Real-world, Multicenter Experience With Meropenem-Vaborbactam for Gram-Negative Bacterial Infections Including Carbapenem-Resistant Enterobacterales and Pseudomonas aeruginosa

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Background. We aimed to describe the clinical characteristics and outcomes of patients treated with meropenem-vaborbactam (MEV) for a variety of gram-negative infections (GNIs), primarily including carbenpemem-resistant Enterobacterales (CRE).

Methods. This is a real-world, multicenter, retrospective cohort within the United States between 2017 and 2020. Adult patients who received MEV for ≥72 hours were eligible for inclusion. The primary outcome was 30-day mortality. Classification and regression tree analysis (CART) was used to identify the time breakpoint (BP) that delineated the risk of negative clinical outcomes (NCOs) and was examined by multivariable logistic regression analysis (MLR).

Results. Overall, 126 patients were evaluated from 13 medical centers in 10 states. The most common infection sources were respiratory tract (38.1%) and intra-abdominal (19.0%) origin, while the most common isolated pathogens were CRE (78.6%). Thirty-day mortality and recurrence occurred in 18.3% and 11.9%, respectively. Adverse events occurred in 4 patients: nephrotoxicity (n = 2), hepatotoxicity (n = 1), and rash (n = 1). CART-BP between early and delayed treatment was 48 hours (P = .04). MEV initiation within 48 hours was independently associated with reduced NCO following analysis by MLR (adjusted odds ratio, 0.277; 95% CI, 0.081–0.941).

Conclusions. Our results support current evidence establishing positive clinical and safety outcomes of MEV in GNIs, including CRE. We suggest that delaying appropriate therapy for CRE significantly increases the risk of NCOs.

Keywords. carbenpemem-resistant Enterobacterales; gram-negative infections; meropenem-vaborbactam; multidrug-resistant.

The prevalence of carbenpemem-resistant Enterobacterales (CRE) has increased dramatically over recent years, causing >13 000 nosocomial infections and contributing to >1000 deaths annually in the United States [1]. CRE requires novel antibiotics with activity against these multidrug-resistant (MDR) organisms. Klebsiella pneumoniae carbenpememase (KPC) is an Ambler class A enzyme that utilizes serine at the active site to hydrolyze almost all beta-lactam (BL) antibiotics and is the most prevalent carbenpememase in the United States [2]. Combination therapy (CT) with 2 or even 3 antibiotics has become the standard of care for suspected CRE by necessity [3]. However, this historical approach is now challenged by the arrival of novel anti-CRE agents with established efficacy and improved safety profiles, particularly in high-risk patients (ie, those with chronic renal insufficiency and/or immunocompromised), who ultimately better represent the patient population with CRE [1, 4, 5].

Meropenem-vaborbactam (MEV) is a novel boronic acid beta-lactamase inhibitor (BLI) combined with a well-known carbenpemem that exhibits activity against MDR Enterobacterales, including KPC-producing strains [6].
The US Food and Drug Administration (FDA) approved MEV for the management of complicated urinary tract infections on the basis of the TANGO I trial [7, 8]. In TANGO I, MEV was associated with improved overall success (defined as clinical cure or improvement and microbiological eradication) when compared with piperacillin-tazobactam meeting the prespecified margin for noninferiority. In another trial, TANGO II, MEV was associated with improved clinical cure, decreased mortality, and decreased adverse events when compared with the best available therapy against a variety of CRE infections [9]. Since then, MEV has been used in clinical practice at a wider scale and for indications beyond those evaluated in the TANGO I and TANGO II trials [8]. Noninferiority studies do not optimally address outcomes in specific patient populations where new agents maybe most beneficial [10, 11]. This introduces a tremendous challenge for clinicians when attempting to extrapolate the results of noninferiority clinical trials to patients who were excluded from them. In fact, these patients benefit the most from these novel agents in a real-world setting. Thus, real-world studies that are conducted after initial drug approval are essential for clinicians, as they provide invaluable health outcomes information regarding the utility of newly approved drugs in specific conditions and/or patient populations beyond conventional randomized controlled trials (RCTs) and tend to include those who are older, have more critical illness or a more immunocompromised state, or have chronic end organ damage such as renal insufficiency [10, 12, 13].

Therefore, we sought to describe the clinical characteristics, microbiology, and clinical outcomes of patients treated with MEV for MDR gram-negative infections (GNIs) in the real-world setting.

METHODS

Study Design and Population
We conducted a retrospective, multicenter study at 13 academic and community centers in the United States between September 2017 and July 2020. Patients were eligible for inclusion if they met the following criteria: (1) age ≥ 18 years and (2) receipt of ≥ 72 hours of MEV for suspected or confirmed MDR GNIs. Only the first eligible MEV treatment course during the study period was included.

Ethical Review
This study design and work were reviewed and approved by the Wayne State University Human Investigational Review Board and the DMC Research Review Committee before initiation.

Patient Consent
Patient consent was not required for this retrospective analysis.

Data Collection and Study Definitions
For eligible patients, demographics, comorbid conditions, microbiology, and clinical and treatment data were extracted from the electronic medical record and entered into Research Electronic Data Capture (REDCap; Vanderbilt University) [14]. All cultures, bacterial identifications, and antibiotic susceptibilities were performed at each center according to local procedures. Minimum inhibitory concentration (MIC) results were interpreted per the Clinical and Laboratory Standards Institute (CLSI), and CRE were defined as Enterobacteriaceae intermediate or resistant to carbapenems using the current US Centers for Disease Control and Prevention criteria [15]. MEV susceptibility testing was done using Etest or Liofilchem based on availability. Variables associated with GNI as well as infection source were determined based on clinical notes and microbiological/diagnostic reports. Onset of GNI was based on the date and time when the index culture was collected. The Charlson Comorbidity Index (CCI) was used to measure the degree of patient comorbidity. Severity of illness was assessed using the Acute Physiology and Chronic Health evaluation II (APACHE II) score and the Sequential Organ Failure Assessment (SOFA) score at GNI onset [16, 17]. Creatine clearance (CrCl) and glomerular filtration rate (GFR) were calculated based on the Cockcroft-Gault and Chronic Kidney Disease–Epidemiology Collaboration equations, respectively [18]. The CrCl was calculated relative to the index culture. Because the GFR is the primary recommendation for MEV dosing, it was calculated relative to the MEV start time. Appropriate, under–, or over–renally adjusted doses of MEV were defined according to the GFR package insert instructions [19]. Nephrotoxicity was defined as an increase in serum creatinine (≥ 0.5 mg/dL or ≥ 50% from baseline, whichever was greater, on 2 consecutive measurements while on MEV and up to 72 hours following the last dose). Nosocomial GNIs were defined as infections with index culture obtained ≥ 48 hours after admission. CT was defined as receiving a concomitant gram-negative targeted antibiotic for ≥ 48 hours with MEV. Recurrence was defined as microbiological recurrence while on treatment or within 30 days of the end of MEV treatment.

Outcome
The primary outcome was 30-day mortality. Secondary clinical end points included 90-day mortality, 30-day recurrence, and hospital length of stay. Safety outcomes that were presumed to be attributable to MEV included nephrotoxicity, dermatological reactions, hematological reactions, central nervous system disturbances, gastrointestinal (GI) intolerances, Clostridioides difficile–associated diarrhea, and others. All clinical and safety outcome time points were measured from time of culture collection. Nephrotoxicity was evaluated in patients not receiving renal replacement therapy or in hemodialysis patients at the time of MEV initiation.
Descriptive statistics were used to evaluate patients’ demographics. Nominal data were reported as percentages and frequencies, and continuous data were reported as medians and interquartile ranges (IQRs) or means and SDs, as appropriate. The t test and Mann-Whitney U were used for continuous variables that were parametric and nonparametric, respectively, as appropriate. Classification and regression tree (CART) analysis was performed to determine the time to start MEV that was most predictive of negative clinical outcomes (NCOs). In this analysis, patients with unknown index culture dates were excluded. Additionally, because we are assessing the impact of timely initiation of MEV only, patients who received other appropriate antibiotics for GNIs were excluded. Negative clinical outcomes were defined as 30-day mortality and/or 30-day microbiological recurrence measured from the index culture collection date. Time to start MEV, along with all the variables associated with NCOs, was assessed in a similar manner to the primary analysis. When performing CART, the minimum parent node was specified at 30 cases, and the terminal node at 15 cases. Multivariable logistic regression was used to assess the independent predictors of NCOs while adjusting for confounding variables. Clinically relevant variables were selected for model entry based on bivariate analysis at a P value <.2; when the number of patients in subgroups was too small to allow for meaningful analysis, the subgroups were collapsed into single composite variables. These variables were entered into the model simultaneously and removed using a backward stepwise approach. Covariates were retained in the model if the P value for the likelihood ratio test for their removal was <.1. The variance inflation factor was used to assess the multicollinearity of covariates in the model, with values in the acceptable range of 1–5 considered acceptable. The Hosmer-Lemeshow goodness-of-fit test was used to assess the model’s fit. All tests were 2-tailed, with P values ≤.5 considered statistically significant. IBM SPSS software, version 26.0 (SPSS, Inc., Chicago, IL, USA), was used for all analyses.

RESULTS

Patient Baseline Demographics and Clinical and Infection Characteristics

Demographics

Overall, 126 patients were included from 13 academic medical centers and community hospitals located in 10 states. A description of patient baseline, clinical, and infection characteristics is displayed in Table 1. In general, patients had a median age (IQR) of 56.0 (37.0–68.0) years and were mostly male (79, 62.7%) and of Caucasian race (60, 47.6%). Patients had a high burden of medical comorbidity, with a median APACHE II score (IQR) of 18.0 (12.0–26.0), a median SOFA score (IQR) of 7 (4–10), and a median CCI score (IQR) of 4.0 (2.0–6.0). The CrCl median (IQR) was 28.3 (20.1–55.7) mL/min, and the

<table>
<thead>
<tr>
<th>Table 1. Baseline Demographics and Clinical and Infection Criteria</th>
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<tbody>
<tr>
<td>Criteria</td>
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</tr>
<tr>
<td>Demographics</td>
</tr>
<tr>
<td>Age, y</td>
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<tr>
<td>Age ≥65 y</td>
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<tr>
<td>Sex, male</td>
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<td>Race</td>
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<tr>
<td>Caucasian</td>
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<td>Others</td>
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<tr>
<td>BMI</td>
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<td>BMI ≥30 kg/m²</td>
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<td>Baseline serum creatinine</td>
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<tr>
<td>CrCl</td>
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<tr>
<td>CrCl &gt;50 mL/min</td>
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<td>CrCl 30–49 mL/min</td>
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<td>CrCl 15–29 mL/min</td>
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<tr>
<td>CrCl &lt;15 mL/min</td>
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<tr>
<td>Residence before admission</td>
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<tr>
<td>Home</td>
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<tr>
<td>Transfer from outside hospital</td>
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<tr>
<td>Nursing home, skilled nursing facility, long-term care facility</td>
</tr>
<tr>
<td>Others</td>
</tr>
<tr>
<td>Comorbid conditions</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
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<tr>
<td>Chronic pulmonary disease</td>
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<tr>
<td>Moderate to severe kidney disease or on chronic dialysis</td>
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<tr>
<td>Chronic dialysis</td>
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<tr>
<td>Connective tissue disease</td>
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<tr>
<td>Cystic fibrosis</td>
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<tr>
<td>Dementia</td>
</tr>
<tr>
<td>Diabetes disease, any</td>
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<tr>
<td>Without end organ damage</td>
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<tr>
<td>With end organ damage</td>
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<tr>
<td>Heart failure</td>
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<tr>
<td>Hemiplegia</td>
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<td>Immunodeficient condition, any</td>
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<td>AIDS (CD4 &lt;200)</td>
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<td>HIV</td>
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<tr>
<td>Leukemia</td>
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<tr>
<td>Lymphoma</td>
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<tr>
<td>Tumor without metastasis</td>
</tr>
<tr>
<td>Tumor with metastasis</td>
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<td>Liver disease, any</td>
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<tr>
<td>Mild</td>
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<tr>
<td>Moderate or severe liver disease</td>
</tr>
<tr>
<td>Myocardial infarction</td>
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<tr>
<td>No conditions</td>
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<tr>
<td>Peptic ulcer disease</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
</tr>
<tr>
<td>MDR risk factors</td>
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<tr>
<td>Admitted from nursing home or extended care facility</td>
</tr>
<tr>
<td>Chronic dialysis in 30 d before index culture</td>
</tr>
<tr>
<td>Colonization with resistant organisms</td>
</tr>
<tr>
<td>Home infusion</td>
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<tr>
<td>Home wound care</td>
</tr>
</tbody>
</table>
The majority had a CrCl of 15–29 mL/min (50, 39.7%). The GFR median (IQR) was 67.5 (28.0–116.5) mL/min/1.73 m$^2$, and the majority had a GFR of $\geq$ 50 mL/min/1.73 m$^2$ (71, 56.4%). The most common MEV dose was 4 g every 8 hours (60, 51.7%), followed by 2 g every 12 hours (27, 23.3%). Overall, 81 (64.2%) received the appropriate dose based on renal function, 25 (19.8%) received lower doses, and 20 (15.8%) received higher/wrong doses. Nearly half of the cohort (62, 49.2%) was residing in the intensive care unit (ICU) at any point. The majority of patients had been exposed to prior antimicrobials for >24 hours in the 90 days before index culture (88, 69.8%), and patients were often previously infected with an MDR organism (49, 38.9%). Overall, patients with CRE (n = 99) shared similar demographics and clinical and infection characteristics with the entire cohort.

### Infection Characteristics

The most common infection sources were respiratory tract (48, 38.1%), intra-abdominal (24, 19.0%), and urinary tract (17, 13.5%). Most of the infections (74, 58.7%) were nosocomial, with a median time from admission to index culture collection (IQR) of 19.8 (7.6–33.7) days. Polymicrobial infections were 44.1%.

### Table 1. continued

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Population (n = 126)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior antimicrobials $&gt;24$ h in $90$ d before index culture</td>
<td>88 (69.8)</td>
</tr>
<tr>
<td>Prior infection with resistant organisms</td>
<td>49 (38.9)</td>
</tr>
<tr>
<td>Prior hospitalization for at least 48 h in 90 d before index culture</td>
<td>83 (65.9)</td>
</tr>
<tr>
<td>Prior surgery in 30 d preceding index culture</td>
<td>16 (12.7)</td>
</tr>
<tr>
<td>PWID</td>
<td>8 (6.3)</td>
</tr>
<tr>
<td>Sources of infection</td>
<td></td>
</tr>
<tr>
<td>Bone and joint</td>
<td>3 (2.4)</td>
</tr>
<tr>
<td>Infective endocarditis</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>Intraabdominal</td>
<td>24 (19.0)</td>
</tr>
<tr>
<td>Intravenous catheter</td>
<td>4 (3.2)</td>
</tr>
<tr>
<td>Other$^i$</td>
<td>2 (1.6)</td>
</tr>
<tr>
<td>Primary bacteremia</td>
<td>12 (9.5)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>48 (38.1)</td>
</tr>
<tr>
<td>Mechanically ventilated for 48 h before pneumonial</td>
<td>25 (19.8)</td>
</tr>
<tr>
<td>Skin and soft tissue</td>
<td>13 (10.3)</td>
</tr>
<tr>
<td>Urinary</td>
<td>17 (13.5)</td>
</tr>
<tr>
<td>Unknown</td>
<td>2 (1.6)</td>
</tr>
<tr>
<td>Pathogens targeted</td>
<td></td>
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<tr>
<td>Carbapenem-resistant pathogen</td>
<td>99 (78.6)</td>
</tr>
<tr>
<td>Acinetobacter baumannii</td>
<td>2 (1.6)</td>
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<tr>
<td>Citrobacter freundii</td>
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<tr>
<td>Enterobacter cloacae</td>
<td>21 (16.7)</td>
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<tr>
<td>Escherichia coli</td>
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<td>Klebsiella aerogenes</td>
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<tr>
<td>Klebsiella oxytoca</td>
<td>4 (3.2)</td>
</tr>
<tr>
<td>Klebsiella pneumoniae</td>
<td>53 (42.1)</td>
</tr>
<tr>
<td>Morganella morgani</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>Proteus mirabilis</td>
<td>4 (3.2)</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa$^i$</td>
<td>11 (8.7)</td>
</tr>
<tr>
<td>Serratia marcescens</td>
<td>4 (3.2)</td>
</tr>
<tr>
<td>Stenotrophomonas maltophilia</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>Markers of disease progression</td>
<td></td>
</tr>
<tr>
<td>APACHE II</td>
<td>18.0 (12.0–28.0)</td>
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<tr>
<td>APACHE $\geq$30</td>
<td>15 (11.9)</td>
</tr>
<tr>
<td>CCI</td>
<td>4.0 (2.0–6.0)</td>
</tr>
<tr>
<td>CCI $\geq$5</td>
<td>54 (42.9)</td>
</tr>
<tr>
<td>MEV dosing</td>
<td></td>
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<tr>
<td>4 g every 8 h</td>
<td>61 (48.7)</td>
</tr>
<tr>
<td>Correct dose</td>
<td>55 (77.5)</td>
</tr>
<tr>
<td>2 g every 8 h</td>
<td>31 (24.6)</td>
</tr>
<tr>
<td>Correct dose</td>
<td>8 (57.1)</td>
</tr>
<tr>
<td>2 g every 12 h</td>
<td>8 (6.3)</td>
</tr>
<tr>
<td>Correct dose</td>
<td>5 (25.0)</td>
</tr>
<tr>
<td>1 g every 12 h</td>
<td>23 (18.3)</td>
</tr>
<tr>
<td>Correct dose</td>
<td>13 (61.9)</td>
</tr>
<tr>
<td>Others$^i$</td>
<td>3 (2.4)</td>
</tr>
<tr>
<td>Others factors</td>
<td></td>
</tr>
<tr>
<td>Inhaled antibiotics, any</td>
<td>20 (15.9)</td>
</tr>
<tr>
<td>Aztreonam</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>Colistin</td>
<td>13 (10.3)</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>6 (4.8)</td>
</tr>
<tr>
<td>Combination therapy for $\geq$48 h$^j$</td>
<td>43 (34.1)</td>
</tr>
<tr>
<td>Aminoglycoside</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>Aztreonam</td>
<td>6 (4.8)</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>1 (0.8)</td>
</tr>
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</table>

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation; BMI, body mass index; CCI, Carlson Comorbidity Index; CD4, cluster of differentiation 4; COPD, chronic obstructive pulmonary disease; DVT, deep venous thrombosis; IQR, interquartile range; MDR, multidrug resistant; MEV, meropenem-vaborbactam; OA, osteoarthritis; PWID, person who inject drugs; SOFA, Sequential Organ Failure Assessment; TIA, transient ischemic attack.

$^a$Data presented as median (IQR) and/or n (percentages) as appropriate

$^b$Stroke or TIA.

$^c$Asthma or COPD.

$^d$Hemodialysis or peritoneal dialysis.

$^e$OA or rheumatic arthritis.

$^f$Chronic hepatitis without cirrhosis.

$^g$Portal hypertension or cirrhosis.

$^h$DVT, chronic venous disease.

$^i$Suggestive of ventilator-associated pneumonia.

$^j$Other included prosthetic artiervenous graft (n = 1), retroperitoneal infection (n = 1).

Only 8 patients were targeted by MEV only for Pseudomonas aeruginosa, while the remaining (n = 3) patients had other pathogens that were primarily targeted by MEV.

In = 1, each, received 4 g q12, 2 g q24, and 1 g q24.

Combination therapy occurred in 7 (87.5%) patients with P aeruginosa and 36 (30.5%) patients with other pathogens.

Others include ampicillin-sulbactam, cefepime, doxycycline, and eravacycline (n = 1, each).

### Table 1. continued

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Population (n = 126)</th>
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<tbody>
<tr>
<td>Colistin</td>
<td>5 (4.0)</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>2 (0.6)</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>7 (5.6)</td>
</tr>
<tr>
<td>Minocycline</td>
<td>6 (4.8)</td>
</tr>
<tr>
<td>Polymyxin B</td>
<td>5 (4.0)</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>2 (1.6)</td>
</tr>
<tr>
<td>TMP-SMX</td>
<td>5 (4.0)</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>6 (4.8)</td>
</tr>
<tr>
<td>Others$^i$</td>
<td>4 (3.2)</td>
</tr>
<tr>
<td>Intensive care upon index culture</td>
<td>62 (49.2)</td>
</tr>
<tr>
<td>SOFA score</td>
<td>7 (4–10)</td>
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</table>
identified in 15 (11.9%) patients. Positive blood cultures were demonstrated in 40 (31.7%) patients (n = 12 primary bacteremia, n = 9 intra-abdominal source, n = 8 respiratory tract, n = 4 intravenous catheter, n = 3 urinary tract, n = 1 infective endocarditis, n = 2 unknown, n = 1 other).

A total of 232 GN isolates were cultured from the entire cohort. CRE were isolated in 99 (78.6%) culture specimens. The majority were K. pneumoniae (53/99, 53.5%), followed by Escherichia coli (25/99, 25.3%), Enterobacter spp. (24/99, 24.2%), and Citrobacter freundii (4/99, 4%).

Among strains that were tested for MEV susceptibility, K. pneumoniae (n = 43), E. cloacae (n = 16), and E. coli isolates (n = 15), the MIC \(50\) (range) was 0.064/8 (0.032/8–8/8) mg/L, 0.38/8 (0.047/8–6.00/8) mg/L, and 0.219/8 (0.023/8–4.0/8) mg/L, respectively. For P. mirabilis (n = 3), the MIC \(50\) (range) was 0.094/8 (0.064/8–0.25/8) mg/L. For P. aeruginosa (n = 2), the MIC \(50\) (range) was 18.0 (4/8–32/8). For A. baumannii (n = 1), C. freundii (n = 1), and M. morganii (n = 1), the MIC \(50\) was 256/8, 0.094/8, and 0.38/8, respectively. The S. marcescens MEV MIC \(50\) was not reported.

Among strains that were tested for ceftazidime/avibactam (CZA) susceptibility, the MIC \(50\) (range) was 2.0/4 (0.25/4–256/4) mg/L for K. pneumoniae (n = 43), 3.0/4 (0.25/4–256/4) mg/L for E. cloacae (n = 14), and 0.75/4 (0.125/4–256/4) mg/L for E. coli (n = 15) isolates. As for P. aeruginosa (n = 5), the CZA MIC \(50\) (range) was 16/4 (2.0/4–256/4). For P. mirabilis (n = 2), the CZA MIC \(50\) (range) was 0.185/4 (0.12/4–0.25/4) mg/L, while for C. freundii (n = 2) it was 2.75/4 (1.5/4–4/4) mg/L. The A. baumannii and S. marcescens isolates had a CZA MIC \(50\) of 256/4 and ≤8/4 mg/L, respectively. The M. morganii CZA MIC \(50\) was not reported.

Among non-CRE strains (n = 27) that were tested for meropenem susceptibility, the MIC \(50\) was 0.125 (0.125–4) for E. coli (n = 4), 6 [4–8] for P. aeruginosa (n = 2), 8 for A. baumannii (n = 1), and 0.125 for for K. pneumoniae (n = 1).

### Table 2. Treatment-Related Outcomes

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total Study (n = 126)</th>
<th>PsA Spp. (n = 8)*</th>
<th>Non PsA Spp. (n = 118)</th>
<th>CRE Spp. (n = 99)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active antibiotics before MEV*</td>
<td>31 (24.6)</td>
<td>4 (50.0)</td>
<td>27 (22.9)</td>
<td>24 (24.2)</td>
</tr>
<tr>
<td>Time to active antibiotics, h</td>
<td>14.3 (0.0–75.5)</td>
<td>41.7 (0.05–83.2)</td>
<td>14.3 (0.0–74.3)</td>
<td>36.5 (0.75–75.2)</td>
</tr>
<tr>
<td>ID consult</td>
<td>125 (99.2)</td>
<td>7 (87.5)</td>
<td>118 (100)</td>
<td>99 (100.0)</td>
</tr>
<tr>
<td>ID consult within 48 h</td>
<td>93 (73.8)</td>
<td>6 (75.0)</td>
<td>87 (73.7)</td>
<td>71 (71.7)</td>
</tr>
<tr>
<td>Time to ID consult, h</td>
<td>6.7 (0.0–48.9)</td>
<td>0.0 (0.0–8.3)</td>
<td>8.6 (0.0–62.5)</td>
<td>11.1 (0.0–56.8)</td>
</tr>
<tr>
<td>Surgical consult</td>
<td>39 (30.9)</td>
<td>3 (37.5)</td>
<td>36 (30.5)</td>
<td>35 (35.4)</td>
</tr>
<tr>
<td>Source control*</td>
<td>40 (31.7)</td>
<td>3 (37.5)</td>
<td>37 (31.4)</td>
<td>35 (35.4)</td>
</tr>
<tr>
<td>Time to MEV, h</td>
<td>78.6 (29.8–124.3)</td>
<td>81.0 (56.2–116.7)</td>
<td>78.6 (28.5–126.5)</td>
<td>85.1 (48.6–133.1)</td>
</tr>
<tr>
<td>MEV duration, d</td>
<td>11.7 (6.9–15.2)</td>
<td>14.4 (5.3–15.2)</td>
<td>11.7 (6.0–14.9)</td>
<td>11.8 (6.7–16.0)</td>
</tr>
</tbody>
</table>

Abbreviations: ID, infectious diseases; MEV, meropenem vaborbactam; PsA, Pseudomonas aeruginosa.

*All values represent number (%) or median (interquartile range).

*Patients were grouped in this group if Pseudomonas aeruginosa was the only pathogen targeted by MEV. There are (n = 3) patients with Pseudomonas aeruginosa and other pathogens who are grouped in others (n = 118).

*Active antibiotics were amikacin (n = 7), ceftazidime-avibactam (n = 2), ceftriaxone (n = 3), etrapenem (n = 1), levofloxacine (n = 1), meropenem (n = 4), pipicillin-tazobactam (n = 1), polymyxin B (n = 2), tigecycline (n = 2), TMP-SMX (n = 1), tobramycin (n = 1), other (n = 1).

*Source control includes the following: debridement (n = 10), intravenous catheter removal (n = 3), valvular repair (n = 1), new prostatic valve (n = 1), amputation (n = 1), other (n = 19).

### Infection Treatment Course and Clinical Outcomes

Nearly all patients received an infectious diseases (ID) consultation (125, 99.2%), and the majority were consulted within 48 hours (93, 73.8%). In all sites (n = 13), MEV requires ID consult and/or stewardship approval. Nearly a third of patients (39, 31.0%) received a surgical consult, and among these, 31 (24.6%) received a surgical intervention. Further MEV treatment information is described in Table 2. Over half of patients (74, 58.7%) did not have follow-up cultures. Only 34.1% of MEV patients were on CIT; of these, only 6 had polymicrobial infections. Patients’ outcomes are described in Table 3. In the entire cohort, 30-day mortality occurred in 23 (18.3%) patients. Among those (n = 23), only 12 (52.2%) received the appropriate package insert–recommended dose based on renal function, while 7 (5.5%) received lower doses and 4 (3.2%) received higher doses. Additionally, only 3 (13.0%) had polymicrobial infections, 16 (69.6%) had nosocomial infections, and 22 (95.7%) received monotherapy with MEV for the GNI. No patients with P. aeruginosa (n = 2) experienced 30-day or 90-day mortality. Infection sources among patients who experienced 30-day mortality (n = 23) were respiratory (n = 12), intra-abdominal (n = 4), primary bacteremia (n = 2), skin and soft tissue (n = 2), unknown (n = 2), and urinary tract (n = 1). Thirty-day recurrence occurred in 15 (11.9%), where recurrence occurred in 4 during treatment with MEV and in 11 within 30 days of the end of treatment.

Thirty-day readmission occurred in 23 (18.3%), and 90-day mortality occurred in 40 (31.7%) patients. The median length of hospital stay (IQR) was 34.5 (17.8–62.3) days. None of the isolates from patients with available repeat cultures (n = 25) demonstrated MEV resistance. As illustrated in Table 3, outcomes were fairly similar between patients who had CRE and Pseudomonas spp. isolated.

At least 1 adverse event was documented for 4 (3.1%) patients. These included acute kidney injury in 2 (1.6%) patients and severe...
dermatological reaction and hepatotoxicity in 1 (0.8%) patient each. The case of severe dermatological reaction was reported and described prior (Alosaimy et al [8]). Among patients who experienced adverse events (n = 4), 2 (50%) were on CT. Patients were mostly discharged to home (36, 28.5%) or skilled nursing facilities (SNFs)/long-term care facilities (LTACs; 45, 35.7%).

In order to perform CART analysis, patients who received appropriate antibiotics for GNI other than MEV and patients with unknown index culture dates were excluded (n = 35). Overall, 91 patients were included in this subanalysis. When CART analysis was performed, the time breakpoint for NCO was >48 hours (Figure 1). Upon multivariable logistic regression analysis, timely MEV administration was independently associated with fewer NCOs (ie, within 48 hours; odds ratio, 0.277; 95% CI, 0.081–0.941) (Table 4). Other independent predictors of NCOs included APACHE II scores, nosocomial infections, heart failure, and intra-abdominal infections. Examination of the different time delays to appropriate therapy within the 48-hour CART-derived breakpoint is shown in Figure 1. Of the 91 patients, 11 received MEV within 12 hours, 9 received MEV within 12–24 hours, and 14 received MEV within 24–48 hours. In Figure 2, we stratify patients outcomes by delay in receiving appropriate therapy.

**DISCUSSION**

The increase in prevalence of CRE infections continues to burden clinicians, and the lack of effective and safe antimicrobials against these pathogens exacerbates this concern [4, 5]. These patient populations typically have substantial comorbidities and experience high mortality and low clinical cure rates with historical antibiotics, reflecting the immediate need for improved antibiotic treatment agents demonstrating clinical evidence of positive outcomes [4, 5, 20]. After initial approval of these agents, real-world observational studies are fundamental, as they provide valuable clinical outcomes data beyond that reported in most large registrational trials [10, 12, 13]. Extrapolating efficacy and safety data from the limited patient populations and small sample sizes in RCTs to real-world, underserved, and seriously ill patients is challenging. Ultimately, real-world data can better represent patients who are encountered by clinicians in their daily practice, who are often excluded in registrational RCTs [12, 13].

Our patient population represented a high-risk group; roughly a third of our patients were age 65 years and older, a third had moderate to severe kidney disease or were on dialysis, ~40% were obese, and many had pneumonia or primary bacteremia as a source of infection. MDR risk factors were common in our study, as almost 70% of patients received prior antimicrobials and experienced previous hospitalization. This underscores the significance of our study findings, as these variables exemplify the real-world patient who is typically excluded from RCTs. The proportion of patients who experienced mortality in our study was 18.3%, which

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**Table 3. Clinical Outcomes Overview**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Total Study (n = 126)</th>
<th>PsA Spp. (n = 8)</th>
<th>Non-PsA (n = 118)</th>
<th>CRE Spp. (n = 99)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30-d mortality</td>
<td>23 (18.3)</td>
<td>0 (0)</td>
<td>23 (19.5)</td>
<td>19 (19.2)</td>
</tr>
<tr>
<td>90-d mortality</td>
<td>39 (33.1)</td>
<td>1 (12.5)</td>
<td>40 (31.7)</td>
<td>34 (34.3)</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>30 (23.8)</td>
<td>1 (12.5)</td>
<td>29 (24.6)</td>
<td>25 (25.3)</td>
</tr>
<tr>
<td>30-d recurrence</td>
<td>15 (11.9)</td>
<td>2 (25.0)</td>
<td>13 (11.0)</td>
<td>13 (13.1)</td>
</tr>
<tr>
<td>30-d readmission</td>
<td>23 (18.3)</td>
<td>0 (0)</td>
<td>23 (19.5)</td>
<td>21 (21.2)</td>
</tr>
<tr>
<td>Worsen or failure to improve while on MEV</td>
<td>30 (23.8)</td>
<td>2 (25.0)</td>
<td>28 (23.7)</td>
<td>25 (25.3)</td>
</tr>
<tr>
<td>Development of MEV resistance (n = 25)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Length of hospital stay, d</td>
<td>34.5 (178–62.3)</td>
<td>37.0 (14.5–95.5)</td>
<td>34.5 (18.0–62.3)</td>
<td>40.0 (18.0–64.0)</td>
</tr>
<tr>
<td>Safety</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any adverse event</td>
<td>4 (3.2)</td>
<td>1 (12.5)</td>
<td>3 (2.5)</td>
<td>2 (2.0)</td>
</tr>
<tr>
<td>Acute kidney injury*</td>
<td>2 (1.6)</td>
<td>0 (0)</td>
<td>2 (1.7)</td>
<td>2 (2.0)</td>
</tr>
<tr>
<td>Clostridiodes difficile infection</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Hepatotoxicity*</td>
<td>1 (0.8)</td>
<td>1 (12.5)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Severe dermatological reaction</td>
<td>1 (0.8)</td>
<td>0 (0)</td>
<td>1 (0.8)</td>
<td>1 (1.0)</td>
</tr>
<tr>
<td>Discharge disposition</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Home</td>
<td>36 (28.5)</td>
<td>5 (62.5)</td>
<td>31 (26.2)</td>
<td>22 (22.2)</td>
</tr>
<tr>
<td>SNF/LTAC</td>
<td>45 (35.7)</td>
<td>2 (25.0)</td>
<td>43 (36.4)</td>
<td>37 (37.4)</td>
</tr>
<tr>
<td>Inpatient rehabilitation facility</td>
<td>8 (6.3)</td>
<td>0 (0)</td>
<td>8 (6.8)</td>
<td>8 (8.1)</td>
</tr>
<tr>
<td>Hospice</td>
<td>8 (6.3)</td>
<td>0 (0)</td>
<td>8 (6.8)</td>
<td>7 (7.1)</td>
</tr>
</tbody>
</table>

Abbreviations: ALT, alanine aminotransferase; AST, alanine aminotransferase; CRE, carbapenem-resistant Enterobacterales; MEV, meropenem vaborbactam; LTAC, long-term care facilities; PsA, Pseudomas aeruginosa; SNF, skilled nursing facility; ULN, upper limit of normal.

*All values represent number (%) or median (interquartile range).

*Patients receiving hemodialysis excluded. None of the patients who experienced nephrotoxicity were on a concomitant nephrotoxin.

*Defined as an elevation in the serum concentration of ALT, AST exceeding 2× the ULN [29].
is somewhat comparable to what was reported in TANGO II and other published MEV real-world studies (ie, 7.5% to 15.6%) [8, 9, 21, 22].

It is important to note several differences between our cohort and previously published MEV real-world studies [8, 21, 22]. First, only 48.7% of our patients were on the full MEV dose, vs 54.7%–69.3% on other anti-CRE agents in real-world studies [23–25]. Notably, renally adjusted doses of these novel agents are common in real-world studies in various GNIs and range from 30% to 45% [23–25]. Additionally, only 55 (43.7%) and 26 (20.6%) patients in our study received appropriate full and reduced MEV doses, respectively. Remarkably, only 12 (52.2%) patients who experienced 30-day mortality received the appropriate package insert–recommended dose based on renal function. The impact of renal dose adjustment, particularly when BL/BLI antibiotics are inappropriately adjusted upon clinical failure, might be more pronounced in patients with certain infections and/or higher minimum inhibitory concentrations.

Additionally, we included patients who received MEV for MDR pathogens other than CRE, including 2 cases of A. baumannii and 8 cases of P. aeruginosa in our cohort. To the best of our knowledge, this is the largest study of patients with these infections treated with MEV for these organisms. Although the clinical outcomes of these 10 isolates were positive, the sample is too small to draw concrete conclusions.

Table 4. Independent Predictors of Negative Clinical Outcomes

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI)</th>
<th>P Value</th>
<th>aOR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Timely MEV</td>
<td>0.387 (0.098–1.522)</td>
<td>.174</td>
<td>0.277 (0.081–0.941)</td>
<td>.040</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>1.083 (1.012–1.159)</td>
<td>.021</td>
<td>1.095 (1.029–1.166)</td>
<td>.004</td>
</tr>
<tr>
<td>Nosocomial infection</td>
<td>2.298 (0.583–9.055)</td>
<td>.234</td>
<td>4.041 (1.132–14.426)</td>
<td>.031</td>
</tr>
<tr>
<td>Heart failure</td>
<td>5.313 (1.188–23.763)</td>
<td>.029</td>
<td>4.216 (1.129–15.733)</td>
<td>.032</td>
</tr>
<tr>
<td>Intra-abdominal infection</td>
<td>0.162 (0.022–1.206)</td>
<td>.76</td>
<td>0.151 (0.027–0.835)</td>
<td>.030</td>
</tr>
</tbody>
</table>

Hosmer-Lemeshow goodness-of-fit: 0.302. Variance inflation factor for all factors in the model: 1–5. Variables in the model: age, APACHE, admission from nursing home, CCI, chronic kidney disease, chronic dialysis, dementia, heart failure, timely MEV, tumor without metastasis, source is an intra-abdominal infection, source is a respiratory tract infection, liver disease, nosocomial infection, surgery within the past 30 days of index culture.

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation; CCI, Charlson Comorbidity Index; CART, classification and regression tree analysis; MEV, meropenem–vaborbactam.

*Timely MEV is defined as MEV within 48 hours (ie, at CART breakpoint).

†Defined as infection within 48 hours of inpatient admission date/time.
Of interest, the use of CT in our study (34.1%) was similar to what was previously reported in other real-world data with BL/BLIs in various GNIs (24.7%–39.7%) [23–25]. The use of CT is controversial, particularly for the treatment of CRE infections and particularly with new CRE agents, as they lack sufficient data to demonstrate improved clinical outcomes and carry a higher risk of toxicities, particularly nephrotoxicity with agents such as polymyxin-based therapy and/or aminoglycosides [1, 3, 4, 23, 24]. In our study, 50% of patients who experienced adverse events were on CT; nevertheless, the number (n = 4) is too small to draw specific conclusions. Overall, our safety outcomes were favorable, with only 3.2% of patients experiencing any adverse event attributable to MEV, and this rate is significantly lower than the rates reported in RCTs and observational studies [7, 9, 21].

The time to initiate MEV (ie, 79 hours) in our study was similar to what we have previously found in other comparator CRE agents at around 72–96 hours [23, 24]. We found an association between starting MEV within 48 hours of culture collection and patient survival [26]. This adds to the body of literature that demonstrates that early (ie, within 48 hours) initiation of appropriate therapy in GNI is essential for patient survival [27, 28].

Similar to previously published studies, a significant proportion of real-world patients in our study had bacteremia and/or pneumonia [21, 22]. Such infections are associated with a high bacterial burden and poor clinical outcomes. Additionally, infectious diseases and surgery consultations were common in our cohort. This closely resembles real-world practice, where multidisciplinary teams are involved with the decision for source control as well as the approval/restriction of new broad-spectrum agents.

Our study is not without limitations. Real-world studies are subject to inherent biases and limitations related to their retrospective design and reliance on medical chart review. First, important information such as results of follow-up cultures was not available for all patients. However, this is reflective of real-world practice, where clinicians may not routinely obtain follow-up cultures. Therefore, it remains unclear when patients cleared their infection or if they ultimately developed MEV resistance, particularly with the absence of MEV susceptibility. Third, our study lacked a comparator arm, hindering our ability to interpret the effectiveness and safety of MEV compared with other anti-CRE agents. Additionally, because our methodology included only patients who received MEV for a minimum of 72 hours, we may have excluded patients who received MEV briefly and did not respond well (ie, switched to alternative anti-CRE agents or died). Of interest was the relatively low MIC50 for CZA in our cohort. It remains unknown if these patients would have had favorable clinical outcomes if treated with CZA rather than MEV. Lastly, we were not able to find sufficient data regarding the mechanisms responsible for antibiotic resistance, particularly as we did not detect resistance in the few isolates tested.

In conclusion, our multicenter observational study adds to the existing literature describing health outcomes in patients treated with MEV for serious GNIs, including CRE, from geographically diverse health care settings and underscores the important need for continued research with this agent in various types of GNI.

Supplementary Data
Supplementary materials are available at Open Forum Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility...
of the authors, so questions or comments should be addressed to the corresponding author.

Acknowledgments

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Potential conflicts of interest. M.J.R. has received research support or fees for consulting or speaking from Allergan, Melinta, Merck, Motif, Nabriva, Paratek, Tetraphase, Shionogi, and Spero and is partially supported by NIAID AI121400. S.C.J.J. has received speaker’s fees from Sunovion and Melinta. K.C.C. has received financial support (grant) from Merck & Co. L.M.A. is a consultant for the Ferring, Nabriva, and Achaogen advisory boards and has received honoraria for speaking from Pfizer and MSD in Latin America for an antimicrobial stewardship continuing education lecture. M.V. has received funding or served on an advisory board for Paratek Pharmaceuticals, Cumberland Pharmaceuticals, Summit Therapeutics, Merck & Co., and Melinta Therapeutics. All other authors have nothing to disclose. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Prior presentation. A proportion of patients in this analysis were presented, in part, at the Infectious Diseases Society of America (IDSA) Meeting 2020 virtual meeting, the Making-a-Difference in Infectious Diseases 2019 meeting, and in the following publication: Alosaímy et al. [8].

References