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Real-world clinical outcomes of meropenem/vaborbactam for treatment of carbapenem-resistant Enterobacterales infections

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Abstract

Objectives: Real-world data regarding the effectiveness of meropenem/vaborbactam (MVB) in the treatment of carbapenem-resistant Enterobacterales (CRE) infections remain limited. In this retrospective case series, we describe the outcomes of patients who received MVB for serious CRE infections.

Methods: This study included adult patients with MVB-susceptible CRE infection who received ≥48 h of MVB. Clinical and microbiological outcomes were ascertained via chart review.

Results: Among 15 patients with CRE infection who were treated with MVB, 9 (60.0%) had a positive clinical response. Among five patients with CRE bone and joint infection, three (60.0%) experienced a positive clinical response. One patient developed a microbiologically confirmed recurrent CRE infection and one patient developed *Clostridioides difficile* infection.

Conclusion: MVB was well tolerated and effective for the majority of patients in this case series.

Keywords

Meropenem/vaborbactam; Carbapenem-resistant Enterobacterales; CRE; Multidrug-resistant organisms

1. Introduction

Infections caused by carbapenem-resistant Enterobacterales (CRE) pose a significant clinical challenge due to the limited armamentarium of effective therapies and poor outcomes [1].

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Fortunately, the past several years have brought forth new treatment options for CRE infections, including meropenem/vaborbactam (MVB), a β-lactam/β-lactamase inhibitor combination antibiotic with in vitro activity against *Klebsiella pneumoniae* carbapenemase (KPC) and other class A carbapenemases [2,3]. The results of TANGO II, a small pathogen-directed randomised clinical trial, support the efficacy of MVB in the treatment of CRE infections [4]. However, real-world clinical data remain scarce and existing data are primarily limited to short courses of therapy for respiratory, urinary tract and bloodstream infections. In this study, we describe the clinical outcomes of patients who received MVB for treatment of CRE infections.

2. Materials and methods

This retrospective case series was conducted at the Hospital of the University of Pennsylvania, Penn Presbyterian Medical Center, Pennsylvania Hospital and The Specialty Hospital at Rittenhouse. Adult inpatients who received ≥48 h of MVB between 1 January 2018 and 30 September 2020 and had a clinical culture with CRE within 14 days prior to MVB initiation were identified via medication administration records and microbiology reports. Five patients were excluded due to inclusion in a separate study [5]. Two patients were excluded due to documentation by infectious diseases specialists that the CRE culture represented colonisation. Two patients were excluded due to MVB non-susceptibility as per Clinical and Laboratory Standards Institute (CLSI) guidelines [minimum inhibitory concentration (MIC) ≥8/8 μg/mL], and one was excluded due to lack of MVB susceptibility data.

Microbial identification and antimicrobial susceptibility testing were performed using standard semi-automated techniques (VITEK® 2; bioMérieux). CRE was defined as Enterobacterales bacteria with resistance to at least one carbapenem antibiotic according to CLSI breakpoints. Because the study sites did not routinely perform carbapenemase testing, carbapenemase production was not included in the study definition. MVB susceptibility was determined by Etest (bioMérieux).

Clinical data were abstracted via chart review. A positive clinical response was defined as the composite of survival, resolution or significant improvement in signs and symptoms of infection, and lack of recurrent infection or microbiological failure at 30 days after infection onset. A negative clinical response was defined as failure to meet one or more of these criteria. The clinical outcome was deemed uncertain if the patient had recurrent or intermittent symptoms not clearly attributable to the index infection. Among patients for whom follow-up cultures were obtained at the discretion of the clinical provider, ‘microbiological success’ and ‘microbiological failure’ were defined as microbiological eradication or persistent isolation of the index CRE species, respectively, and were ascertained at 3 days and 7 days following MVB initiation. Infection recurrence was defined as a culture with the same organism plus signs/symptoms of infection following end of treatment (EOT) and clinical resolution of the index infection. Recurrence was uncertain if signs/symptoms recurred following clinical resolution of the index infection but cultures were not obtained. Tests of statistical inference were not performed owing to the small sample.

3. Results

Among 15 patients who received ≥48 h of MVB, the median (range) age was 62 (36–90+) years and 9 (60.0%) were male, with a median (range) Charlson comorbidity index of 6 (0–10). Two patients (13.3%) were receiving renal replacement therapy. Among seven patients (46.7%) who were in the intensive care unit at the time of MVB initiation, the median (range) Sequential Organ Failure Assessment (SOFA) score was 7 (2–13), 5 (71.4%) were receiving mechanical ventilation and 3 (42.9%) were receiving vasopressors.

Infections comprised bone and joint infections (5; 33.3%), primary bacteraemia (3; 20.0%), complicated intra-abdominal infection (2; 13.3%), pneumonia (2; 13.3%), urinary tract infection (2; 13.3%) and soft tissue infection with secondary bacteraemia (1; 6.7%) (Table 1). CRE species comprised *K. pneumoniae* (10; 66.7%), *Escherichia coli* (3; 20.0%), *Klebsiella aerogenes* (1; 6.7%) and *Citrobacter koseri* (1; 6.7%). Seven patients (46.7%) had a polymicrobial index culture. A total of 14 patients (93.3%) received other anti-Gram-negative antibiotics prior to MVB initiation, including 13 on inactive agents (4 cefepime, 4 meropenem, 1 ceftazidime/avibactam, 1 ceftriaxone, 1 ertapenem, 1 levofloxacin and 1 piperacillin/tazobactam) and 1 patient on an active agent (ceftazidime/avibactam). The median (range) time from culture acquisition to MVB initiation was 73 (25–261) h. The median (range) duration of MVB therapy was 17 (4–50) days. Five patients (33.3%) received renally dose-adjusted MVB regimens and 9 patients (60.0%) received combination antimicrobial therapy. All patients received infectious diseases consultation, 8 (53.3%) had a surgical primary team or consultation and 4 (26.7%) received interventional radiology consultation. Nine patients (60.0%) underwent source control interventions.

Clinical response was positive among 9 patients (60.0%), negative among 5 patients (33.3%) and uncertain in 1 patient (6.7%). The median (range) time from culture acquisition to MVB initiation among patients with a positive and negative clinical response were 78 (35–191) h and 73 (25–261) h, respectively. Among the nine patients with a positive clinical response, one developed recurrent MVB-susceptible CRE bacteraemia within 30 days of EOT despite adequate source control of the index infection, one had recurrent signs/symptoms of the index infection within 30 days of EOT despite adequate source control but did not undergo repeat cultures, and seven had no recurrence within 90 days of EOT. Among the five patients with a negative clinical response, one died of a related cause, one died of an unrelated cause prior to EOT, and three (60.0%) were determined by the infectious diseases consultant to have inadequate source control (two with incomplete drainage of intra-abdominal abscesses and one with retention of infected arthroplasty hardware).

Among six patients with repeat cultures within 3 days of therapy, four (66.7%) had a positive microbiological response. Of the two patients with a negative microbiological response at Day 3, one had a positive microbiological response by Day 7 and one did not have additional cultures.

One patient (6.7%) developed *Clostridioides difficile* infection (CDI) on Day 2 of MVB, noting that other broad-spectrum antibiotics had been administered prior to MVB. No other

drug-related adverse reactions were documented. Twelve patients (80.0%) were alive at 30 days and 90 days after EOT.

4. Discussion

More than one-half of patients (60.0%) in this case series experienced a positive clinical response to treatment of CRE infection using MVB. These findings are similar to those of the TANGO II trial, which reported 65.6% clinical cure at EOT, as well as other early reports of MVB use in clinical practice [4–10]. Among patients with a negative clinical response, most had suboptimal source control of deep-seated CRE infections, for which MVB efficacy data do not otherwise exist. Notably, our study is the first to describe outcomes of patients who received prolonged courses of MVB for CRE bone and joint infections, with the majority (60.0%) experiencing a positive clinical response. Larger studies are needed to validate these findings.

MVB was well tolerated by most patients, including 10 (66.7%) who received ≥14 days of therapy. One patient developed CDI while on MVB, although a causal relationship cannot be confirmed owing to receipt of other antibiotics. Recurrence was uncommon, with only one episode of culture-proven recurrence with retained MVB susceptibility. This study has several limitations. The small sample size and single-centre nature limit the generalisability of the findings. Additionally, limited follow-up microbiology data were available because repeat cultures were not obtained on a routine basis. Larger studies are also needed to further characterise real-world outcomes, treatment-related adverse events, and the incidence and mechanisms of treatment-emergent resistance to MVB.

In conclusion, this case series demonstrates the potential utility of MVB in the treatment of serious CRE infections, including bone and joint infections.

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Highlights

- 60% of patients with carbapenem-resistant Enterobacterales infection improved on meropenem/vaborbactam (MVB).
- Recurrent infection was uncommon with MVB.
- First description of MVB for carbapenem-resistant Enterobacterales osteoarticular infection.

Table 1

Clinical characteristics and outcomes of patients treated with meropenem/vaborbactam (MVB) for infections caused by carbapenem-resistant Enterobacterales (CRE)

Age (years)	Sex	CRE species (source)	Other susceptibilities	Primary infection	Major comorbidities	ICU	Source control	MVB dosing regimen (CrCl)[a]	Duration of therapy (days)	Clinical response	Microbiological response at Day 3/7	Recurrence free at Day 30/90
83	F	*K. pneumo* (tissue)	AMK, GEN, MIN	PJI	CKD, DM	N	Partial	2 g q12h (31 mL/min)	45	Neg.	ND/ND	−/−
62	M	*K. pneumo* (urine)	CZA	UTI	DLBCL, IBD	Y	N/A	2 g q12h (22 mL/min)	4	Neg.	Pos./Pos.	−/−
38	F	*C. Koseri* (tissue)	AMK, CZA, SXT	Osteomyelitis	DM	N	Yes	Full dose[b]	41	Pos.	ND/ND	UC/−
53	M	*K. pneumo* (blood)	AMK, CZA, GEN, TET, SXT, TOB	Soft tissue abscess with secondary bacteraemia	CLD	N	Yes	Full dose[b]	14	Pos.	Pos./Pos.	N/−
63	M	*E. coli* (tissue)	CZA, GEN, LVX	Osteomyelitis	PVD	N	Yes	Full dose[b]	39	Pos.	ND/ND	Y/Y
46	M	*E. coli* (abscess)	AMK, CZA, SXT	Intra-abdominal abscess	CKD, DM, SOT	N	Yes	Full dose[b]	27	Pos.	ND/ND	Y/Y
52	F	*K. pneumo* (sputum)	AMK, CZA, GEN	VAP	CAD, CHF, CKD, DM	Y	N/A	Full dose[b]	7	Neg.	Neg./−	−/−
79	F	*K. pneumo* (blood)	CZA	CLABSI	CHF, CLD, DM	Y	Yes	2 g q8h (33 mL/min)	17	Pos.	Neg./Pos.	Y/Y
53	M	*E. coli* (tissue)	AMK, CZA, GEN, SXT, TOB	Osteomyelitis/ SS TI	CHF, CLD, CVA, DM, ESRD, PVD	N	Yes	1 g q12h (<15 mL/min)	50	UC	ND/ND	UC/−
62	M	*K. pneumo* (sputum)	CZA, SXT	PNA	mSCC	Y	N/A	Full dose[b]	8	Pos.	ND/Pos.	Y/Y
36	M	*K. aerogenes* (abscess)	AMK, GEN, SXT, TOB	Intra-abdominal abscess	None	Y	Partial	Full dose[b]	7	Neg.	ND/ND	−/−
82	F	*K. pneumo* (tissue)	CZA	Osteomyelitis	CKD, COPD, DM	N	Yes	Full dose[b]	34	Pos.	ND/ND	Y/Y
70	M	*K. pneumo* (blood)	None	Primary bacteraemia	ALL, CAD, CHF	Y	N/A	Full dose[b]	14	Pos.	Pos./Pos.	Y/Y
90+	F	*K. pneumo* (urine)	AMK, CZA, GEN, TET, SXT, TOB	UTI	CAD	Y	N/A	2 g q8h (60 mL/min)	5	Neg.	ND/ND	−/−

Age (years)	Sex	CRE species (source)	Other susceptibilities	Primary infection	Major comorbidities	ICU	Source control	MVB dosing regimen (CrCl)[a]	Duration of therapy (days)	Clinical response	Microbiological response at Day 3/7	Recurrence free at Day 30/90
68	M	*K. pneumo* (blood)	AMK, CZA, FDC	Primary bacteraemia	CAD, COPD, PVD	N	N/A	Full dose[b]	27	Pos.	Pos./Pos.	Y/Y

ALL, acute lymphoblastic leukaemia; AMK, amikacin; CAD, coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease; *C. koseri, Citrobacter koseri*; CLABSI, central line-associated bloodstream infection; CLD, chronic liver disease; COPD, chronic obstructive pulmonary disease; CrCl, creatinine clearance; CVA, cerebrovascular accident; CZA, ceftazidime/avibactam; DLBCL, diffuse large B-cell lymphoma; DM, diabetes mellitus; *E. coli, Escherichia coli*; ESRD, end-stage renal disease; FDC, cefiderocol; GEN, gentamicin; IBD, inflammatory bowel disease; ICU, intensive care unit; *K. aerogenes, Klebsiella aerogenes*; *K. pneumo, Klebsiella pneumoniae*; LVX, levofloxacin; MIN, minocycline; mSCC, metastatic squamous cell carcinoma; N, no; N/A, not applicable; ND, not determined; Neg., negative response; PJI, prosthetic joint infection; PNA, pneumonia; Pos., positive response; PVD, peripheral vascular disease; q12h, every 12 h; q8h, every 8 h; SOT, solid organ transplant; SSTI, skin and soft-tissue infection; SXT, trimethoprim/sulfamethoxazole; TET, tetracycline; TOB, tobramycin; UC, uncertain; UTI, urinary tract infection; VAP, ventilator-associated pneumonia; Y, yes; –, not applicable.

[a] CrCl calculated using the Cockcroft–Gault equation.

[b] MVB full dose = 4 g q8h.