Vaborbactam: perspective of a new β-lactamase inhibitor in the antimicrobial chemotherapy

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Summary

Infections due to carbapenem-resistant *Enterobacterales, Pseudomonas aeruginosa*, and *Acinetobacter baumannii* constitute a global public health threat and are associated with high morbidity and mortality rates. Resistance is mainly due to the production of various types of carbapenemases. Vaborbactam is a novel boronic acid-based β-lactamase inhibitor with high potency against class A carbapenemases, including KPC variants. Combined with meropenem, it almost fully restores its activity against KPC carbapenemase-producing *Enterobacterales*. However, it has limited activity against carbapenem-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. Clinical efficacy and safety of the combination were evaluated in two clinical trials, TANGO I and II: it was proved to be non-inferior compared to other therapeutic

options. It was also found safe, having few serious adverse effects, especially in terms of nephrotoxicity. Based on available *in vitro* and *in vivo* data it appears to retain a low propensity for resistance selection. Vaborbactam exhibits pharmacokinetic properties similar to those of meropenem. Meropenem-vaborbactam has been approved for use in adults with complicated urinary tract and intrabdominal infections, hospital-acquired and ventilator-associated pneumonia, as well as infections due to aerobic Gram-negative organisms in adults with limited treatment options. Studies regarding its use in real-life settings show promising clinical cure rates and lower rates of adverse effects, even when it comes to cases of very fragile patients.

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Introduction

Carbapenem-resistant organisms constitute an urgent health threat as they have spread worldwide and cause infections with increased morbidity and mortality.[1,2] Notably, in 2017, the WHO deemed carbapenem-resistant *Enterobacterales* (CRE), carbapenem-resistant *Pseudomonas aeruginosa* (CRPA), and carbapenem-resistant *Acinetobacter baumannii* (CRAB) as the three critical pathogens demanding new antimicrobial options.[3]

The main mechanism leading to carbapenem resistance in Gram-negative pathogens is the production of carbapenemases. Less often, it is due to the loss of outer membrane proteins and the presence of efflux pumps.[4] The most significant carbapenemases are *Klebsiella pneumoniae* carbapenemases (KPCs), class B or metallo-β-lactamases (MBLs), and class D or OXA-type carbapenemases.[5] The development of new combinations based on a β-lactam molecule and a novel β-lactamase inhibitor active on carbapenemases is one of the promising strategies in the treatment of infections due to carbapenem-resistant organisms.[6]

Recently meropenem-vaborbactam joined ceftazidime-avibactam in the group of β-lactam/β-lactamase inhibitor combinations available for the treatment of CRE infections.

Mechanism of action

Vaborbactam is a novel cyclic boronic acid-based β-lactamase inhibitor. The boron atom of vaborbactam forms a covalent bond with the catalytic serine side chain of β-lactamases, mimicking β-lactam hydrolysis and inhibiting the activity of the enzymes. While the bond is reversible, the rate of dissociation of the complex varies depending on the enzyme. The most stable complex forms between vaborbactam and enzymes KPC-2 and KPC-3.[7] Using a series of *Escherichia coli* strains expressing different types of β-lactamases, vaborbactam was found to be a potent inhibitor of KPC carbapenemases and other class A carbapenemases, such as SME and NMC. However, it

did not appear to inactivate SHV and TEM β-lactamases, making meropenem the most proper option for a combination. It exhibited no activity against metallo-β-lactamases (MBLs) and class D carbapenemases.[8] It is also inactive against mammalian serine proteases.[9] Vaborbactam uses porins OmpK35 and OmpK36 to cross the outer membrane in *Klebsiella pneumoniae*, but OmpK36 appears to play a more significant role.[8]

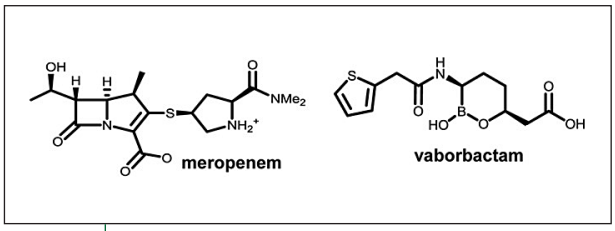

Figure 1 Chemical structure of vaborbactam.[8]

Spectrum of activity

Given its β-lactamase inhibition profile, vaborbactam restores the activity of meropenem against carbapenem-resistant *Enterobacterales* that produce KPC and other class A carbapenemases. As for carbapenem-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, the activity of meropenem-vaborbactam is similar to that of meropenem alone, since resistance is mostly mediated by different mechanisms.[12-18]

Regarding Gram-positive organisms, vaborbactam does not improve the activity of meropenem.[10] Against anaerobes, it does not potentiate the activity of biapenem, therefore it is not expected to potentiate the activity of meropenem either.[11]

Epidemiological studies

The degree to which vaborbactam restores the activity of meropenem against carbapenem-resistant Gram-negative bacteria has been explored in various *in vitro* studies. In a 2016 study, 315 carbapenemase-producing *Enterobacterales* strains were examined. Most were *K. pneumoniae* producing KPC- 2 or KPC-3. When combined with increasing doses of vaborbactam, up to 32 μg/ml, the activity of meropenem at a concentration of 2 μg/ml was restored against 98.1% of strains.[12] Earlier, 131 out of 133 KPC-producing *Enterobacterales* strains (98,5 %) were inhibited in the presence of meropenem-vaborbactam at a concentration of 1/8 μg/ml.[13] Similarly, in other studies meropenem-vaborbactam was active against 99-100% of KPC-producing *Enterobacterales* strains.[14,16] In all studies involving *P. aeruginosa* and *A. baumannii* strains, as well as *Enterobacterales* strains that produced MBLs or OXA-48 carbapenemases, vaborbactam did not improve the activity of meropenem.[13,14,16] In the cases of KPC-producing *Enterobacterales* where vaborbactam failed to restore the activity of meropenem, defects of porins OmpK35, OmpK36 were detected.[13,15] In a study comparing the activity of meropenem-vaborbactam against CRE to other antibiotics, it was 99,2% effective against KPC-producers. Compared to other antibiotics, only tigecycline could produce similar results. A KPC-producing *Citrobacter freundii* strain was non-susceptible to meropenem-vaborbactam due to defects in OmpF and OmpC, the outer membrane proteins that are homologous to OmpK35 and OmpK36.[17]

Experimental infections

In a neutropenic mouse thigh infection model using carbapenem-resistant *K. pneumoniae, E. coli,* or *Enterobacter cloacae* strains, the use of meropenem alone had the same results as leaving the mice untreated. The addition of various doses of vaborbactam increased bacterial killing in a dose-dependent manner. Similar results were obtained in a mouse lung infection model.[18]

As for neutropenic mouse thigh infections caused by *P. aeruginosa* or *A. baumannii*, the activity of meropenem-vaborbactam was found to be similar to that of meropenem alone, as meropenem resistance is largely mediated by mechanisms other than KPC production (e.g. outer membrane impermeability, upregulation of efflux pumps, hyperproduction of class C β-lactamases, MBLs, class D carbapenemases).[19]

Clinical studies

The clinical efficacy and safety of meropenem-vaborbactam were evaluated in two phase 3 clinical studies.[20,21]

The TANGO I (Targeting Antibiotic Non-Susceptible Gram-Negative Organisms) was a multicenter, double-blind, randomized, phase 3 study comparing the use of meropenem-vaborbactam (M/V, 2 g/2 g over a 3-hour intravenous infusion every 8 hours) to piperacillin-tazobactam (TZP, 4 g/0.5g over a 30-minute intravenous infusion every 8 hours) in adult patients with complicated urinary tract infections (cUTIs) including

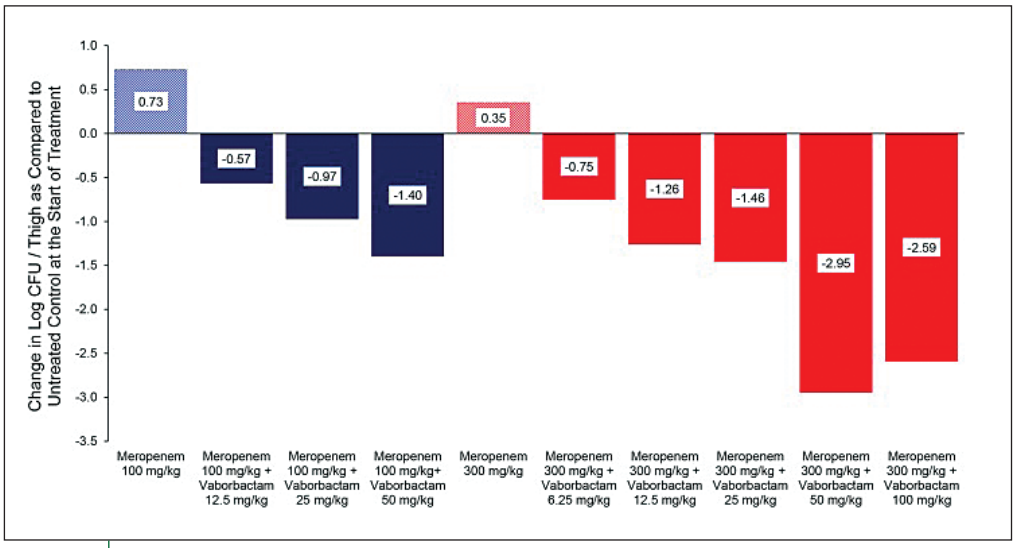

Figure 2 Activity in a neutropenic mouse thigh infection model.[18]

acute pyelonephritis. If patients met certain clinical criteria for oral stepdown therapy, after a minimum of 15 doses of study drug, they switched to levofloxacin 500 mg oral tablets once a day. Total treatment duration was 10 days. The primary endpoint for FDA was overall success, a combination of clinical cure and microbiological eradication at the end of intravenous treatment (EOIVT), whereas for EMA primary endpoint was microbiological eradication at test-of-cure visit (TOC, 7 days after the end of treatment). A total of 545 patients were randomized and received at least one dose of study drug, and 374 of them (microbiological modified intent to treat population – mMITT, 192 vs 182) had a positive urine culture (>100.000 cfu/ml) or had the same pathogen in both urine and blood cultures. Almost all pathogens were susceptible to meropenem. Overall success was achieved in a high proportion of patients in both groups (M/V 98.4% vs TZP 94%). Microbiological eradication at test-of-cure visit was achieved in 66.7% for M/V, and in 57.7% for TZP. The difference met the established non-inferiority margin. Among patients in both groups, the number experiencing any adverse effect was similar. Meropenem-vaborbactam appeared to be well-tolerated, with headache being the most common adverse effect (8.8%).[20]

TANGO II was a randomized, open-label phase 3 clinical in patients with cUTI, including acute pyelonephritis, hospital-acquired pneumonia or ventilator-associated pneumonia, bloodstream infection, or complicated intraabdominal infection, due to known or suspected CRE. Patients were randomized 2:1 to receive meropenem-vaborbactam (2 g/ 2g over 3-hour IV infusion, every 8 hours) or best available treatment (BAT). BAT included monotherapy or combination therapy of a carbapenem, aminoglycoside, colistin, tigecycline, or ceftazidime-avibactam (monotherapy only). Among the 75 patients who received the study drugs, 47 had a confirmed infection with a CRE isolate (mCRE-MITT population). The most common pathogen was KPC-producing *K. pneumoniae*. The primary endpoint was clinical cure, defined as complete resolution of signs and symptoms. Meropenem-vaborbactam was associated with higher rates of clinical cure both at the end of treatment (65.6% vs 33.3%) and at TOC (59.4% vs 26.7%). In the subgroup of patients with cUTI/AP overall success was higher for meropenem-vaborbactam (75% vs 50%). As for drug-related adverse effects, they occurred in a lower rate in the meropenem-vaborbactam group (24.4% vs 44%). The most common ones were diarrhea, anemia, hypokalemia. In the BAT group, they included sepsis/septic shock, diarrhea, anemia, hypotension, and acute renal failure. Not surprisingly, fewer renal-related adverse effects were noticed in the M/V group, considering that BAT regimens usually contained aminoglycosides and colistin.[21]

TANGOKIDS, an open label, dose-finding, pharmacokinetics, safety, and tolerability study of a single dose infusion of meropenem-vaborbactam in pediatric subjects from birth to less than 18 years of age with serious bacterial infections, is ongoing (ClinicalTrials.gov Identifier: NCT02687906).[22]

Pharmacokinetic properties

According to data from preclinical studies and phase 1 studies, its pharmacokinetic properties are similar to those of β-lactams, that is high maximum serum concentration (Cmax) and area under the curve (AUC), short half-life time, and low volume of distribution. Exposure to vaborbactam, as defined by Cmax and AUC, increased proportionately with dose, and no accumulation was observed following multiple doses in healthy adults. The average plasma protein binding was found to be 33%, and its clearance is mainly renal, with almost 90% of vaborbactam excreted unchanged in urine.[23] All pharmacokinetic properties were similar when meropenem and vaborbactam were given together, implying no drug-to-drug interactions, and the combination was well tolerated.[24]

The combination has also been studied in subjects with chronic renal impairment receiving a single dose of 1 g/1 g over a 3-hour intravenous infusion, in a phase 1, open-label study. The plasma clearance of both meropenem and vaborbactam decreased in a similar manner with decreasing renal function, increasing exposure to the drugs and indicating the need of dose adjustment in patients with renal impairment. Both meropenem and vaborbactam were removed by hemodialysis. The combination was well tolerated regardless of the degree of decrease in renal function.[25]

The penetration of vaborbactam in the epithelial lining fluid of healthy adults has also been evaluated. Both meropenem and vaborbactam achieved and maintained over time similar concentrations, with penetration of 63% and 53% respectively.[26]

Pharmacokinetic/pharmacodynamic evaluation

Meropenem exhibits time-dependent activity, and the concentration of the drug needs to be maintained above the MIC value for a prolonged amount of time to achieve bactericidal activity (%f T>MIC of 40%).[27]

An *in vitro* study using a hollow-fiber model was conducted in order to estimate the exposure to meropenem-vaborbactam that would bring about bacterial killing and would prevent the development of resistance. A total of 17 *K. pneumoniae, E. coli, E. cloacae* strains that combined KPC production with other possible resistance mechanisms, such as porin loss or other β-lactamases, were studied using high inoculum and concentrations of meropenem-vaborbactam based on dose regimens of phase 1 and phase 3 trials. When the lowest dose was used, development of resistance in a *K. pneumoniae* strain was observed (an MIC value of >32mg/l was developed while the initial value was 1 mg/l). However, when exposure was adjusted to resemble that of phase 3 trials, the free 24-h AUC value was ~550 mg x h/l, and bacterial killing was achieved, even against strains with a MIC value of 16 mg/l. Also, the combination suppressed any development of resistance.[28]

A second study using the same CRE strains evaluated the PK/PD parameter that would best describe the activity of meropenem-vaborbactam. Using the hollow-fiber model, authors concluded that it is best described by the free 24-h AUC/MIC ratio. A ratio value of 24 or more leads to both bactericidal activity and suppression of resistance development. The dose regimen of 2 g/2 g given over a 3-hour intravenous infusion, every 8 hours results in bacterial killing and suppression of resistance development against *Enterobacterales* strains with MIC values of up to 8 mg/l.[29]

Resistance mechanisms

So far, resistance to meropenem-vaborbactam in KPC-producing *Enterobacterales* is associated with permeability disorders due to porin mutations, along with increased β-lactamase expression and increased efflux pump production.[30]

In vitro experiments highlight the effect of porins OmpK35, OmpK36 on the activity of vaborbactam. In particular, inactivation of OmpK35 reduces the activity of vaborbactam, but much less than inactivation of OmpK36. A variant of OmpK36 frequently found in clinical strains of *K. pneumoniae* carries a duplication of glycine (G) and aspartic acid (D) at positions 134 and 135 of the protein (GD repeat), and the porin in this case has a narrower inner channel. In the experiment, the strain carrying the GD repeat mutation had a higher meropenem MIC value and vaborbactam showed lower activity against it compared to a strain whose sole difference was the absence of the repeat.[8]

The AcrAB-TolC efflux pump is a common mechanism of resistance to many antibiotics, but it does not seem to contribute to resistance to meropenem-vaborbactam. A mutation in the *ramR* gene causes down-regulation of the porin OmpK35 and increased expression of the pump, but does not affect the *in vitro* activity of meropenem-vaborbactam. However, increased expression of the pump combined with inactivation of the porins OmpK35, OmpK36 causes an increase in the MIC value of meropenem-vaborbactam.[8]

Another *in vitro* study of meropenem-vaborbactam activity against carbapenem-resistant *Enterobacterales*

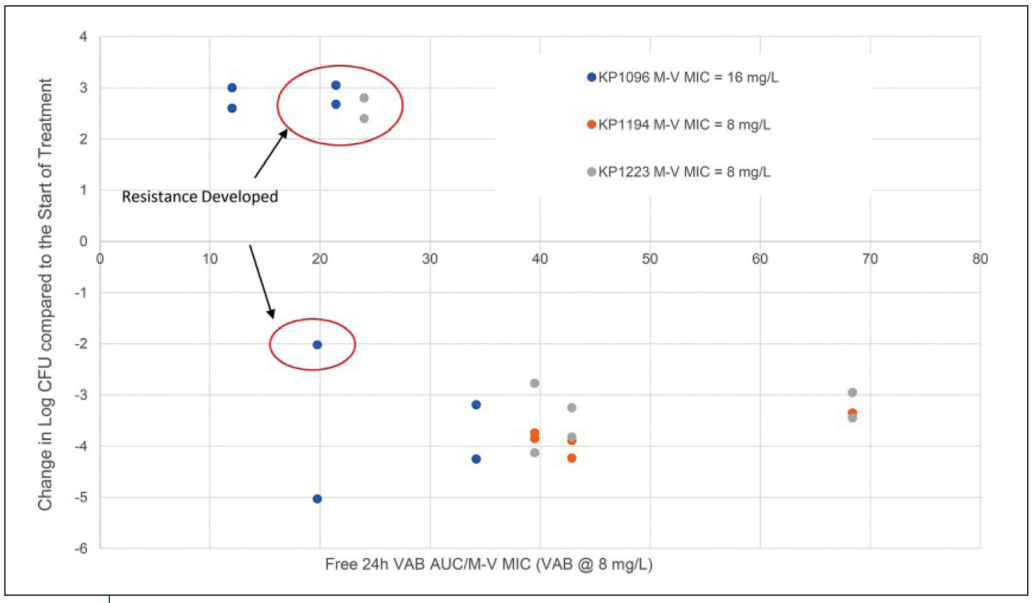

Figure 3 Relationship between 24-h AUC/MIC and resistance suppression in *K. pneumoniae* strains.[29]

highlighted the IS5 addition to the *ompK36* promoter as a mutation leading to reduced susceptibility. This mutation results in reduced expression of OmpK36 porin.[31]

Reduced susceptibility to meropenem-vaborbactam due to loss of the KvrA protein has also been described in KPC-3 -producing *K. pneumoniae* strains. KvrA acts as a transcription factor. This loss, caused by mutations in the kvrA gene, ultimately results in reduced expression of the OmpK35 and OmpK36 porins and reduced meropenem-vaborbactam activity.[32]

Regarding KPC, there is no report of a mutation conferring reduced susceptibility or resistance to meropenem-vaborbactam. In a recent study, the effect of two mutations conferring resistance to ceftazidime-avibactam on the activity of meropenem-vaborbactam was investigated. The most common mutations reported cause the D179Y amino acid substitution in KPC-2 and KPC-3, and the L169P substitution in KPC-2. Both mutations confer resistance to ceftazidime-avibactam but lead to loss of resistance to carbapenems and susceptibility to meropenem-vaborbactam. In *P. aeruginosa* strains engineered to express the KPC-2 mutations, the ability of vaborbactam to enhance the activity of ceftazidime, cefepime, and piperacillin was reduced less than twofold, compared to avibactam, whose activity was reduced from 8 to 32 times for D179Y, and from 4 to 16 times for L169P, depending on the antibiotic.[33]

Another study aimed at defining the concentration of meropenem and vaborbactam that would not allow the emergence of strains with reduced susceptibility due to mutations. Eighteen KPC-producing *K. pneumoniae* strains with varying degrees of susceptibility to meropenem and meropenem-vaborbactam were used. Meropenem and vaborbactam, at 8 μg/ml each, reduced the incidence of mutations to $<1 \times 10^{-8}$ in 77.8% of strains (14/18), and in all strains when meropenem was increased to 16 μg/ml. Mutations detected at low concentrations of meropenem-vaborbactam mainly involved OmpK36 inactivation and bla_{KPC} copy number increase. It is noted that no mutations were found in the coding region of bla_{KPC}. Mutations in OmpK36 were associated with the greatest increase in meropenem-vaborbactam MIC values, while bla_{KPC} copy number increase is significant when combined with a partially functional OmpK36.[34]

No resistant isolates were identified during the TANGO II clinical trial. The microbiological analysis revealed only one isolate with a fourfold MIC increase, from 0.25 to 1 mg/l, that remained in the susceptibility range.[21]

Susceptibility testing

Both EUCAST and CLSI have set susceptibility and resistance breakpoints for meropenem-vaborbactam (at a dose of 2g/2g every 8 hours in a 3-hour infusion) with a fixed concentration of vaborbactam of 8 mg/l. EUCAST has set the breakpoints for susceptibility and resistance at MIC values of less than or equal to 8 mg/l

and greater than 8 mg/l, respectively, for both *Enterobacterales* and *P. aeruginosa*,[35] while CLSI has set them at an MIC value less than or equal to 4 mg/l and greater than 8 mg/l only for *Enterobacterales*.[36] Susceptibility can be tested using the method of broth microdilution, with a fixed concentration of vaborbactam of 8 mg/l. Gradient diffusion tests (Etest, bioMerieux or MIC Test Strips, Liofilchem) are also available, as well as testing in semi-automated commercial systems (e. g. Microscan, Beckman Coulter).[37] Disk diffusion can be used for susceptibility testing according to both CLSI and EUCAST.[35,36]

Data from the clinical use

In August 2017, FDA approved the use of meropenem-vaborbactam for the treatment of adults with complicated UTI, including pyelonephritis.[38] EMA then approved its use in adults with complicated UTI, including pyelonephritis, complicated intra-abdominal infection, hospital-acquired pneumonia (HAP), and ventilator-associated pneumonia (VAP), bacteremia associated with the above infections, and infections due to aerobic Gram-negative bacteria in adults with limited treatment options.[39] Since then, data from the clinical use of meropenem-vaborbactam have appeared in the literature, providing important information as they come from patients who are mainly elderly, critically ill, more severely immunosuppressed, and more likely to have vital organ damage, for example renal failure.

In 2020, Shields et al. published an observational study of 20 critically ill patients with carbapenem-resistant *Enterobacterales* infections treated for >48 hours with meropenem-vaborbactam. The dose they received was 2g/2g intravenously every 8 hours, with adjustment in case of impaired renal function. Infections included bacteremia (n=8), pneumonia (n=6, VAP 5/6), tracheobronchitis (n=2, ventilator-associated 1/2), skin and soft tissue infections (n=2), pyelonephritis (n =1), and peritonitis with intra-abdominal abscess (n=1). The main pathogen was *Klebsiella pneumoniae* (n=14), followed by *Klebsiella oxytoca* (n=2), *Escherichia coli* (n=2), *Enterobacter cloacae* (n=1), and *Citrobacter freundii* (n=1). Eighteen strains produced KPC enzymes, including one *K. pneumoniae* strain that produced KPC-31, resistant to ceftazidime-avibactam but sensitive to carbapenems. Two strains did not produce KPC (one *E. coli* carrying bla_{CMY} and one *K. oxytoca* carrying bla_{CMY}, bla_{ACC} and bla_{DHA}). In 80% of patients the combination was administered as monotherapy. Clinical success was noted in 65% of patients, and more specifically in 63% in the case of bacteremia and in 67% of pneumonia. APACHE-II score was higher where no clinical success was observed. Microbiological failure within 90 days occurred in 6 of 20 patients. Notably, one failure involved a patient with bacteremia due to a KPC-31-producing *K. pneumoniae* strain, with resistance to ceftazidime-avibactam and a meropenem-vaborbactam MIC of 0.12 μg/ml. On day 12 of meropenem-vaborbactam treatment, the patient developed an abdominal wall abscess, from which a *K. pneumoniae* strain with a meropenem-vaborbactam MIC of 8 μg/ml was isolated. WGS analysis revealed an IS5 insertion in the promoter of the *OmpK36* gene that was not present initially, while the bla_{KPC} gene remained unchanged. This was the first report of a treatment-emergent non-susceptible strain. Regarding adverse effects, one patient developed eosinophilia.[40]

A retrospective study by Alosaimy et al. included 40 patients from 7 US centers who had received meropenem-vaborbactam for more than 72 hours for infections due to multidrug resistant Gram-negative pathogens. Infections included pneumonia (13/40), urinary tract infection (8/40), intra-abdominal infection (5/40) and skin and soft tissue infections (5/40). Clinical success was noted in 70% of patients. Failure was due to persistence of symptoms, relapse, and death. Only 5 patients were screened for development of resistance to meropenem-vaborbactam, none developing. One patient developed Stevens-Johnson syndrome/toxic epidermal necrolysis 3 days after initiation of meropenem-vaborbactam therapy.[41]

A multicenter retrospective study of patients treated with ceftazidime-avibactam or meropenem-vaborbactam for >72 hours was published in 2020. Of the 131 patients included, 105 had received ceftazidime-avibactam and 26 meropenem-vaborbactam. The main pathogen was *K. pneumoniae*. Clinical success was similar, at 61.9% in the ceftazidime-avibactam group and 69.2% in the meropenem-vaborbactam group (P=0.49). The most common adverse effect was nephrotoxicity, with a rate of 29.2% for ceftazidime-avibactam and 14.3% for meropenem-vaborbactam. The difference was not statistically significant, while it is noted that the majority of patients receiving ceftazidime-avibactam were also receiving any of the following in combination: colistin, tigecycline, quinolone, aminoglycoside. Regarding the development of resistance, 3 patients receiving ceftazidime-avibactam monotherapy developed resistant strains. No cases of emergence of resistance to meropenem-vaborbactam were noted.[42]

A retrospective study of 15 patients with CRE infections was the first to include bone and joint infections (5, 33.3%), other than primary bacteremia (3, 20%),

complicated intra-abdominal infections (2, 13.3%), pneumonia (2, 13.3%), urinary tract infections (2, 13.3%), and soft tissue infection with secondary bacteremia (1, 6.7%). Bacteria isolated were *K. pneumoniae* (10, 66.7%), *E. coli* (3, 20%), *Klebsiella aerogenes* (1, 6.7%), *Citrobacter koseri* (1, 6.7%). Fourteen patients had received antibiotic therapy prior to initiation of meropenem-vaborbactam. The mean time to initiation of meropenem-vaborbactam treatment was 73 hours. The outcome was positive for 9 patients (60%), negative for 5 (33.3%), and uncertain for 1 patient (6.7%). For both cases the mean time to initiation of treatment was similar. One patient developed recurrent bacteremia from a meropenem-vaborbactam-susceptible strain within 30 days of the end of treatment. Three out of 5 cases of bone and joint infections had a positive clinical outcome. Regarding the patients with a negative response, 3 (60%) were found to have inadequate source control, 1 died of an infection-related cause, and 1 of another cause before the end of treatment. Repeat cultures within 3 days of starting treatment were obtained in 6 patients, of whom 4 (66.7%) had a positive microbiological response. As for adverse effects, one patient developed *C. difficile* diarrhea on day 2 of meropenem-vaborbactam therapy, although other broad-spectrum antibiotics had already been used.[43]

Few case reports about the successful use of meropenem-vaborbactam have also been published. Jorgensen et al. presented the case of a young HIV patient with a complex clinical history and bacteremia due to carbapenem-resistant *Serratia marcescens* and *Enterobacter aerogenes*. The patient was initially treated with ceftazidime-avibactam, which failed to clear the bacteremia. Subsequently, the infection was treated successfully with meropenem-vaborbactam plus source control.[44] Another case report describes the case of a liver transplant recipient who developed bacteremia and a liver abscess due to KPC-producing *K. pneumoniae* (KPC-Kp) strain. After initial monotherapy with ceftazidime-avibactam, the strain developed *de novo* resistance, and treatment was changed to colistin plus gentamicin. Due to renal failure, meropenem-vaborbactam was used as salvage therapy. Renal function improved and bacteremia was cleared, allowing retransplantation.[45] In the case of a woman with septic thrombosis and bacteremia due to KPC-Kp, meropenem-vaborbactam was successfully combined with fosfomycin, after failing to treat her, first with ceftazidime-avibactam, and then with colistin plus fosfomycin.[46] Most recently, a case report about the use of meropenem-vaborbactam in a thoracic aorta graft infection due to a ceftazidime-avibactam-resistant KPC-Kp strain has been published. The infection was treated successfully with the combination of meropenem-vaborbactam with tigecycline. Tigecycline was then discontinued, and the patient showed no sign of recurrence until dying of another cause.[47]

Treatment of infections due to carbapenem-resistant Gram-negative bacteria

Treatment of infections with carbapenem-resistant Gram-negative bacteria is challenging and requires a multifactorial strategy. Given the need for early initiation of treatment, it is important to identify patients at increased risk for such infections based on their individual history, and at the same time to have knowledge of the local epidemiology of resistance mechanisms. The use of phenotypic and molecular techniques to identify resistance mechanisms can also contribute to applying the appropriate therapy.[48] Before the novel β-lactam/β-lactamase inhibitor combinations became available, treatment of infections due to carbapenem-resistant Gram-negative bacteria relied on the use of colistin (except for intrinsically resistant bacteria), as monotherapy or in combination with tigecycline, fosfomycin, high doses of carbapenems, and sulbactam, depending on the pathogen and the site of infection.[48]

When it comes to less severe *Enterobacterales* infections, the use of older antibiotics is preferred.[49,50] In uncomplicated cystitis, quinolones, trimethoprim-sulfamethoxazole, aminoglycosides, nitrofurantoin, remain good options. However, in case of resistance or failure, the use of novel β-lactam/β-lactamase inhibitor combinations, that is meropenem-vaborbactam, ceftazidime-avibactam, and imipenem-relebactam, is recommended. If these are also ineffective, cefiderocol, a novel siderophore cephalosporin, may be used.[49] In severe infections, both complicated urinary tract infections and non-urinary tract infections, administration of meropenem-vaborbactam or ceftazidime-avibactam or imipenem-relebactam is recommended.[49] Alternatively, cefiderocol can be used in case of resistance to the available combinations.[49,50]

If metallo-β-lactamase production is detected, the use of cefiderocol is recommended. A combination of ceftazidime-avibactam with aztreonam can also be used.[49,50] In case of OXA-48 production, the first choice is ceftazidime-avibactam and, alternatively, cefiderocol.[49]

Given the fact that vaborbactam does not restore the activity of meropenem against carbapenem-resistant *P. aeruginosa* and carbapenem-resistant *A. baumannii*, meropenem-vaborbactam has no place in the treatment of such infections. As for *P. aeruginosa*,

the first choice for severe infections is ceftolozane/tazobactam,[49,50] while for milder infections the use of older antipseudomonal antibiotics, such as aminoglycosides, is recommended.[49] For severe *A. baumannii* infections, the European Society for Clinical Microbiology and Infection currently recommends a combination of colistin, aminoglycoside, tigecycline, sulbactam.[50]

Conclusion

The addition of vaborbactam to meropenem restores the activity of the latter against Gram-negative bacteria producing class A β-lactamases, as it is highly active against KPC, as shown by large surveillance studies. It is important to emphasize that the combination is not effective against class B and class D carbapenemases, nor does it improve the activity of meropenem against multidrug-resistant *P. aeruginosa* and *A. baumannii*. The results of clinical studies highlight its efficacy in urinary tract infections, as well as other serious infections caused by Gram-negative bacteria. At the same time, it is characterized as safe, with a low occurrence of serious adverse effects, while it can be used safely in cases of reduced renal function. Based on the so far scarce data after its introduction in clinical practice, it appears to be effective even in complicated cases of patients, and less toxic than the regimens used until now. The so far low frequency of resistance development both *in vitro* and *in vivo* is significant. Therefore, meropenem-vaborbactam constitutes a promising solution in the treatment of serious infections caused by multidrug-resistant Gram-negative bacteria. However, it is necessary to follow a strict surveillance strategy to ensure its appropriate use in order to minimize the chance of resistance. At the same time, it is vital to continue the search for agents that will fill the gap regarding metallo-β-lactamases and multidrug-resistant *P. aeruginosa* and *A. baumannii*, and maintain an armamentarium against the non-stop evolution of bacteria and their ability to develop resistance to available antibiotics.

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Conflict of interest

All authors declare no conflict of interest.

Περίληψη

Vaborbactam: perspective of a new β-lactamase inhibitor in the antimicrobial chemotherapy

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Οι λοιμώξεις που οφείλονται σε ανθεκτικά στις καρβαπενέμες *Enterobacterales, Pseudomonas aeruginosa* και *Acinetobacter baumannii* αποτελούν παγκοσμίως απειλή για τη δημόσια υγεία και συνδέονται με υψηλά ποσοστά νοσηρότητας και θνητότητας. Η αντοχή οφείλεται κυρίως στην παραγωγή διαφόρων τύπων καρβαπενεμασών. Η βαμπορβακτάμη είναι ένας νέος αναστολέας β-λακταμασών, χημικά προερχόμενος από το βορονικό οξύ και με υψηλή ισχύ έναντι των καρβαπενεμασών τάξης Α, συμπεριλαμβανομένης της KPC. Σε συνδυασμό με τη μεροπενέμη, αποκαθιστά σχεδόν πλήρως τη δραστικότητά της έναντι *Enterobacterales* που παράγουν καρβαπενεμάση KPC. Ωστόσο, έχει περιορισμένη δράση έναντι των ανθεκτικών στις καρβαπενέμες *Pseudomonas aeruginosa* και *Acinetobacter baumannii*. Η κλινική αποτελεσματικότητα και η ασφάλεια του συνδυασμού αξιολογήθηκαν σε δύο κλινικές δοκιμές, τις TANGO I και II, όπου αποδείχθηκε ότι είναι μη-κατώτερος σε σύγκριση με άλλες θεραπευτικές επιλογές. Έχει λίγες σοβαρές ανεπιθύμητες ενέργειες, ειδικά όσον αφορά τη νεφροτοξικότητα. Φαίνεται να διατηρεί χαμηλή τάση για ανάπτυξη αντοχής. Εμφανίζει φαρμακοκινητικές ιδιότητες παρόμοιες με αυτές της μεροπενέμης. Έχει εγκριθεί για χρήση σε ενήλικες με επιπλεγμένες ουρολοιμώξεις και ενδοκοιλιακές λοιμώξεις, νοσοκομειακή πνευμονία και πνευμονία σχετιζόμενη με αναπνευστήρα, καθώς και λοιμώξεις λόγω αερόβιων Gram-αρνητικών οργανισμών σε ενήλικες με περιορισμένες θεραπευτικές επιλογές. Μελέτες χρήσης σε πραγματικές συνθήκες δείχνουν υποσχόμενα ποσοστά ίασης και χαμηλότερα ποσοστά ανεπιθύμητων ενεργειών, ακόμη και σε περιπτώσεις βεβαρυμένων ασθενών.

Λέξεις κλειδιά
αντοχή στις καρβαπενέμες, Klebsiella pneumoniae
καρβαπενεμάση, βαμπορβακτάμη, μεροπενέμη-βαμπορβακτάμη

References

1. van Duin D, Kaye KS, Neuner EA, Bonomo RA. Carbapenem-resistant Enterobacteriaceae: a review of treatment and outcomes. *Diagn Microbiol Infect Dis* 2013; 75:115-120.
2. Cai B, Echols R, Magee G, Arjona Ferreira JC, Morgan G, Ariyasu M *et al.* Prevalence of carbapenem-resistant Gram-negative infections in the United States predominated by *Acinetobacter baumannii* and *Pseudomonas aeruginosa. Open Forum Infect Dis* 2017; 4:ofx176.
3. World Health Organization, 2017. WHO publishes list of bacteria for which new antibiotics are urgently needed. Available online from https://www.who.int/news/item/27-02-2017-who-publishes-list-of-bacteria-for-which-new-antibiotics-are-urgently-needed (last accessed 31 January 2023).
4. Nordmann P, Poirel L. Epidemiology and diagnostics of carbapenem resistance in Gram-negative bacteria. *Clin Infect Dis.* 2019;69(Suppl 7):S521-S528. doi: 10.1093/cid/ciz824.
5. Queenan AM, Bush K. Carbapenemases: the versatile beta-lactamases. *Clin Microbiol Rev* 2007; 20:440-458.
6. Drawz SM, Bonomo RA. Three decades of beta-lactamase inhibitors. *Clin Microbiol Rev* 2010; 23:160-201.
7. Tsivkovski R, Lomovskaya O. Biochemical activity of Vaborbactam. *Antimicrob Agents Chemother* 2020; 64:e01935-19.
8. Lomovskaya O, Sun D, Rubio-Aparicio D, Nelson K, Tsivkovski R, Griffith DC *et al.* Vaborbactam: Spectrum of beta-lactamase inhibition and impact of resistance mechanisms on activity in Enterobacteriaceae. *Antimicrob Agents Chemother* 2017; 61:e01443-17.
9. Hecker SJ, Reddy KR, Totrov M, Hirst GC, Lomovskaya O, Griffith DC *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.
10. Bhowmick, T., Weinstein, M.P. Microbiology of meropenem-vaborbactam: A novel carbapenem beta-lactamase inhibitor combination for carbapenem-resistant Enterobacterales infections. *Infect Dis Ther* 2020; 9:757–767.
11. Goldstein EJ, Citron DM, Tyrrell KL, Merriam CV. 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.
12. Castanheira M, Rhomberg PR, Flamm RK, Jones RN. Effect of the β-lactamase inhibitor vaborbactam combined with meropenem against serine carbapenemase-producing Enterobacteriaceae. *Antimicrob Agents Chemother* 2016; 60:5454-5458.
13. Lapuebla A, Abdallah M, Olafisoye O, Cortes C, Urban C, Quale J *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.
14. 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:e00567-17.
15. Pfaller MA, Huband MD, Mendes RE, Flamm RK, Castanheira M. *In vitro* activity of meropenem/vaborbactam and characterisation of carbapenem resistance mechanisms among carbapenem-resistant Enterobacteriaceae from the 2015 meropenem/vaborbactam surveillance program. *Int J Antimicrob Agents* 2018; 52:144-150.
16. 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:e01904-17.
17. Castanheira M, Doyle TB, Kantro V, Mendes RE, Shortridge D. Meropenem-vaborbactam activity against carbapenem-resistant Enterobacterales isolates collected in U.S. hospitals during 2016 to 2018. *Antimicrob Agents Chemother* 2020; 64:e01951-19.
18. Sabet M, Tarazi Z, Nolan T, Parkinson J, Rubio-Aparicio D, Lomovskaya O *et al*. Activity of meropenem-vaborbactam in mouse models of infection due to KPC-producing carbapenem-resistant Enterobacteriaceae. *Antimicrob Agents Chemother* 2017; 62:e01446-17.
19. 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:e01665-18.
20. Kaye KS, Bhowmick T, Metallidis S, Bleasdale SC, Sagan OS, Stus V *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.
21. Wunderink RG, Giamarellos-Bourboulis EJ, Rahav G, Mathers AJ, Bassetti M, Vazquez J *et al.* Effect and safety of meropenem-vaborbactam versus best-avail-

able therapy in patients with carbapenem-resistant Enterobacteriaceae infections: The TANGO II randomized clinical trial. *Infect Dis Ther* 2018; 7:439-455.
22. Dose-finding, pharmacokinetics, and safety of VABOMERE in pediatric subjects with bacterial infections (TANGOKIDS). Available from https://clinicaltrials.gov /ct2/show/NCT02687906 (last accessed 31 January 2023).
23. Griffith DC, Loutit JS, Morgan EE, Durso S, Dudley MN. Phase 1 study of the safety, tolerability, and pharmacokinetics of the β-lactamase inhibitor vaborbactam (RPX7009) in healthy adult subjects. *Antimicrob Agents Chemother* 2016; 60:6326-6332.
24. Rubino CM, Bhavnani SM, Loutit JS, Morgan EE, White D, Dudley MN *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:e02228-17.
25. Rubino CM, Bhavnani SM, Loutit JS, Lohse B, Dudley MN, Griffith DC. Single-dose pharmacokinetics and safety of meropenem-vaborbactam in subjects with chronic renal impairment. *Antimicrob Agents Chemother* 2018; 62:e02103-17.
26. Wenzler E, Gotfried MH, Loutit JS, Durso S, Griffith DC, Dudley MN *et al.* Meropenem-RPX7009 concentrations in plasma, epithelial lining fluid, and alveolar macrophages of healthy adult subjects. *Antimicrob Agents Chemother* 2015; 59:7232-7239.
27. Jorgensen SCJ, Rybak MJ. Meropenem and Vaborbactam: Stepping up the battle against carbapenem-resistant enterobacteriaceae. *Pharmacotherapy* 2018; 38:444-461.
28. Sabet M, Tarazi Z, Rubio-Aparicio D, Nolan TG, Parkinson J, Lomovskaya O *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:e01969-17.
29. Griffith DC, Sabet M, Tarazi Z, Lomovskaya O, Dudley MN. Pharmacokinetics / Pharmacodynamics of vaborbactam, a novel beta-lactamase inhibitor, in combination with meropenem. *Antimicrob Agents Chemother* 2018; 63:e01659-18.
30. Gaibani P, Giani T, Bovo F, Lombardo D, Amadesi S, Lazzarotto T *et al.* Resistance to ceftazidime/avibactam, meropenem/vaborbactam and imipenem/relebactam in Gram-negative MDR bacilli: Molecular mechanisms and susceptibility testing. *Antibiotics (Basel)* 2022; 11:628.
31. Wilson WR, Kline EG, Jones CE, Morder KT, Mettus RT, Doi Y *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:e02048-18.
32. Dulyayangkul P, Wan Nur Ismah WAK, Douglas EJA, Avison MB. Mutation of *kvr*A causes OmpK35 and OmpK36 porin downregulation and reduced meropenem-vaborbactam susceptibility in KPC-producing *Klebsiella pneumoniae. Antimicrob Agents Chemother* 2020; 64:e02208-19.
33. Tsivkovski R, Lomovskaya O. Potency of vaborbactam is less affected than that of avibactam in strains producing KPC-2 mutations that confer resistance to ceftazidime-avibactam. *Antimicrob Agents Chemother* 2020; 64:e01936-19.
34. Sun D, Rubio-Aparicio D, Nelson K, Dudley MN, Lomovskaya O. Meropenem-vaborbactam resistance selection, resistance prevention, and molecular mechanisms in mutants of KPC-producing *Klebsiella pneumoniae*. *Antimicrob Agents Chemother* 2017; 61:e01694-17.
35. The European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters. Version 12.0, 2022. Available from http://www.eucast.org (last accessed 31 January 2023).
36. Clinical and Laboratory Standards Institute (CLSI). Performance standards for antimicrobial susceptibility testing. 31st ed. CLSI supplement M100. Clinical and Laboratory Standards Institute, USA, 2021.
37. 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; 18:643-655.
38. Vabomere™ (meropenem and vaborbactam) for injection, for intravenous use, package insert. Available from https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209776lbl.pdf (last accessed 31 January 2023)
39. Vaborеme (previously Vabomere), European Medicines Agency. Available from https://www.ema.europa.eu/en/medicines/human/EPAR/vaborem#authorisation-details-section (last accessed 31 January 2023).
40. Shields RK, McCreary EK, Marini RV, Kline EG, Jones CE, Hao B *et al.* Early experience with meropenem-vaborbactam for treatment of carbapenem-resistant Enterobacteriaceae infections. *Clin Infect Dis* 2020; 71:667-671. Erratum in: *Clin Infect Dis* 2020; 70:1265.
41. Alosaimy S, Jorgensen SCJ, Lagnf AM, Melvin S, Mynatt RP, Carlson TJ *et al.* Real-world multicenter analysis of clinical outcomes and safety of meropenem-vaborbactam in patients treated for serious Gram-negative bacterial infections. *Open Forum Infect Dis* 2020; 7:ofaa051.
42. Ackley R, Roshdy D, Meredith J, Minor S, Anderson WE, Capraro GA *et al.* Meropenem-vaborbactam versus ceftazidime-avibactam for treatment of carbapenem-resistant Enterobacteriaceae infections. *Antimicrob Agents Chemother* 2020; 64:e02313-19.

43. Zhang HL, Cressman L, Lautenbach E. Real-world clinical outcomes of meropenem/vaborbactam for treatment of carbapenem-resistant Enterobacterales infections. *J Glob Antimicrob Resist* 2021; 27:299-302.
44. Jorgensen SCJ, McDonald P, Mynatt RP, Pogue JM, Lerner SA, Dhar S *et al.* Averting the post-antibiotic era: successful use of meropenem/vaborbactam for carbapenem-resistant *Serratia marcescens* and *Enterobacter aerogenes* bacteraemia in a haemodialysis patient. *J Antimicrob Chemother* 2018;73:3529-3531.
45. Athans V, Neuner EA, Hassouna H, Richter SS, Keller G, Castanheira M *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:e01551-18.
46. Oliva A, Curtolo A, Volpicelli L, Cogliati Dezza F, De Angelis M, Cairoli S *et al.* Synergistic meropenem/vaborbactam plus fosfomycin treatment of KPC producing *K. pneumoniae* septic thrombosis unresponsive to ceftazidime/avibactam: From the bench to the bedside. *Antibiotics (Basel)* 2021; 10:781.
47. Belati A, Novara R, Bavaro DF, Procopio A, Fico C, Diella L *et al.* Thoracic aorta graft infection by avibactam-resistant KPC-producing *K. pneumoniae* treated with meropenem/vaborbactam: a case report and literature review. *Infez Med* 2022; 30:277-284.
48. Bassetti M, Kanj SS, Kiratisin P, Rodrigues C, Van Duin D, Villegas MV *et al.* Early appropriate diagnostics and treatment of MDR Gram-negative infections. *JAC Antimicrob Resist* 2022; 4:dlac089.
49. Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van Duin D, Clancy CJ. Infectious Diseases Society of America 2022 guidance on the treatment of extended-spectrum β-lactamase producing Enterobacterales (ESBL-E), carbapenem-resistant Enterobacterales (CRE), and *Pseudomonas aeruginosa* with difficult-to-treat resistance (DTR-P. aeruginosa). *Clin Infect Dis* 2022; 75:187-212.
50. Paul M, Carrara E, Retamar P, Tängdén T, Bitterman R, Bonomo RA *et al.* European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines for the treatment of infections caused by multidrug-resistant Gram-negative bacilli (endorsed by European Society of Intensive Care Medicine). *Clin Microbiol Infect* 2022; 28:521-547.