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Short Communication

Aggressive joint pharmacokinetic/pharmacodynamic target attainment of TDM-guided continuous infusion meropenem-vaborbactam monotherapy: A valuable strategy for maximizing the microbiological outcome of documented KPC-producing *Enterobacterales* infections?

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ABSTRACT

Objective: To assess whether attaining an aggressive joint pharmacokinetic/pharmacodynamic (PK/PD) target of therapeutic drug monitoring (TDM)-guided continuous infusion (CI) meropenem-vaborbactam monotherapy may be a valuable strategy for maximizing the microbiological outcome of documented KPC-producing *Enterobacterales* infections.

Methods: This retrospective cohort study was performed in patients receiving CI meropenem-vaborbactam monotherapy for KPC-producing *Enterobacterales* infections and undergoing real-time TDM. Free fractions of plasma steady-state concentrations (fC_{ss}) of meropenem and vaborbactam were calculated according to a protein binding of 2% and 33%, respectively. Aggressive joint PK/PD target attainment was defined as a meropenem fC_{ss}/MIC ratio >4 coupled with a vaborbactam free area under time-to-concentration curve (*f*AUC)/target concentration (C_T) ratio >24. Multivariate analysis was performed for assessing potential independent predictors of microbiological failure.

Results: Overall, 55 patients were included. Aggressive joint PK/PD target of meropenem-vaborbactam was attained in 96.3% (53/55) of cases. Among 44/55 patients having follow-up cultures (80.0%), 9 experienced microbiological failure (20.5%), and 2 developed 90-day resistance (4.5%). Continuous renal replacement therapy (OR, 15.00; 95% CI: 1.75–128.40; $P = 0.013$) and intrabdominal infection (OR, 10.00; 95% CI: 1.36–73.33; $P = 0.024$) emerged as independent predictors of microbiological failure. Aggressive joint PK/PD target was non-attained more frequently among patients having microbiological failure than in those having microbiological eradication (22.2% vs. 0.0%; $P = 0.038$), although not statistically significant at multivariate analysis.

Conclusions: Our findings suggest that a TDM-guided monotherapy of documented KPC-producing *Enterobacterales* infections focused on aggressive joint PK/PD target attainment with CI meropenem-vaborbactam could represent a valuable strategy either for granting microbiological cure and for counteracting resistance development.

1. Background

The widespread diffusion of *Klebsiella pneumoniae* carbapenemase (KPC) variants represents nowadays a major health concern, and may make the appropriate choice of antimicrobial treatment challenging [1]. Several international guidance and guidelines

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recommend ceftazidime-avibactam and meropenem-vaborbactam as first-line choices for treating infections caused by KPC-producing *Enterobacterales* [2]. However, some concerns on the use of ceftazidime-avibactam may raise in some settings, since nowadays several KPC variants are producing resistance to this agent [1].

Meropenem-vaborbactam is a novel beta-lactam/beta-lactamase inhibitor combination (BL/BLIc) with valuable *in vitro* activity against class A carbapenemases, including KPC-producing *Enterobacterales* [3]. Different real-world clinical evidence supported its efficacy in the treatment of KPC-producing *Enterobacterales* infections [2]. Notably, according to the IDSA guidance for the treatment of KPC-producing *Enterobacterales*, meropenem-vaborbactam should be slightly preferred over ceftazidime-avibactam, based on the rationale that it may be less prone to resistance development [2]. However, as a consequence of the selective pressure associated with use, resistance is emerging also to this agent [4]. Adopting valuable strategies for counteracting this trend should represent a compelling need in daily clinical practice. In this regard, a recent meta-analysis including critically ill patients having Gram-negative related infections treated with beta-lactams showed that attaining higher PK/PD targets of beta-lactams, defined as aggressive (namely 100% of time with free beta-lactam concentrations persisting above 4-8-fold the MIC [100%$fT_{>4\text{-}8xMIC}$]) may both decrease the risk of microbiological failure and minimize that of resistance occurrence compared to the conservative ones (namely 100% of time with free beta-lactam concentrations persisting above the MIC [100%$fT_{>MIC}$]) [5]. Prolonged or CI delivery emerged as the only independent protective predictor against the risk of early aggressive PK/PD target non-attainment [5]. Based on this assumption, at our hospital we started to administer meropenem-vaborbactam by CI and to optimize aggressive PK/PD target attainment by means of a TDM-guided approach [6]. Preliminary findings in a small case series of 8 critically ill patients having TDM-guided treatment with CI meropenem-vaborbactam for documented ventilator-associated pneumonia (VAP) due to KPC-producing *K. pneumonia* supported the helpfulness of this strategy [7]. Aggressive PK/PD target was attained in all cases and microbiological eradication was granted in the vast majority of them [7].

The aim of this study was to assess whether attaining an aggressive joint PK/PD target of TDM-guided CI meropenem-vaborbactam monotherapy may be a valuable strategy for maximizing the microbiological outcome of documented KPC-producing *Enterobacterales* infections.

2. Methods

This retrospective study included a cohort of adult patients having treatment of documented KPC-producing *Enterobacterales* infections with a TDM-guided monotherapy of CI meropenem-vaborbactam in the period 01st March 2023–31st October 2025 at the IRCCS Azienda Ospedaliero-Universitaria of Bologna, Italy.

Demographic (age, sex, and body mass index), clinical/laboratory [underlying diseases, admission ward, presence of immunosuppression, baseline creatinine clearance (CL_{CR}), need for vasopressors, mechanical ventilation, and/or continuous renal replacement therapy (CRRT), occurrence of augmented renal clearance (ARC)], microbiological (site/type of infection, isolated KPC-producing *Enterobacterales* strain, punctual MIC values of the clinical isolate), meropenem-vaborbactam treatment (baseline daily dosing regimen, overall TDM assessments and number of TDM per patient, plasma meropenem and vaborbactam concentrations, aggressive joint PK/PD target attainment or non-attainment), and outcome data (microbiological eradication/failure, 90-day resistance development, clinical cure, and 30-day mortality rate) were collected in each case. Immunosuppression was defined as the presence of at least one of the following conditions: long-term treatment with corticosteroids and/or biologic and/or antineoplastic agents, solid or hematologic malignancies, solid organ or hematopoietic stem cell transplantation, HIV disease or autoimmune disease [8]. CRRT was implemented always by means of standardized conditions [continuous venovenous hemodiafiltration (CVVHDF) by means of a Prisma Flex System equipped with an AN69 high-flux ST-150 filter membrane with replacement solution delivered post-filter, and with total effluent flow rate set at 30–40 mL/kg/h]. Definition of the different types of infection is detailed in Supplementary materials.

CL_{CR} was estimated according to the CKD-EPI formula, whereas ARC was defined as a normal serum creatinine level coupled with an estimated CL_{CR} > 130 mL/min/1.73m^2 in males and >120 mL/min/1.73m^2 in females.

Meropenem-vaborbactam susceptibility was tested by means of the broth microdilution method (panel provided by Merlin Diagnostika GmbH, Bornheim-Hersel, Germany). The tested MIC values of meropenem ranged from 0.016 to 128 mg/L in presence of a fixed vaborbactam target concentration (C_T) of 8 mg/L, and were interpreted according to the EUCAST guidelines [9]. Microbiological failure was defined as the persistence of the index KPC-producing *Enterobacterales* strain at the infection site documented at follow-up microbiological cultures [6,7]. Microbiological eradication was defined as the absence of the index KPC-producing *Enterobacterales* strain at the infection site after at least 7 days of treatment [6,7]. Resistance development was defined as an increase to >8 mg/L of the MIC value of the index KPC-producing *Enterobacterales* strain within 90-days after starting treatment [9]. Genomic characterization of meropenem-vaborbactam resistant isolates was performed by means of Whole Genome Sequencing, as detailed in the Supplementary materials. Clinical cure was defined as the complete resolution of signs and symptoms of infection associated with documented microbiological eradication at end of treatment, absence of recurrence/relapse at 30-day follow-up, and of attributable mortality due to KPC-related infection [6].

Meropenem-vaborbactam was always started with a loading dose of 2 g/2 g over 3 h immediately followed by a maintenance dose (MD) administered by CI, namely q8h over 8 h infusions [10]. The MD was initially selected based on the patient's CL_{CR} estimate (namely 2 g/2 g q8h over 8 h [12 g/24 h] if CL_{CR} ≥40 mL/min/1.73m^2; 1 g/1 g q8h over 8 h [6 g/24 h] if CL_{CR} 20–39 mL/min/1.73m^2; 0.5 g/0.5 g q8h over 8 h [3 g/24 h] if CL_{CR} 10–19 mL/min/1.73m^2; 0.25 g/0.25 g q8h over 8 h [1.5 g/24 h] if CL_{CR} <10 mL/min/1.73m^2 or in case of intermittent hemodialysis). A full MD was initially administered also to all patients undergoing CVVHDF or having sepsis-associated acute kidney injury to counteract the potential risk of having an underexposure in the first 24–48 hours of treatment.

Subsequently, dosing regimens were adjusted by means of TDM focusing on an aggressive joint PK/PD target attainment. This latter was defined as a meropenem fC_{ss}/MIC ratio >4 (equivalent to 100%$fT_{>4\ x\ MIC}$) coupled with a vaborbactam free area under time-to-concentration curve (fAUC)/target concentration (C_T) ratio > 24 (where C_T is the fixed target vaborbactam concentration threshold used by the EUCAST for testing the *in vitro* standard susceptibility of the agent, namely 8 mg/L) [7]. The vaborbactam AUC was calculated as AUC (mg·h/L) = dose (mg/24 h)/CL (L/h) ratio, where CL was equal to the infusion rate (mg/h)/C_{ss} (mg/L) ratio. Non-attainment was defined as an attainment of only one or none of the two thresholds [7].

TDM of meropenem-vaborbactam was assessed first after at least 24 hours from starting therapy, and subsequently reassessed every 48–72 hours whenever feasible. Total plasma C_{ss} of both meropenem and vaborbactam were measured by means of a validated liquid chromatography-tandem mass spectrometry method [11]. The fC_{ss} were calculated by subtracting from the total C_{ss} the

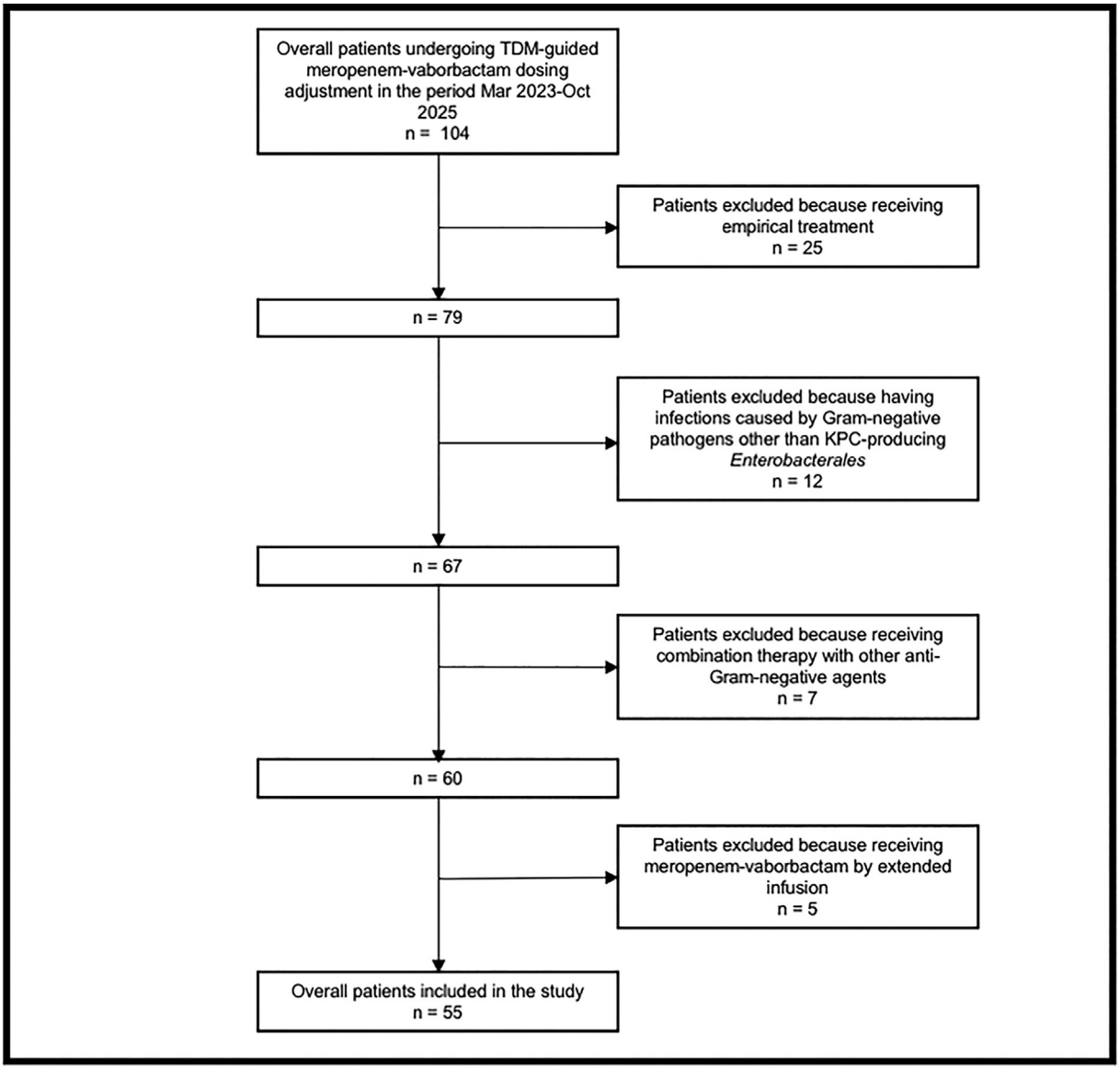

Fig. 1. Flowchart of patients' inclusion and exclusion criteria.

corresponding bound rate based on the plasma protein binding reported in the literature, namely 2% [9] and 33% [3] for meropenem and vaborbactam, respectively.

Demographics and clinical features of included patients were summarized as median and interquartile ranges (IQR) for continuous variables, and as absolute values and percentages for categorical variables. Univariate and multivariate analyses were performed for testing variables potentially associated with microbiological outcome. In univariate analysis, categorical variables were compared by means of the Fisher's exact test or the chi-squared test, whereas the continuous ones were compared by means of the Mann–Whitney U test. All the independent covariates being associated at the univariate analysis with a P value <0.10 were included in the multivariate logistic regression model. Adjustment for age and sex was also performed for minimizing the risk of confounding factors. Statistical analysis was performed by means of MedCalc for Windows (MedCalc statistical software, version 19.6.1, MedCalc Software Ltd., Ostend, Belgium), and significance was defined as a P value <0.05.

3. Results

Overall, 55 patients having treatment of a documented KPC-producing *Enterobacterales* infection with a TDM-guided monotherapy of CI meropenem-vaborbactam were retrieved (Fig. 1), and the corresponding demographics and clinical features are summarized in Table 1.

The median (IQR) age was 61 years (55.0–73.5 years), with a male preponderance (70.9%). Solid organ transplantation (15 cases; 27.2%), bowel perforation (14 cases; 25.5%), and acute pancreatitis (6 cases; 10.9%) were the most frequent underlying diseases. Approximately half of patients were immunosuppressed (26 cases; 47.3%), and most were ICU admitted (33 cases; 60.0%). Mechanical ventilation and vasopressors support were required in 25 (45.5%) and 24 cases (43.6%), respectively. Some patients experienced ARC during treatment (6 cases; 10.9%) and/or needed CVVHDF (6 cases; 10.9%).

HAP/VAP and BSI (14 cases each; 25.5%) were the two most prevalent types of infection, followed by IAI (10 cases; 18.2%). A

Table 1
Demographics and clinical features of included patients treated with CI meropenem-vaborbactam monotherapy for documented infections caused by KPC-producing *Enterobacterales*.

Demographics and clinical features	Patients (n = 55)
Demographics	
Age (years) (Median; [IQR])	61.0 (55.0-73.5)
Gender (male/female; n [%])	39/16 (70.9/29.1)
Body mass index (Kg/m^2) (Median; [IQR])	24.2 (21.8-26.2)
Obesity (n [%])	4 (7.3)
Underlying disease (n [%])	
Solid organ transplantation	15 (27.2)
Bowel perforation	14 (25.5)
Acute pancreatitis	6 (10.9)
Oncohematological disease	5 (9.1)
Urolithiasis	5 (9.1)
Hepatic cirrhosis	4 (7.3)
Acute respiratory distress syndrome	4 (7.3)
Cardiocirculatory arrest	1 (1.8)
Metformin-associated lactic acidosis	1 (1.8)
Immunosuppression	26 (47.3)
Setting (n [%])	
ICU	33 (60.0)
Medical ward	13 (23.6)
Surgical ward	7 (12.7)
Hematology	2 (3.6)
Pathophysiological conditions (n [%])	
Vasopressors (n [%])	24 (43.6)
Mechanical ventilation (n [%])	25 (45.5)
Baseline CLC_R (mL/min/1.73m^2) (Median; [IQR])	85.5 (39.6-108.3)
Continuous veno-venous hemodiafiltration (n [%])	6 (10.9)
Augmented renal clearance (n [%])	6 (10.9)
Site of infection (n [%])	
HAP/VAP	14 (25.5)
BSI	14 (25.5)
IAI	10 (18.2)
UTI + BSI	5 (9.1)
HAP/VAP + BSI	4 (7.3)
UTI	3 (5.4)
IAI + HAP/VAP	3 (5.4)
IAI + BSI	2 (3.6)
Overall HAP/VAP	21 (38.2)
Overall BSI	25 (45.5)
Isolated KPC-producing isolates (n [%])	
Klebsiella pneumoniae	51 (92.8)
Escherichia coli	2 (3.6)
Klebsiella pneumoniae + *Escherichia coli*	2 (3.6)
Meropenem-vaborbactam MIC (Median; [IQR])	0.5 (0.06-2)
Meropenem-vaborbactam treatment regimens	
Starting daily dosing regimens (g) (Median; [IQR])	2 g/2 g q8h CI (1.5 g/1.5 q8h CI – 2 g/2 g q8h CI)
Average meropenem fC_{ss} (mg/L) (Median; [IQR])	25.2 (15.5-42.8)
Average vaborbactam fC_{ss} (mg/L) (Median; [IQR])	21.4 (11.9-36.3)
Average meropenem fC_{ss}/MIC ratio (Median; [IQR])	78.4 (24.5-311.8)
Average vaborbactam fAUC/C_T ratio (Median; [IQR])	74.7 (58.8-128.1)
Overall TDM assessments	155
No. of TDM per patient (Median; [IQR])	2 (1-4)
Aggressive joint PK/PD target attainment (n [%])	53 (96.4)
Outcome (n [%])	
Microbiological eradication*	35/44 (79.5)
Clinical cure	38 (69.1)
90-day resistance development*	2/44 (4.5)
30-day mortality rate	10 (18.2)

* 44/55 patients had follow-up cultures

AUC: area under time-to-concentration curve; BSI: bloodstream infection; CL_{CR}: creatinine clearance; C_{ss}: steady-state concentrations; C_T: target concentration; HAP: hospital-acquired pneumonia; IAI: intrabdominal infection; ICU: intensive care unit; IQR: interquartile range; MIC: minimum inhibitory concentration; PK/PD: pharmacokinetic/pharmacodynamic; UTI: urinary tract infection; VAP: ventilator-associated pneumonia.

total of 57 KPC-producing *Enterobacterales* isolates were yielded, being *K. pneumoniae* the most frequent (53 cases, 51 of which alone and 2 in association with an *E. coli*). All of the isolates were susceptible to meropenem-vaborbactam at baseline. The median (IQR) MIC was 0.5 mg/L (0.06-2 mg/L), and only 1 strain had a borderline MIC value of 8 mg/L.

Overall, 155 TDM assessments were performed, accounting for a median (IQR) of 2 (1–4) assessments per patient. Median (IQR) meropenem fC_{ss}/MIC ratio and vaborbactam fAUC/C_T ratio were 78.4 (24.5–311.8) and 74.7 (58.8–128.1), respectively. Aggressive joint PK/PD target was attained in 53/55 cases (96.4%). Both patients with non-attainment had ARC, and one of the two had a

Table 2
Univariate and multivariate analysis comparing patients having microbiological eradication vs. microbiological failure treated with meropenem-vaborbactam for documented infections caused by KPC-producing *Enterobacterales*.

Variables	Microbiological eradication (n = 35)	Microbiological failure (n = 9)	Univariate *P* value	Multivariate analysis* (OR; 95% CI)
Demographics				
Age (Median; [IQR])	62.0 (55.5-74.0)	61.0 (48.0-62.0)	0.50	
Gender (male/female; n [%])	26/9 (74.3/25.7)	6/3 (66.7/33.3)	0.69	
Body mass index (Median; [IQR])	24.5 (21.8-26.5)	24.2 (23.4-26.2)	0.83	
Obesity (n; [%])	4 (11.4)	0 (0.0)	0.57	
Immunosuppression (n; [%])	17 (48.6)	4 (44.4)	0.99	
Setting (n; [%])				
ICU	22 (62.9)	6 (66.7)	0.99	
Pathophysiological conditions				
Vasopressors (n; [%])	14 (40.0)	7 (77.8)	0.06	
Mechanical ventilation (n; [%])	20 (57.1)	4 (44.4)	0.71	
Baseline CL_{CR} (mL/min/1.73m^2; Median; [IQR])	86.0 (37.9-112.0)	82.0 (33.0-104.0)	0.83	
Continuous veno-venous hemodiafiltration (n; [%])	2 (5.7)	3 (33.3)	**0.05**	**15.00 (1.75-128.40)** ***P* = 0.013**
Augmented renal clearance (n; [%])	3 (8.6)	2 (22.2)	0.25	
Site of infection (n; [%])				
HAP/VAP	8 (22.9)	2 (22.2)	0.99	
BSI	11 (31.4)	3 (33.3)	0.99	
IAI	3 (8.6)	3 (33.3)	0.09	**10.00 (1.36-73.33)** ***P* = 0.024**
UTI + BSI	4 (11.4)	0 (0.0)	0.57	
HAP/VAP + BSI	2 (5.7)	1 (11.1)	0.51	
UTI	2 (5.7)	0 (0.0)	0.99	
IAI + HAP/VAP	3 (8.6)	0 (0.0)	0.99	
IAI + BSI	2 (5.7)	0 (0.0)	0.99	
Meropenem-vaborbactam MIC (n; [%])				
≥2 mg/L	11 (31.4)	2 (22.2)	0.70	
Meropenem-vaborbactam treatment regimens				
Aggressive PK/PD target non-attainment (n; [%])	0 (0.0)	2 (22.2)	**0.038**	

BSI: bloodstream infection; CI: confidence interval; CL_{CR}: creatinine clearance; HAP: hospital-acquired pneumonia; IAI: intrabdominal infection; ICU: intensive care unit; IQR: interquartile range; MIC: minimum inhibitory concentration; OR: odds ratio; PK/PD: pharmacokinetic/pharmacodynamic; UTI: urinary tract infection; VAP: ventilator-associated pneumonia.

clinical isolate exhibiting borderline susceptibility to meropenem-vaborbactam (8 mg/L).

Clinical cure was reported of 69.1% (38/55 patients), and the 30-day mortality rate was of 18.2%. Among the 44 out of 55 patients having microbiological cultures available at follow-up, microbiological eradication was of 79.5% (35/44), and the 90-day resistance development was of only 4.5% (2/44, both having IAI). Detailed results of the WGS analysis is available as Supplementary materials. No patient discontinued meropenem-vaborbactam treatment due to safety concerns or experienced drug-related neurotoxicity. No *Clostridium difficile* infection occurred during meropenem-vaborbactam treatment.

Univariate and multivariate analyses testing potential predictors of microbiological outcome among the 44 patients having microbiological cultures available at follow-up are reported in Table 2. Independent predictors of microbiological failure that emerged at the multivariate analysis were CVVHDF (OR, 15.00; 95% CI: 1.75–128.40; $P = 0.013$) and IAI (OR, 10.00; 95% CI: 1.36–73.33; $P = 0.024$). Although aggressive joint PK/PD target non-attainment was associated with the risk of microbiological failure at the univariate analysis (22.2% vs. 0.0%; $P = 0.038$), this association disappeared at the multivariate analysis.

4. Discussion

To the best of our knowledge, this is the first study that investigated the impact of an aggressive joint PK/PD target attainment of TDM-guided CI meropenem-vaborbactam monotherapy on the microbiological outcome of documented KPC-producing *Enterobacterales* infections. Overall, the findings showed that the aggressive joint PK/PD target was attained in the vast majority of cases, resulting both in high microbiological eradication rate (79.5%) and in low prevalence of resistance development to meropenem-vaborbactam (4.5%). Additionally, CRRT and IAI were identified as independent predictors of microbiological failure.

The findings of our strategy are in agreement with those of a recent meta-analysis showing that a TDM-guided approach of beta-lactams was significantly associated with a higher likelihood of PK/PD target attainment (RR 1.85; 95% CI: 1.08-3.16) and with a better microbiological cure (RR, 1.14; 95% CI: 1.03-1.27) compared to standard approach [12].

The propensity of causing aggressive PK/PD target non-attainment with meropenem-vaborbactam is lower than observed with ceftazidime/avibactam under the same conditions [13]. The well balanced proportion existing between the two components in the fixed formulation of meropenem-vaborbactam (1:1) may favor the aggressive joint PK/PD target attainment compared to ceftazidime-avibactam (4:1) [13]. Factors affecting non-attainment in our cohort were ARC and/or borderline susceptibility of the clinical isolate (MIC of 8 mg/L), consistently with findings concerning other beta-lactams [5]. Indeed, the only two patients experiencing aggressive joint PK/PD target non-attainment had these underlying conditions, one both and the other only the former one. Intensifying the meropenem-vaborbactam dosing regimen up to 2 g/2 g q6h over 6 h by CI resulted successful in attaining the aggressive joint PK/PD target in that having ARC, but unfortunately not in the other one having both ARC and an infection caused by a KPC-producing isolate with a borderline MIC value of 8 mg/L. In this latter case, the intensified dosing approach was insufficient to achieve a meropenem fC_{ss} of 32 mg/L. Irrespective of this, the fact that microbiological failure occurred in both cases may pose questions about the need of early aggressive joint PK/PD target attainment for maximizing the likelihood of microbiological eradication.

The high microbiological eradication rate observed in this study is in line with what we previously documented with other novel BL/BLIc by applying a similar approach of treatment optimization (81.0%–91.4%) [7,14,15]. Interestingly, patients having microbiological failure experienced more frequently aggressive joint PK/PD target non-attainment. This is consistent with previous evidence concerning other novel BL/BLIc [14,15], although the limited sample size of our cohort hindered the possibility of testing this variable as being significantly associated at multivariable analysis.

In our cohort, the resistance development rate to meropenem-vaborbactam was below the range of the prevalences observed previously in some other comparable settings (4.9%–13%), although caused by similar molecular mechanisms [16,17]. Indeed, it should be recognized that in another one [18] the reported resistance rate was even lower (1.7%), but a potential selection bias could not be ruled out in that study since it was not specified whether or not all of the included patients underwent follow-up microbiological cultures. Unfortunately, the limited number of cases with resistance development precluded us from performing a statistical analysis looking at the impact that PK/PD target attainment might have had. However, this is consistent with the findings of the aforementioned meta-analysis showing that aggressive PK/PD target attainment of beta-lactams was very protective against the risk of resistance development (OR, 0.06; 95% CI: 0.01–0.29) [5]. Likewise, we showed in a recent pre-post quasi-experimental study that aggressive joint PK/PD target attainment of CI ceftazidime-avibactam was protective against 90-day resistance development to ceftazidime-avibactam in the management of KPC-producing *Klebsiella pneumoniae* infections (OR, 0.07; 95% CI: 0.01–0.69) [15]. The relevance of attaining an aggressive PK/PD target for minimizing resistance emergence in clinical practice may be supported by some preclinical data. A hollow-fibre infection model showed that during exposure of Gram-negatives to beta-lactams a Cmin/MIC ratio of 3.8 was significantly associated with regrowth prevention avoiding resistance development [19].

IAI and CRRT were independent predictors of microbiological failure. Regarding IAI, several factors may explain this finding. First, it should not be overlooked that adequate source control may play a key role in granting cure in this type of infection. A prospective observational study found that among 104 patients receiving meropenem-vaborbactam for the treatment of multidrug-resistant Gram-negative infections, source control was independently associated with a reduced risk of clinical failure (OR, 0.16; 95% CI: 0.03–0.89; $P = 0.036$) [20]. Second, the activity of meropenem-vaborbactam against KPC-producing *Enterobacterales* could be affected by the inoculum effect when dealing with deep-seated infections, namely IAI. A preclinical study testing the susceptibility of meropenem-vaborbactam among 40 carbapenemase-producing *Enterobacterales* clinical isolates showed that in 50% of these MIC values increased by at least 8-fold when dealing with a high inoculum (10^7 CFU/mL) compared to the standard one (10^5 CFU/mL) [21]. Third, the penetration of this agent in complicated IAI may sometimes be limited. A case series of critical orthotopic liver transplant recipients receiving treatment with CI meropenem-vaborbactam showed that aggressive joint PK/PD target at the infection sited was attained only in 3 out of 4 cases [22].

Regarding CVVHDF as a predictor of microbiological failure, the finding during treatment with CI meropenem-vaborbactam was consistent with those reported under similar conditions with ceftazidime-avibactam [23]. Indeed, several factors may hinder aggressive joint PK/PD target attainment in this scenario (namely, the effluent flow rate, the presence of residual diuresis and or of highly-adsorptive filters) [24]. However, it should also be mentioned that a recent population PK study conducted among 18 critically ill patients with various degrees of renal dysfunction (including 3 undergoing CVVHDF with a total effluent flow rate of 25 mL/kg/h) found that the standard 2 g/2 g q8h over 3-h MD regimen was likely of attaining only a conservative PK/PD target against pathogens having an MIC value up to only 1 mg/L [25].

Attaining an aggressive rather than a conservative PK/PD target could theoretically pose some questions in terms of enhanced selective pressure and/or potential increased toxicity. Indeed, the former apprehension seems unjustified. In fact, it should be noticed that the real-time TDM-guided strategy allowed to decrease the meropenem-vaborbactam dosing regimens in the vast majority of cases. This was due to the fact that delivering meropenem-vaborbactam by CI may allow to attain an aggressive joint PK/PD target with lower daily dosing regimens compared to both intermittent and/or extended infusion [6]. This is especially true whenever highly susceptible clinical isolates are detected by means of broth microdilution method, as occurred in most cases of our cohort. By the way, this approach was effective also in limiting the rate of resistance development to meropenem-vaborbactam. Regarding the latter apprehension, delivering lower daily dosing regimens by CI may potentially minimize the risk of dose-dependent toxicity, as witnessed by the fact that no case of neurotoxicity attributable to meropenem-vaborbactam was reported. This is consistent with other previous studies concerning aggressive PK/PD target attainment with meropenem in which the rate of toxicity was equal to 0.0%–0.7% [26,27].

Limitations of our study should be recognized. The retrospective monocentric study design and the limited sample size could limit the generalizability of our findings. The lack of a control group could limit the generalizability of our findings in setting different from ours. Microbiological cultures at follow-up were unavailable in approximately 20% of cases, thus potentially representing a selection bias. Total meropenem and vaborbactam concentrations were measured, and the free fractions were only calculated according to the plasma protein binding retrieved in the literature. The potential role of source control on microbiological outcome of IAI was not assessed. Conversely, the adoption of stringent inclusion criteria to make the sample highly homogenous, the absence of confounding factors such as combination therapy and the use of an adjusted multivariate regression analysis may represent points of strength.

In conclusion, our findings suggest that a TDM-guided monotherapy of documented KPC-producing *Enterobacterales* infections with CI meropenem-vaborbactam focused on aggressive joint PK/PD target attainment could represent a valuable strategy either for granting microbiological cure or for counteracting resistance development to meropenem-vaborbactam. Prospective studies are warranted for hopefully confirming our findings.

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Ethical approval: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the local ethical committee (No. 308/2021/Oss/AOUBo on 17 May 2021, EM232–2022_308/ 2021/Oss/AOUBo on 16 March 2022, and EM449–2023_308/ 2021/Oss/AOUBo on 17 April 2024, and CE AVEC: 272/2024/Sper/AOUBo on 16 May 2024). Informed written consent was waived due to the retrospective and observational nature of the study.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijantimicag.2026.107811.

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