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Thoracic aorta graft infection by avibactam-resistant KPC-producing *K. pneumoniae* treated with meropenem/vaborbactam: a case report and literature review

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SUMMARY

Meropenem/vaborbactam (M/V) is a new carbapenem-carbapenemase inhibitor combination drug active against extensively drug resistant Gram-negative pathogens. Studies about its efficacy and place in therapy are limited in "real-life" and no data are available for deep site infections, like vascular graft infections.
We present a case of a patient successfully treated with M/V for a thoracic aorta graft infection, placed for a traumatic penetrating aortic ulcer, due to an extensively KPC-producing *Klebsiella pneumoniae* resistant to ceftazidime/avibactam.
Furthermore, we conducted a systematic literature review concerning vascular graft infections caused by carbapenem-resistant *Klebsiella pneumoniae* and the papers published until now about the use of M/V for the treatment of ceftazidime/avibactam-resistant *K. pneumoniae*.
Meropenem/vaborbactam is a promising antibiotic for difficult-to-treat Gram-negative bacteria with limited therapeutic options. Only few reports have been published and more studies are needed to assess which is the best place in therapy of M/V.

Keywords: meropenem/vaborbactam, KPC-*Klebsiella pneumoniae,* thoracic aorta graft infection, antimicrobial resistance, hospital acquired infections.

INTRODUCTION

The progressive increase of antimicrobial resistance in recent years, particularly diffuse among Gram-negative bacteria (GNB), represents a major concern for public health in terms of morbidity and mortality, leading to a critical need for new antimicrobials to face this threat [1].

In this scenario, new molecules have been recently commercialized: cefiderocol, imipenem/cilastatin/relebactam and meropenem/vaborbactam represent the newest therapeutic options for "difficult-to-treat" GNB infections but data are still limited to clinical trials or small case series [2, 3].
Of these, meropenem/vaborbactam (M/V) is the first carbapenem/β-lactamase inhibitor combination, which is used to treat multidrug-resistant (MDR) GNB infections, specifically KPC-producing carbapenem-resistant Enterobacteriaceae (KPC-CRE). It combines an old carbapenem (meropenem) with vaborbactam, a non-β-lactam cyclic

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boronic acid pharmacophore, highly efficient at hydrolyzing serine β-lactamases including class A (KPC, CTX-M, SHV, and TEM) and class C (P99, MIR, and FOX) β -lactamases [4, 5].
Interestingly, 90% of carbapenem-resistant GNB tested in a recent *in vitro* study exhibited a minimum inhibitory concentration (MIC) less than or equal to the susceptible Food and Drug Administration (FDA)-approved breakpoint for Enterobacteriaceae (≤4/8 μg/mL), suggesting an important place in therapy of M/V in this setting [6].
Currently, the European Medicines Agency and the FDA approved M/V with limited indications, on the basis of the published trials TANGO I and TANGO II: complicated urinary tract infections (cUTI), complicated intra-abdominal infections (cIAI); hospital-acquired pneumonia (HAP), including ventilator associated pneumonia (VAP), and for the treatment of patients with bacteremia that occurs in association with, or is suspected to be associated with, any of the infections listed above. M/V is also indicated for the treatment of infections due to aerobic GNB in adults with limited treatment options [7-9].
However, important knowledge gaps persist in terms of "real-life" data, including treatment of very complex clinical pictures, such as device/biofilm-related infections by KPC-CRE. For instance, vascular graft/endograft infections (VGEIs) lie within the most challenging and threatening complication of graft implantation. Although uncommon (occurring in 0.2-0.7% of patients), they are associated with a very intricate management, costs, morbidity, and mortality.
In this paper, we report the first case of a thoracic aorta graft infection, due to a KPC-producing *Klebsiella pneumoniae* (KPC-Kp), extensively resistant to antimicrobials, including ceftazidime/avibactam (CAZ/AVI), but effectively treated with M/V.

CASE REPORT

Due to multiple vertebral fractures following an accidental 2-meters-drop, in April 2021 a 71-year-old male was admitted to the Neurosurgery ward of our hospital, where he underwent a surgical vertebral stabilization of D9-D12. Nevertheless, the trauma resulted in paraplegia, sternal fracture, costal fractures, multiple contusive hemorrhagic focuses, and a post-traumatic penetrating aortic ulcer (PAU). After the surgery, he was hos-

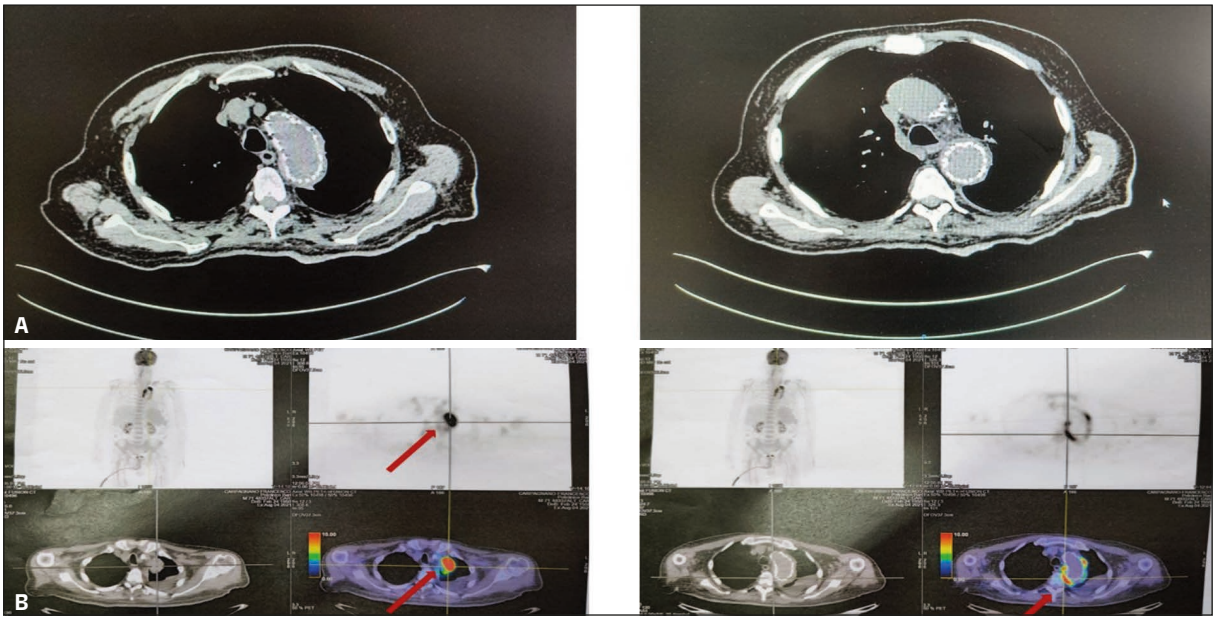

Figure 1 – Imaging. **1a.** Computed tomography. *Note: no evidence of sources of infection. The thoracic aorta graft appeared free from signs of endoleak or infection.* **1b.** 18-FDG-PET/CT. *Note: the red arrows show the areas of radiopharmaceutical hyperaccumulation at the level of the aortic prosthesis. Graft infection, SUV max = 17.6; By-pass infection, SUVmax = 4.3.*

pitalized in the intensive care unit (ICU) where he remained one month, until the discharge to a rehabilitation facility in May 2021. The rectal swab performed at the time of discharge showed a colonization by KPC-Kp, while the culture of tracheal aspirate was positive for carbapenem-resistant *Acinetobacter baumannii*. Unfortunately, we did not have access to the medical records of the previous hospitalizations and administered antibiotic therapies.

He was newly admitted to the vascular surgery unit on May 27th, 2021, to undergo a thoracic aorta graft positioning for PAU with left subclavian artery exclusion and carotid-subclavian bypass. The surgical procedure was well tolerated, and he was discharged back to the rehabilitation facility after few days. Unfortunately, due to the prolonged orotracheal intubation, the patient developed a swallowing disfunction related to the incoordination of the deglutition muscles; therefore, on June 10th a central venous catheter (CVC) was positioned to allow rehydration and parenteral nutrition until full recovery of dysphagia. At the end of June, the patient had fever with chills and hypotension, so he started an empiric therapy with meropenem (2 g, three times daily) and tigecycline (50 mg, two times daily) in the rehabilitation facility, but, for the persistence of symptomatology, on June 28th he was conducted to our Emergency Department. Blood cultures and the culture of the tip of removed CVC resulted all positive for KPC-Kp with a high MIC to CAZ/AVI=4 mg/L (Vitek2 automated system). He also performed a CT-scan with no evidence of sources of infection; also, the thoracic aorta graft appeared free from signs of endoleak or infection (Figure 1a).

On July 6th he was admitted to our ward. The CVC was immediately removed, and the patient became quickly apyretic showing also a significantly reduction of inflammation markers. Moreover, three negative follow-up blood cultures were obtained after CVC removal; accordingly, the therapy with meropenem and tigecycline was stopped. Hence, the patient was transferred to the rehabilitation unit of our hospital. Unfortunately, the patient presented a new episode of fever, chills and hypotension: new blood cultures were performed which resulted positive for KPC-Kp resistant to CAZ/AVI (MIC >8 mg/L with Vitek2 automated system). Microdilution test (Sensititre™, Thermo Fisher Scientific) for colistin and E-test (ETEST® Meropenem/Vaborbactam Liofilchem®) for M/V were performed, showing MIC of 0.5 ug/mL and 3 ug/mL, respectively. According to the clinical breakpoints established by the European Committee on Testing (EUCAST), the isolate was considered susceptible to both M/V and colistin (Table 1). It was not possible to evaluate the mechanism of CAZ/AVI resistance as no sequencing/genetic tests are available in our hospital.

The patient was then evaluated by the Infectious Diseases (IDs) consultant: a combination therapy with M/V 4 gr *tid* in 3-h infusion associated with colistin 9 MIU as first dose followed by 4.5 MIU *bid* in 1-h infusion was started, in accordance with the patient body mass index (26,4 kg/m^2, weight

Table 1 - *Klebsiella pneumoniae* susceptibility testing.

Pathogen	*Klebsiella pneumoniae*		
	Antimicrobial	*MIC*	*Interpretation*
AST-profile	Amoxicillin/ clavulanate	>16	*Resistant*
	Cefepime	>16	*Resistant*
	Cefotaxime	>32	*Resistant*
	Ceftazidime	>32	*Resistant*
	Ceftazidime/ avibactam	>8	*Resistant*
	Ceftolozane/ tazobactam	>8	*Resistant*
	Ciprofloxacin	>2	*Resistant*
	Gentamycin	<1	***Sensitive***
	Imipenem	>8	*Resistant*
	Meropenem	>8	*Resistant*
	Piperacilline/ tazobactam	>64	*Resistant*
	Tobramycin	8	*Resistant*
	Trimetropim/ sulphametoxazole	>160	*Resistant*
	Colistin*	0.5	***Sensitive***
	Meropenem/ vaborbactam**	3	***Sensitive***

Legend: AST = antimicrobial susceptibility test; MIC= Minimum Inhibitory Concentration.
*Tested by broth microdilution.
**Tested by E-test.
Note: the table reports the antibiotic susceptibility test of *Klebsiella pneumoniae* strain isolated in the blood of the patient. It was performed in the laboratory of Microbiology, and referred in accordance with EUCAST breakpoints published in 2021.

78 kg, height 172 cm). Follow up blood cultures were prescribed, starting after 48 hours of effective antimicrobial therapy.
At the 72h-IDs follow-up evaluation, the inflammatory markers were persistently elevated along with fever. Therefore, the patient was transferred back to our ID Unit, suspecting a deep-site infection. On the sixth day of therapy, given the acquisition of the 2 of 3 positive and 1 of 3 negative follow-up blood cultures, and the persistence of high inflammatory markers associated with irregular episodes of low-grade fever, diagnostic tests to seek sources of infection were requested, and colistin was replaced by tigecycline 100 mg *bid* in 1-h infusion in order to ensure a higher activity on a possible deep-site of infection along with a better tolerability.
Consequently, the patient underwent a trans-thoracic echocardiography (negative for endocarditic vegetations) and an 18-FDG PET/CT scan, evidencing an aortic prosthesis infection (SUV max= 17.6) and a by-pass infection (SUV max=4.3) with no other areas of hyperaccumulation of the radiopharmaceutical (Figure 1b). Based on current guidelines on VGEIs, this case was considered compatible with a KPC-Kp-caused thoracic aorta graft infection [10].
Additionally, a new vascular surgery evaluation was performed: a diagnosis of early VGEI was established, but the high risk of mortality contraindicated the procedure of explantation/reimplantation of the graft.
After 3 weeks of combination therapy, thanks to the achieved clinical stability of the patient, and because of a suspected toxicity (hyperbilirubinemia), tigecycline was stopped and M/V was continued until the discharge, for a total of 6 weeks of therapy. Persistent negative blood cultures were obtained during hospitalization, after the start of targeted therapy. No adverse event to M/V was reported.
Consequently, the patient was discharged, in stabilized clinical conditions, with no antibiotic therapy.
According to our internal clinical practice, in absence of oral suppressive chronic antibiotic therapy strategies, the patient was addressed to a tight follow-up, in order to immediately start a new inpatient antibiotic therapy in case of infection recrudescence.
Anyway, after 2 months from discharge, no relapse of the infection was recorded. The patient unfortunately died before completing further follow-up due to a breakthrough pneumonia com-

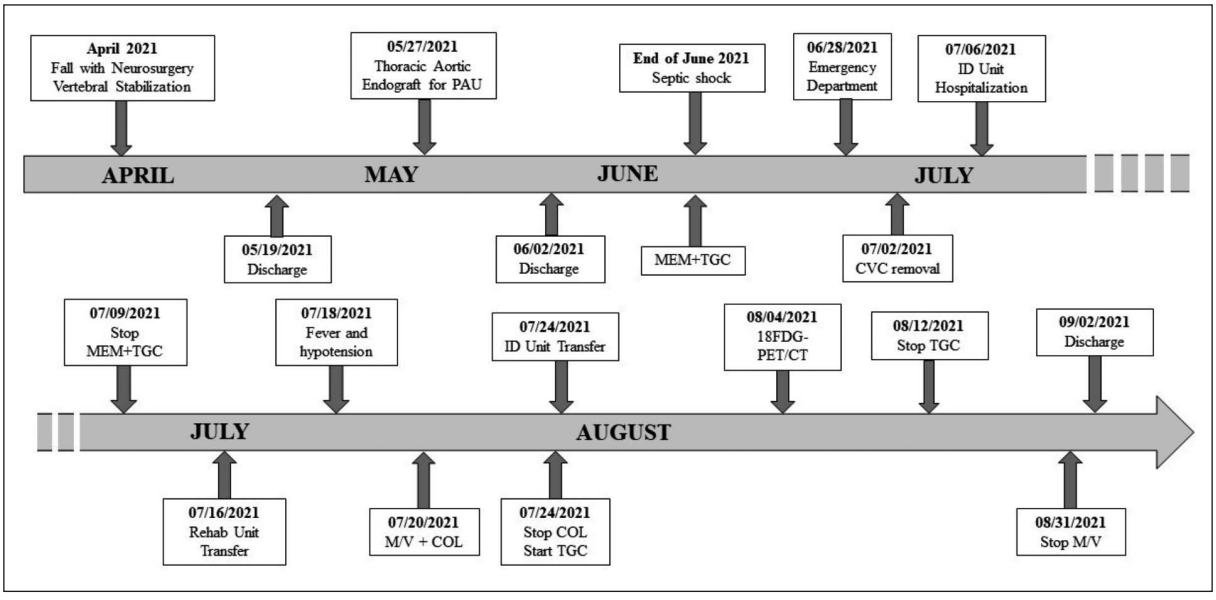

Figure 2 - Timeline of events. *Note: PAU = Penetrating aortic ulcer; MEM = Meropenem; TGC = Tigecycline; CVC = Central Venous Catheter; ID = Infectious Diseases; Rehab = Rehabilitation; M/V = Meropenem/Vaborbactam; COL = Colistin.*

plicated by acute respiratory distress syndrome and acute heart failure.
Timeline of events is summarized in Figure 2.

LITERATURE REVIEW

We conducted a literature search on PubMed, Scopus, Google Scholar, EMBASE and Cochrane Library starting from January 1996, the year when the first KPC-Kp has been identified, to November 2021, in order to identify articles concerning VGEIs caused by KPC-Kp [11]. For this, we included the words "KPC" "carbapenem resistant" matched with "endovascular infections" or "graft infections". Reviews and meta-analyses have been excluded. A total of 514 papers have been screened and finally only 2 papers have been included.
Carbapenem-resistant Enterobacterales are rarely reported as causative agents of VGEIs. Usually, the primary causative agents of these infections are Gram positive bacteria (mostly *Staphylococcus aureus*, Enterococci and coagulase-negative *Staphylococci*) accounting up to 58%, while GNB are reported in 34% of cases [12]. In this scenario, the optimal treatment strategies in VGEIs are still unknown and the management should be decided by a multidisciplinary team, including IDs specialists, vascular surgeons, radiologists, microbiologists, anaesthetists to guide the patient diagnostic and therapeutic pathway.
To date, the only two studies that report of VGEIs due to KPC-Kp, describe respectively a case series (including 3 patients) and a case report [13, 14].
In the study of Yun-Shi Cai *et al.*, three patients received organ transplantation (liver and kidneys) from the same donor with CR-Kp BSI at the time of death [13]. The recipients experienced a graft

Table 2 - Case series and case reports identified by literature search.

Case series						
Ref.	*Authors*	*Type of the study*	*N. cases*	*Goal of the study*	*Outcomes*	*Results (p)*
[16]	Ackley et al.	Multicenter, retrospective cohort study	131	Compare the use of CAZ/AVI with M/V	Clinical success	62% vs 69% (0.49)
					Recurrence	14% vs 11% (1)
					Development of resistance	20% vs 0% (1)
					AE	34% vs 23% (0.27)
[17]	Alosaimy et al.	Real-world, multicenter, retrospective cohort study	126	Real life experience of patients treated with M/V	30-day mortality	18% (-)
					Recurrence	12% (-)
					AE	3.2% (-)
[18]	Shields et al.	Prospective, observational study	20	Real life experience of patients treated with M/V	30-day success rate	65% (-)
					30-day survival rate	90% (-)
					90-day microbiological failure	35% (-)
					Recurrent M/V-R infection	1 pt (-)
Case reports						
Ref.	Authors	Type of the study	Sex, Age	Companion drugs	Diagnosis	Outcome
[19]	Athans et al.	Case report	M, 24	–	Hepatic abscess	Alive
[20]	Oliva et al.	Case report	F, 45	Fosfomycin	Septic thrombosis	Alive
[21]	Tiseo et al.	Case report	F, 68	–	Surgical site infection	Alive

Note: Case series and case reports published in literature have been synthesized in the table. Three case series and three case reports have been found, according to our literature review.
AE = Adverse events; CAZ/AVI = Ceftazidime/avibactam; M/V = Meropenem/Vaborbactam; M/V-R = Meropenem/Vaborbactam resistant; F = female; M = male.

arterial rupture due to sepsis from CR-Kp. The liver recipient developed hepatic artery thrombosis and cIAI (hepatic and peritoneal abscesses) and was treated with multiple percutaneous peritoneal drainage and, according to antibiogram, with sulfamethoxazole and polymixin B for 7 months, with normalization of inflammatory markers and reduction in size of the liver and peritoneal abscesses, but the culture of drainage fluid persistently positive for CR-Kp. Finally, the kidney recipients experienced rupture of renal artery anastomosis and underwent graft nephrectomy and haemodialysis, pending for a new transplantation.

Montelione *et al.* described a case of a patient with a late VGEI caused by CR-Kp, treated with endograft removal and *in situ* aortic reconstruction and a double carbapenem-regimen for 4 weeks, with no recurrence of infection after three years [14].

In addition, another issue of our case was the resistance to CAZ/AVI, which represents, nowadays, the cornerstone of the antibiotic regimen against KPC-Kp [15].

Therefore, in addition to the previous literature review already described, we carried out another literature search on the same databases from 2017, the year of approval by the Food and Drug Administration of M/V, until November 2021, directed to investigate the post-marketing real-life experiences of the use of M/V for the treatment of CAZ/AVI-resistant *K. pneumoniae*. We included the words "vaborbactam" "meropenem/vaborbactam" matched with "ceftazidime/avibactam resistant" or "avibactam resistant". Reviews and meta-analyses have been excluded. A total of 532 articles have been screened and finally only 6 papers have been included, particularly 3 case reports and 3 case series, and are summarized in Table 2 [16-21].

Ackley et al., in a multicentre retrospective cohort study of adults with CRE infections, compared the use of CAZ/AVI vs M/V in a 3-years period, including 131 patients (CAZ/AVI, n=105; M/V, n=26) and neither significant difference in clinical success was observed between groups (62% versus 69%; P=0.49), nor in recurrence rate, but the development of resistance was more common with CAZ/AVI monotherapy [16].

Alosaimy et al. recently published a multicenter, retrospective cohort study including 126 patients treated with M/V for a variety of GNB infections, primarily including KPC-CRE. Thirty-day mortality and recurrences occurred in 18.3% and 11.9%, respectively, and adverse events occurred in 4 patients [17].

Shields et al. described the use of M/V in 20 patients with KPC-CRE at a large academic facility. Success was achieved in 65%, and 30-days survival rate was 90%. Microbiological failure occurred in 35% of patients. Only one case of a patient developing an intra-abdominal infection due to a M/V resistant KPC-3 isolate after 12 days of treatment was reported [18].

DISCUSSION

In our case, since the rarity of VGEIs caused by carbapenem-resistant *Klebsiella pneumoniae*, the suspicion of VGEI was based on the persistence of low-grade fever, elevated inflammatory markers and, particularly, positive follow up blood cultures for KPC-Kp, despite effective antibiotic therapy. Indeed, accordingly to our internal guidelines, follow up blood cultures are usually prescribed in all cases of BSIs, independently of the causative pathogen, and are used to assess the effectiveness of the antibiotic therapy, as well as the potential presence of deep-site infections.

The multidisciplinary team in our case posed the diagnosis of early VGEI (<4 months), that is usually caused by a discontinuation of sterility during implantation (a possible explanation of our case) or a previous thrombus infection; conversely, late VGEIs (>4 months) are mostly caused by hematogenous dissemination [10].

Because of the impossible surgical source control, we prescribed a prolonged course of antimicrobial therapy based on M/V, selected on the basis of the high tolerability and noticeable efficacy on biofilm and deep-site infections [19]. Interestingly, this approach could be feasible in subjects without surgical options, as suggested by multiple studies conducted in this setting, where one-year mortality was similar in both conservatively and surgically treated patients [20-22].

Resistance to CAZ/AVI in the case of KPC-Kp would require both a phenotypic and a genotypic approach in order to better understand the mechanism. These tests should be available in all tertiary care facilities facing up complicated infections, to allow a tailored approach to therapy, considering the pathogen susceptibility. In our case,

there are no genotypic or genomic sequencing tests, but, from *in vitro* studies, it would seem that resistance mutations to CAZ/AVI evidenced until now apparently does not affect sensitivity to M/V, which therefore represents a valid therapeutic alternative option, as demonstrated by phenotypic testing, in which Klebsiella maintained sensitivity to M/V (Table 1) [23].

Our case represents a unique challenge, due to the rarity of VGEIs, especially due to a CAZ/AVI-resistant KPC-Kp. In this case, the use of M/V was crucial in obtaining the suppression of acute infection, followed by a careful "watch and wait" strategy in a patient with deep-site infection not eligible for surgery and no available treatments options for long-term suppressive therapy at home.

In this scenario, the correct place in therapy of new drugs is pivotal: in our experience, M/V could represent a first-line therapy particularly for deep-site KPC-Kp disease and for avibactam-resistant KPC-Kp infections.

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None

Conflict of interests
No author has any conflict of interest to declare.

Ethical approval
The research did not require a formal approval from the ethics committee according to the Italian law since it was performed as an observational retrospective study in the context of normal clinical routines (art.1, leg. decree 211/2003). However, the study was conducted in accordance with the Declaration of Helsinki and national and institutional standards. The patient provided informed consent for the use of his data for research purposes. In any case, data were previously anonymized, according to the requirements set by Italian Data protection Code (leg. Decree 196/2003).

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