and thus in an increased risk of seizures [8].

It is generally reported that meropenem may have a lower epileptogenic activity than imipenem, having a lower affinity to GABA-A receptors (may be partially due to the structurally different side-chain at the C2 position) [78,79]. At date, it has not been highlighted that vaborbactam increases the epileptogenic activity of meropenem alone.

M/V has not been studied in patients younger than 18 years old, while it has been studied in patients as old as 92 years [80].

6.3. Data from real-life studies

Evidence regarding M/V use in real-life settings in FDA-approved and non-FDA approved indications is limited indeed. Recently in an international conference promising data have been presented evaluating efficacy and safety outcomes of 40 critically ill (median APACHE score 17) patients treated with M/V for GNB infections (32 (80%) were CRE, *K. pneumoniae,* and *E. cloacae*). Clinical success was 70%. Only one experienced an M/V-related adverse event (skin rash) [81].

Shields et al. recently published an observational study of 20 critically ill patients with CRE infections (mainly *K. pneumoniae* (n. 14), followed by *Klebsiella oxytoca* (n. 2), *E. coli* (n. 2), *E. cloacae* (n. 1), and *Citrobacter freundii* (n.1)) treated with M/V. Among them, an isolate of KPC-3 with a D179Y mutation (responsible for C/A resistance and restore of carbapenem susceptibility) and two non-KPC isolates (one *E. coli* with *bla*CMY and one *K. oxytoca* isolate with *bla*ACC, *bla*CMY, and *bla*DHA) were included. M/V was administered as monotherapy in 80% of patients. Thirty-day survival was 90% while 90-day survival was 80%. Clinical success was achieved in 65% of the patients. In the subgroup of patients with bacteremia was achieved in 63%, while in the subgroup with pneumonia in 67% of the patients. APACHE-II score was higher in patients with clinical failure, compared to those with clinical success. Microbiological failures occurred in 35% of patients (6/20). Among the recurrent isolates, one was categorized as non-susceptible. This treatment-emergent M/V resistant strain differs from the baseline strain by two single nucleotide polymorphisms. Only one patient experienced a side effect due to M/V (eosinophilia) [34].

Few *in vivo* data exist at date about the comparison between C/A and M/V. During the 2019 ID Week and ECCMID Conference, two multicenter retrospective cohort studies comparing M/V and C/A have been presented in CRE infections (except for localized UTI) in terms of clinical success and tolerability. In both studies, the clinical success rate defined as survival at 30 days, clinical resolution of infection, sterilization of blood cultures within 7 days and recurrence was similar. In one study, patients in C/A experienced higher rates of adverse events, specifically nephrotoxicity but it must be noticed that about 63% of patients received combination therapies including C/A. In the other study, the excess of adverse events (specifically nephrotoxicity and hepatotoxicity) was observed more in C/A group even when used as monotherapy. In terms of resistance rate, in patients with recurrent infections was observed a difference in MIC increase in C/A monotherapy compared to M/V monotherapy. These studies are limited by the small sample size and lack of study drug susceptibility and resistance mechanisms testing [82,83].

Further in 2018, Jorgensen et al. presented a case report about the use of M/V in a polymicrobial (*S.marcescens* and *Enterobacter aerogenes*) CRE bacteremia in a young HIV patient with a complex clinical history treated successfully with M/V monotherapy plus source control after failing to clear *Serratia* bacteremia with C/A [84]. Another recent case report has shown how the emergence of *K. pneumoniae* resistant to C/A could be more likely in the previous C/A exposure in solid organ recipients [85] with incomplete source control. The initial infection of this patient was pneumonia which is a risk factor for C/A therapy failure [86]. M/V has been used as a salvage therapy when the patient's renal function worsened on polymyxin and gentamicin. In this patient, M/V created a bridge to retransplantation thanks to the clearance of bacteremia and the improvement of renal function after stopping polymyxin and gentamicin.

7. Conclusions

M/V is a novel β-lactam/b β-lactamase combination that expands the broad spectrum of meropenem against KPC-producing *Enterobacterales*. It has favorable toxicity, pharmacokinetic and pharmacodynamics profiles compared with other older antibiotics used for the treatment of KPC-CRE infections.

Although M/V seems to deserve a prominent place in the panorama of therapeutic alternatives for some CRE infections, larger size clinical studies from the real-world are necessary to confirm the efficacy of monotherapy with M/V in severe infections.

8. Expert opinion

It has become clear that, although clearly superior to previous regimens, C/A cannot be the only solution for the treatment of KPC-CRE infections because of the risk of resistance selection and treatment failure, especially in the context of respiratory infections [86–88].

M/V is a fixed-dose combination product of a carbapenem and a cyclic boronic acid β-lactamase inhibitor. The addition of vaborbactam to meropenem restores the activity of meropenem against *Enterobacterales* that produces Amber class A enzymes, especially potent against KPC-producing organisms. However, it should be noted that this β-lactam/β-lactamase inhibitor does not inhibit Amber class B or D carbapenemases, nor does it improve the activity of meropenem against multidrug-resistant nonfermenting Gram-negative bacilli, notably *Acinetobacter* spp. and *P. aeruginosa*.

Meropenem, inhibiting more than two main PBPs, shows a minimal inoculum effect, no biomass increase, and a negligible endotoxin release and, having a fast bactericidal activity may be preferable to cephalosporins for combination with non-β-lactam carbapenemase inhibitors. Both meropenem and vaborbactam share a low plasma protein binding and have similar favorable kinetic properties with no plasma or urine PK drug–drug interactions. CRRT has no clinically relevant effect on the pharmacokinetics of the combination and both drugs are removed by hemodialysis and efficiently cleared during CVVH. The favorable lung disposition of M/V, with a higher ELF penetration than other β-lactams or β-lactam/β-lactamase combinations, may offer a rationale for the treatment of pulmonary infections due to MDR Gram-negative rods.

The efficacy of M/V for the treatment of complicated urinary tract infections and acute pyelonephritis was demonstrated in a Phase 3 trial (TANGO I), while another Phase 3

study (TANGO II) supported the efficacy of M/V for the treatment of infections caused by CRE. M/V appears to be safe and well-tolerated in clinical trials.

The paucity of data from clinical studies regarding the place in therapy of M/V limits the formulations of conclusive therapeutic indications but emerging evidences seem to suggest that M/V could become one of the major backbone agents for the treatment of microbiologically confirmed KPC-CRE infections, due to its promising efficacy in the setting of pneumonia and/or other severe KPC producing-CRE infections [89].

In addition, few preclinical and anecdotal data suggest that aztreonam plus M/V could have similar activity to aztreonam plus C/A against CRE strains producing metalloenzymes provided that there is no presence of OXA enzymes alongside NDM [90].

However, it should be stressed that a judicious antibiotic stewardship would be crucial in the next years in the initial selection of patients in which to use M/V appropriately in order to minimize the emergence of resistance and to limit the indiscriminate use of carbapenems.

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Declaration of interest

During the past 36 months A Novelli has received personal honoraria for participating in advisory boards and/or for meeting presentations from Angelini, Menarini, Merck, Named, Valeas, Zambon, and research grants to the laboratory from Merck. During the past 36 months GM Rossolini has received personal honoraria for participating in advisory boards and/or for meeting presentations from Angelini, Basilea, Menarini, Merck, Nordic-Pharma, Novartis, Pfizer, Epex, Shionogi, Venator, Zambon, and research grants to the laboratory from Angelini, Basilea, Menarini, Shionogi, Zambon. During the past 36 months M Tumbarello has received personal honoraria for participating in advisory boards and/or for meeting presentations from Angelini, Astellas, Menarini, MSD, Nordic Pharma, Pfizer, Roche, Shionogi.

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References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. European Centre for Disease Prevention and Control. Surveillance of antimicrobial resistance in Europe. Surveillance Report 2017; [cited 2020 Jan 10]. Available from: https://www.ecdc.europa.eu/sites/default/files/documents/EARS-Net-report-2017-update-jan-2019.pdf.
2. World Health Organization. Guidelines for the prevention and control of carbapenem-resistant *Enterobacteriaceae Acinetobacter baumannii* and *Pseudomonas aeruginosa* in health care facilities; 2017 [cited 2020 Jan 10]. Available from: https://apps.who.int/iris/bitstream/handle/10665/259462/9789241550178-eng.pdf;jsessionid=6CB39E386D7B79223329256FF21E7049?sequence=1
3. Shields RK, Nguyen MH, Chen L, et al. Ceftazidime-avibactam is superior to other treatment regimens against carbapenem-resistant *Klebsiella pneumoniae* bacteremia. Antimicrob Agents Chemother. 2017;61(8):e00883–17.
4. Tumbarello M, Trecarichi EM, Corona A, et al. Efficacy of ceftazidime-avibactam salvage therapy in patients with infections caused by *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae*. Clin Infect Dis. 2019;68:355–364.
5. Lee YR, Baker NT. Meropenem-vaborbactam: a carbapenem and beta-lactamase inhibitor with activity against carbapenem-resistant *Enterobacteriaceae*. Eur J Clin Microbiol Infect Dis. 2018;37:1411–1419.
6. Ramos-Castañeda JA, Ruano-Ravina A, Barbosa-Lorenzo R, et al. Mortality due to KPC carbapenemase-producing *Klebsiella pneumoniae* infections: systematic review and meta-analysis: mortality due to KPC *Klebsiella pneumoniae* infections. J Infect. 2018;76:438–448.
7. Pogue JM, Ortwine JK, Kaye KS. Are there any ways around the exposure-limiting nephrotoxicity of the polymyxins? Int J Antimicrob Agents. 2016;48:622–626.
8. Lee Y, Kim J, Trinh S. Meropenem-Vaborbactam (Vabomere™): another option for carbapenem-resistant *Enterobacteriaceae*. P T. 2019;44:110–113.
9. Kaushik A, Ammerman NC, Lee J, et al. In vitro activity of the new β-lactamase inhibitors relebactam and vaborbactam in combination with β-lactams against *Mycobacterium abscessus* complex clinical isolates. Antimicrob Agents Chemother. 2019;63(3):e02623–18.
10. Kaye KS, Bhowmick T, Metallidis S, et al. Effect of meropenem-vaborbactam vs piperacillin-tazobactam on clinical cure or improvement and microbial eradication in complicated urinary tract infection: the TANGO I randomized clinical trial. JAMA. 2018;319:788–799.

•• **Phase 3, multicenter, double-blind, randomized, non-inferiority study comparing M/V to piperacillin/tazobactam in adult patients with cUTI.**

11. Wunderink RG, Giamarellos-Bourboulis EJ, Rahav G, et al. Effect and safety of meropenem-vaborbactam versus best-available therapy in patients with carbapenem-resistant *Enterobacteriaceae* infections: the TANGO II randomized clinical trial. Infect Dis Ther. 2018;7:439–455.

•• **Phase 3, multicenter, double-blind, randomized, controlled trial comparing M/V to best available therapy for the treatment of CRE infections.**

12. Vabomere® (meropenem/vaborbactam) prescribing information. Parsippany, New Jersey: Melinta Therapeutics, Inc.; 2017 cited 2020 Jan 10. Available from: http://www.vabomere.com/media/pdf/vabomere-us-prescribinginformation.pdf.
13. European Medecines Agency. Vaborem product information; [cited 2020 Jan 27]. Available from: https://www.ema.europa.eu/en/documents/product-information/vaborem-epar-product-information_en.pdf
14. Craig WA. The pharmacology of meropenem, a new carbapenem antibiotic. Clinl Infect Dis. 1997;24:S266–75.
15. Moellering RC Jr, Eliopoulos GM, Sentochnik DE. The carbapenems: new broad spectrum/3-lactam antibiotics. J Antimicrob Chemother. 1989;24:1–7.
16. Fukasawa M, Sumita Y, Harabe ET, et al. Stability of meropenem and effect of 10-methyl substitution on its stability in the presence of renal dehydropeptidase I. Antimicrob Agents Chemother. 1992;36:1577–1579.
17. Hecker SJ, Reddy KR, Totrov M, et al. Discovery of a cyclic boronic acid β-lactamase inhibitor (RPX7009) with utility vs class a serine carbapenemases. J Med Chem. 2015;58:3682–3692.
18. Lomovskaya O, Sun D, Rubio-Aparicio D, et al. Vaborbactam: spectrum of beta-lactamase inhibition and impact of resistance mechanisms on activity in *Enterobacteriaceae*. Antimicrob Agents Chemother. 2017;61:e01443–17.

•• **A comprehensive study on spectrum of beta-lactamase inhibition of vaborbactam and on resistance mechanisms that can affect M/V susceptibility.**

19. Griffith DC, Loutit JS, Morgan EE, et al. Phase 1 study of the safety, tolerability, and pharmacokinetics of the β-lactamase inhibitor vaborbactam (RPX7009) in healthy adult subjects. Antimicrob Agents Chemother. 2016;60:6326.
20. Iovleva A, Doi Y. Carbapenem-resistant *Enterobacteriaceae*. Clin Lab Med. 2017;37:303–315.
21. Bassetti M, Giacobbe DR, Giamarellou H, et al. Critically Ill patients study group of the european society of clinical microbiology and infectious disease (ESCMID); Hellenic Society of Chemotherapy (HSC) and Società Italiana di Terapia Antinfettiva (SITA). Management of KPC-producing *Klebsiella pneumoniae* infections. Clin Microbiol Infect. 2018;24:133–144.
22. Wilson WR, Kline EG, Jones, C. E., et al. Effects of KPC variant and porin genotype on the in vitro activity of meropenem-vaborbactam against carbapenem-resistant *Enterobacteriaceae*. Antimicrob Agents Chemother. 2019;63(3): e02048–18.

• **A study demonstrating the activity of M/V against KPC mutants associated with resistance to C/A.**

23. Castanheira M, Doyle TB, Kantro V, et al. Meropenem-vaborbactam activity against carbapenem-resistant *Enterobacterales* isolates collected in U.S. hospitals during 2016–2018. Antimicrob Agents Chemother. 2020;64(2).:e01951–19.
24. Zhou M, Yang Q, Lomovskaya O, et al. In vitro activity of meropenem combined with vaborbactam against KPC-producing *Enterobacteriaceae* in China. J Antimicrob Chemother. 2018;73:2789–2796.
25. Castanheira M, Huband MD, Mendes RE, et al. 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.
26. Pogue JM, Bonomo RA, Kaye KS. Ceftazidime/avibactam,meropenem/ vaborbactam,or both? clinical and formulary considerations. Clin Infect Dis. 2019;68:519–524.
27. Lapuebla A, Abdallah M, Olafisoye O, et al. Activity of meropenem combined with RPX7009, a novel β-lactamase inhibitor, against gram-negative clinical isolates in New York city. Antimicrob Agents Chemother. 2015;59:4856–4860.
28. Patel TS, Pogue JM, Mills JP, et al. Meropenem-vaborbactam: a new weapon in the war against infections due to resistant Gram-negative bacteria. Future Microbiol. 2018;13:971–983.
29. Sabet M, Tarazi Z, Griffith DC. Activity of meropenem-vaborbactam against *Pseudomonas aeruginosa* and *Acinetobacter baumannii* in a neutropenic mouse thigh infection model. Antimicrob Agents Chemother. 2018;63(1):e01665–18.
30. Caverly LJ, Spilker T, Kalikin LM, et al. In vitro activities of β-lactam -β-lactamase inhibitor antimicrobial agents against cystic fibrosis respiratory pathogens. Antimicrob Agents Chemother. 2019;64(1): e01595–19.
31. Goldstein EJ, Citron DM, Tyrrell KL, et al. In vitro activity of Biapenem plus RPX7009, a carbapenem combined with a serine β-lactamase inhibitor, against anaerobic bacteria. Antimicrob Agents Chemother. 2013;57:2620–2630.
32. Sun D, Rubio-Aparicio D, Nelson K, et al. Meropenem-vaborbactam resistance selection, resistance prevention, and molecular mechanisms in mutants of KPC-producing *Klebsiella pneumoniae*. Antimicrob Agents Chemother. 2017;61(12):e01694–17.
33. Pfaller MA, Huband MD, Mendes RE, et al. In vitro activity of meropenem/vaborbactam and characterisation of carbapenem resistance mechanisms among carbapenem-resistant *Enterobacteriaceae* from the 2015 meropenem/vaborbactam surveillance programme. Int J Antimicrob Agents. 2018;52:144–150.
34. Shields RK, McCreary EK, Marini RV, et al. Early experience with meropenem-vaborbactam for treatment of carbapenem-resistant *Enterobacteriaceae* infections. Clin Infect Dis. 2019. pii: ciz1131. Epub ahead of print.
35. Clinical & Laboratory Standards Institute (CLSI). Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically. 11th. CLSI standard M07. Wayne, PA: Clinical and Laboratory Standards Institute; 2018.
36. The European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters. Version 10.0; 2020. Available from: http://www.eucast.org
37. CLSI. Performance standards for antimicrobial susceptibility testing. 29th. CLSI supplement M100. Clinical and Laboratory Standards Institute: Wayne, PA; 2019.
38. Jean S, Garrett S, Anglade C, et al. Multicenter clinical evaluation of etest meropenem-vaborbactam (biomérieux) for susceptibility testing of *Enterobacterales* (*Enterobacteriaceae*) and *Pseudomonas aeruginosa*. J Clin Microbiol. 2019;58(1):e01205–19.
39. Zhanel GG, Wiebe R, Dilay L, et al. Comparative review of the carbapenems. Drugs. 2007;67:1027–1052.
40. Neu HC, Novelli A, Chin NX. In vitro activity and,β-lactamase stability of a new carbapenem, SM-7338. Antimicrob Agents Chemother. 1989;33:1009–1018.
41. Martinez-Martinez L, Pascual A, Hernandez-Alles S, et al. Roles of beta-lactamases and porins in activities of carbapenems and cephalosporins against *Klebsiella pneumoniae*. Antimicrob Agents Chemother. 1999;7:1669–1673.
42. Periti P, Nicoletti P. Classification of betalactam antibiotics according to their pharmacodynamics. J Chemother. 1999;11:323–330.
43. Livermore DM. Clinical significance of beta-lactamase induction and stable derepression in gram-negative rods. Eur J Clin Microbiol. 1987;4:439–445.
44. Moyá B, Zamorano L, Juan C, et al. Affinity of the new cephalosporin CXA-101 to penicillin-binding proteins of *Pseudomonas aeruginosa*. Antimicrob Agents Chemother. 2010;54:3933–3937.
45. Novelli A, Fallani S, Cassetta MI, et al. Postantibiotic leukocyte enhancement of meropenem against gram-positive and gram-negative strains. Antimicrob Agents Chemother. 2000;44:3174–3176.
46. Tsivkovski R, Lomovskaya O. Biochemical activity of vaborbactam. Antimicrob Agents Chemother. 2020;64(2):e01935–19.
47. Bush K. Game changers: new β-lactamase inhibitor combinations targeting antibiotic resistance in gram-negative bacteria. ACS Infect Dis. 2018;4:84–87.
48. King DT, Sobhanifar S, Strynadka NC. One ring to rule them all: current trends in combating bacterial resistance to the beta-lactams. Protein Sci. 2016;4:787–803.
49. Hackel MA, Lomovskaya O, Dudley MN, et al. Activity of meropenem–vaborbactam against clinical isolates of KPC-positive *Enterobacteriaceae*. Antimicrob Agents Chemother. 2017;21(62): e01904–17.

•• **A study on M/V activity against a very large and global collection of KPC-producing Enterobacterales.**

50. Ehmann DE, Jahic H, Ross PL, et al. Kinetics of avibactam inhibition against class A, C, and D beta-lactamases. J Biol Chem. 2013;39:27960–27971.
51. Haidar G, Clancy CJ, Shields RK, et al. Mutations in bla(KPC-3) that confer ceftazidime-avibactam resistance encode novel KPC-3 variants that function as extended-spectrum β-lactamases. Antimicrob AgentChemother. 2017;61(5):e02534–16.
52. Shields RK, Chen L, Cheng S, et al. Emergence of ceftazidime-avibactam resistance due to plasmid-borne bla(KPC-3) mutations during treatment of carbapenem-resistant *Klebsiella pneumoniae* infections. Antimicrob Agents Chemother. 2017;61(3):e02097–16.
53. Nicolau DP, Siew L, Armstrong J, et al. Phase 1 study assessing the steady-state concentration of ceftazidime and avibactam in plasma and epithelial lining fluid following two dosing regimens. J Antimicrob Chemother. 2015;70:2862–2869.
54. Mouton JW, van den Anker JN. Meropenem clinical pharmacokinetics. Clin Pharmacokinet. 1995;28:275–286.
55. Adembri C, Novelli A. Pharmacokinetic and pharmacodynamic parameters of antimicrobials: potentials for providing dosing regimens that are less vulnerable to resistance. Clin Pharmacokinet. 2009;48:517–528.

56. Grupper M, Kuti JL, Nicolau DP. Continuous and prolonged intravenous β-lactam dosing: implications for the clinical laboratory. Clin Microbiol Rev. 2016;29:759–772.
57. Dandekar PK, Maglio D, Sutherland CA, et al. Pharmacokinetics of meropenem 0.5 and 2 g every 8 hours as a 3-hour infusion. Pharmacotherapy. 2003;23:988–991.
58. Novelli A, Adembri C, Livi P, et al. Pharmacokinetic evaluation of meropenem and imipenem in critically ill patients with sepsis. Clin Pharmacokinet. 2005;44:539–549.
59. Rubino CM, Bhavnani SM, Loutit JS, et al. Phase 1 study of the safety, tolerability, and pharmacokinetics of vaborbactam and meropenem alone and in combination following single and multiple doses in healthy adult subjects. Antimicrob Agents Chemother. 2018;62(4):e02228–17.
• **Basic clinical pharmacokinetic study on the PK parameters of meropenem and vaborbactam administered alone or in combination.**
60. Rubino CM, Bhavnani SM, Loutit JS, et al. Single-dose pharmacokinetics and safety of meropenem-vaborbactam in subjects with chronic renal impairment. Antimicrob Agents Chemother. 2018;62(3):e02103–17.
61. Wei X, Jang SH, Florian J, et al. Clinical pharmacology and biopharmaceutics review. Meropenem-vaborbactam. NDA#209776. Remplex pharmaceuticals. Division of anti-infective products. Center or Drug Evaluation and Research. Silver Spring, MD: US Food and Drug Administration; 2017 [cited 2020 Jan 10]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/209776Orig1s000ClinPharmR.pdf
62. Dhillon S. Meropenem/vaborbactam: a review in complicated urinary tract infections. Drugs. 2018;78:1259–1270.
63. Sime FB, Pandey S, Karamujic N, et al. Ex vivo characterization of effects of renal replacement therapy modalities and settings on pharmacokinetics of meropenem and vaborbactam. Antimicrob Agents Chemother. 2018;62(10):e01306–18.
64. Kufel WD, Eranki AP, Paolino KM, et al. In vivo pharmacokinetic analysis of meropenem/vaborbactam during continuous veno-venous haemodialysis. J Antimicrob Chemother. 2019;74:2117–2118.
65. Wenzler E, Gotfried MH, Loutit JS, et al. Meropenem-RPX7009 concentrations in plasma, epithelial lining fluid, and alveolar macrophages of healthy adult subjects. Antimicrob Agents Chemother. 2015;59:7232–7239.
• **Well performed pk research on the penetration in ELF of M/V useful to evaluate the potential efficacy of the combination in lung infections due to sensitive pathogens.**
66. Rodvold KA, Hope WW, Boyd SE. Considerations for effect site pharmacokinetics to estimate drug exposure: concentrations of antibiotics in the lung. Curr Opin Pharmacol. 2017;36:114–123.
67. Hanretty AM, Kaur I, Evangelista AT, et al. Pharmacokinetics of the meropenem component of meropenem-vaborbactam in the treatment of KPC producing *Klebsiella pneumoniae* bloodstream infection in a pediatric patient. Pharmacotherapy. 2018;38:e87–e91.
68. Cies JJ, Moore WS, Enache A, et al. Population pharmacokinetics and pharmacodynamic target attainment of meropenem in critically Ill young children. J Pediatr Pharmacol Ther. 2017;22:276–285.
69. Castanheira M, Rhomberg PR, Flamm RK, et al. Effect of the β-lactamase inhibitor vaborbactam combined with meropenem against serine carbapenemase-producing *Enterobacteriaceae*. Antimicrob Agents Chemother. 2016;60:5454–5458.
70. Sabet M, Tarazi Z, Nolan T, et al. Activity of meropenem-vaborbactam in mouse models of infection due to KPC-producing carbapenem-resistant *Enterobacteriaceae*. Antimicrob Agents Chemother. 2017;62(1):e01446–17.
71. Weiss WJ, Pulse ME, Nguyen P, et al. Activity of meropenem-vaborbactam against carbapenem-resistant *Enterobacteriaceae* in a murine model of pyelonephritis. Antimicrob Agents Chemother. 2017;62(1):e01439–17.
72. Ambrose PG, Lomovskaya O, Griffith DC, et al. β-lactamase inhibitors: what you really need to know. Curr Opin Pharmacol. 2017;36:86–93.
73. Sabet M, Tarazi Z, Rubio-Aparicio D, et al. Activity of simulated human dosage regimens of meropenem and vaborbactam against carbapenem-resistant *Enterobacteriaceae* in an in vitro hollow-fiber model. Antimicrob Agents Chemother. 2018;62(2):e01969–17.
74. Griffith DC, Sabet M, Tarazi Z, et al. Pharmacokinetics/pharmacodynamics of vaborbactam, a novel beta-lactamase inhibitor, in combination with meropenem. Antimicrob Agents Chemother. 2018;63(1):e01659–18.
•• **Interesting study on the impact of PK/PD parameters of M/V to prevent the potential emergence of resistant mutants.**
75. Jorgensen SCJ, Rybak MJ. Meropenem and vaborbactam: stepping up the battle against carbapenem-resistant *Enterobacteriaceae*. Pharmacotherapy. 2019;38:444–461.
76. Bassetti M, Giacobbe DR, Patel N, et al. Efficacy and safety of meropenem-vaborbactam versus best available therapy for the treatment of carbapenem-resistant *Enterobacteriaceae* infections in patients without prior antimicrobial failure: a post hoc analysis. Adv Ther. 2019;36:1771–1777.
77. Lai CC, Chen CC, Tang HJ. Meropenem-vaborbactam in the treatment of acute bacterial infections. J Clin Med. 2019;8(10):E1650.
78. Miller AD, Ball AM, Bookstaver PB, et al. Epileptogenic potential of carbapenem agents: mechanism of action, seizure rates, and clinical considerations. Pharmacotherapy. 2011;31:408–423.
79. Sutter R, Rüegg S, Tschudin-Sutter S. Seizures as adverse events of antibiotic drugs. A systematic review. Neurology. 2015;85:1332–1341.
80. Gibson B. A brief review of a new antibiotic: meropenem-vaborbactam. Sr Care Pharm. 2019;34:187–191.
81. Alosaimy S, Jorgensen SCJ, Lagnf AM, et al. Early multicenter experience of meropenem vaborbactam in patients treated for serious gram-negative infections. Presented at: IDWeek 2019; 2019 Oct 2–6; Washington, DC.
82. Ackley R, Roshdy D, Isip J et al. Meropenem/vaborbactam versus ceftazidime/avibactam for treatment of carbapenem-resistant *Enterobacteriaceae* infections. Presented at: European Congress of Clinical Microbiology and Infectious Disease, 2019; 2019 Apr 13–16; Amsterdam.
83. Ackley R, Roshdy D, Isip J et al. Recurrence of infection and emergence of drug resistance after treatment with meropenem/vaborbactam compared to ceftazidime/avibactam in carbapenem-resistant *Enterobacteriaceae* infections. Presented at: IDWeek 2019; 2019 Oct 2–6; Washington, DC. Poster 662.
84. Jorgensen SCJ, McDonald P, Mynatt RP, et al. Averting the post-antibiotic era: successful use of meropenem/vaborbactam for carbapenem-resistant *Serratia marcescens* and *Enterobacter aerogenes* bacteremia in a hemodialysis patient. J Antimicrob Chemother. 2018;73:3529–3531.
85. Athans V, Neuner EA, Hassouna H, et al. Meropenem-vaborbactam as salvage therapy for ceftazidime-avibactam-resistant *Klebsiella pneumoniae* bacteremia and abscess in a liver transplant recipient. Antimicrob Agents Chemother. 2018;63(1):e01551–18.
86. Shields RK, Nguyen MH, Chen L, et al. Pneumonia and renal replacement therapy are risk factors for ceftazidime-avibactam treatment failures and resistance among patients with carbapenem-resistant *Enterobacteriaceae* infections. Antimicrob Agents Chemother. 2018;62(5):e02497–17.
87. King M, Heil E, Kuriakose S, et al. Multicenter study of outcomes with ceftazidime-avibactam in patients with carbapenem-resistant *Enterobacteriaceae* infections. Antimicrob Agents Chemother. 2017;61(7):e00449–17.
88. Shields RK, Potoski BA, Haidar G, et al. Clinical outcomes, drug toxicity, and emergence of ceftazidime-avibactam resistance among patients treated for carbapenem-resistant *Enterobacteriaceae* infections. Clin Infect Dis. 2016;63:1615–1618.
89. Karaiskos I, Lagou S, Pontikis K, et al. The "old" and the "new" antibiotics for mdr gram-negative pathogens: for whom, when, and how. Front Public Health. 2019;7:151.
90. Biagi M, Wu T, Lee M, et al. Searching for the optimal treatment for metallo- and serine-β-lactamase producing *Enterobacteriaceae*: aztreonam in combination with ceftazidime-avibactam or meropenem-vaborbactam. Antimicrob Agents Chemother. 2019. AAC.01426–19.