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Meropenem-Vaborbactam as Salvage Therapy for Ceftazidime-Avibactam-Resistant *Klebsiella pneumoniae* Bacteremia and Abscess in a Liver Transplant Recipient

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This Journal section presents a real, challenging case involving a multidrug-resistant organism. The case authors present the rationale for their therapeutic strategy and discuss the impact of mechanisms of resistance on clinical outcome. An expert clinician then provides a commentary on the case.

ABSTRACT We report a case of a 24-year-old liver transplant recipient who developed hepatic artery thrombosis and graft failure, which was complicated by subphrenic abscess and persistent *Klebsiella pneumoniae* carbapenemase (KPC)-producing *K. pneumoniae* bacteremia. Ceftazidime-avibactam treatment led to emergence of resistance, and alternative combination therapy failed due to persistent infection and toxicity. The infection resolved after initiation of meropenem-vaborbactam, which created a bridge to retransplantation. Treatment-emergent ceftazidime-avibactam resistance is increasingly recognized, suggesting a role for meropenem-vaborbactam.

KEYWORDS *Klebsiella pneumoniae* carbapenemase, carbapenem-resistant *Enterobacteriaceae*, carbapenemase-producing *Klebsiella pneumoniae*, ceftazidime-avibactam, meropenem-vaborbactam

The *Enterobacterales* (former taxonomy: *Enterobacteriaceae*) are a large family of Gram-negative bacilli that are normal inhabitants of the human gastrointestinal tract (1). Although this family encompasses a large number of diverse organisms, the most frequently encountered species in health care settings are *Escherichia coli*, *Klebsiella* species, and *Enterobacter* species (1, 2). The carbapenems have been a mainstay of treatment for health care-associated infections due to members of *Enterobacterales*. However, over the last several decades, carbapenem-resistant *Enterobacterales* (CRE) bacteria have emerged as a global antimicrobial resistance threat (3), with mortality rates exceeding 40% (4, 5). Carbapenem resistance is complex and may be mediated by multiple overlapping mechanisms, including production of hydrolytic enzymes or carbapenemases. *Klebsiella pneumoniae* carbapenemases (KPCs), most notably, KPC-2 and KPC-3, are among the most prevalent carbapenem resistance determinants in the United States (6). The high transmissibility of KPC-mediated resistance has resulted in global proliferation of multidrug-resistant infections with severely limited treatment options.

Prior to the approval of novel β-lactam/β-lactamase-inhibitor combinations, treat-

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ment of CRE infection consisted of combination therapy with "agents of last resort." Existing options (polymyxins, aminoglycosides, tigecycline, and carbapenems) were limited by inferior efficacy, resistance, suboptimal pharmacokinetics, and/or high toxicity rates (7, 8). The U.S. Food and Drug Administration (FDA) approvals of ceftazidime-avibactam and meropenem-vaborbactam in 2015 and 2017, respectively, alleviated many of the concerns with traditional treatment options for KPC-mediated CRE infections. However, treatment-emergent ceftazidime-avibactam resistance has recently been described in multiple centers (9–12), highlighting the need for additional treatment options. We report the use of meropenem-vaborbactam as salvage therapy for ceftazidime-avibactam-resistant KPC-producing *K. pneumoniae* infection in a liver transplant recipient.

CASE PRESENTATION

A 24-year-old African American male with a history of end-stage liver disease secondary to primary sclerosing cholangitis underwent orthotopic liver transplantation with Roux-en-Y hepaticojejunostomy (defined as day 1). On day 4, he developed a fever and respiratory failure requiring mechanical ventilator support. *K. pneumoniae* was recovered from blood and bronchoalveolar lavage fluid cultures, with the KPC-encoding gene also detected in the blood specimen using rapid nucleic acid microarray technology (Verigene BC-GN; Luminex Corporation, Northbrook, IL). In response, his empirical regimen of vancomycin and piperacillin-tazobactam was changed to ceftazidime-avibactam 2.5 g administered intravenously (i.v.) over 2 h every 8 h. Routine susceptibility testing was performed according to the laboratory protocol for CRE using Vitek 2 (bioMérieux Inc., Durham, NC) and Sensititre GN4F and GNX2F broth microdilution panels (Thermo Fisher Scientific, Waltham, MA). The ceftazidime-avibactam MICs were 4 μg/ml and 2 μg/ml for blood and respiratory isolates, respectively (Clinical and Laboratory Standards Institute [CLSI] susceptibility breakpoint of $\leq$8 μg/ml [13]). Blood cultures obtained on day 8 were negative. On day 18, the patient received enhanced immunosuppression for biopsy-proven moderate acute cellular rejection; therefore, his planned 14-day course of ceftazidime-avibactam was extended to 21 days. The patient was eventually discharged on day 34 in stable clinical condition.

On day 54, the patient was readmitted for an undifferentiated fever. Liver vascular ultrasound revealed no identifiable intrahepatic arterial flow. Computerized tomography (CT) revealed hepatic artery thrombosis near the anastomotic site, hepatosplenic infarcts, and subphrenic fluid collection (5.3 by 6.6 cm). Rapid microarray testing of the blood culture identified *K. pneumoniae* and the KPC determinant, which prompted reinitiation of ceftazidime-avibactam at the previously described dose with metronidazole (500 mg i.v. every 8 h) on day 55. A CT-guided abscess drain was placed. Blood and subphrenic fluid cultures grew carbapenem-resistant *K. pneumoniae* with ceftazidime-avibactam MICs of 4 μg/ml and 2 μg/ml, respectively. A follow-up CT scan demonstrated increasing fluid collection in liver segment VIII, likely representing a bile leak, and, despite placement of an image-guided biloma drain, *K. pneumoniae* bacteremia persisted. On day 63, tigecycline (100 mg i.v. administered once followed by 50 mg i.v. every 12 h) was added. On day 66, after 11 days of ceftazidime-avibactam, susceptibility testing on a repeat blood culture confirmed *de novo* ceftazidime-avibactam resistance with an MIC of 128 μg/ml. At that time, ceftazidime-avibactam was discontinued and polymyxin B treatment was initiated (2.5 mg/kg of body weight/dose i.v. administered once, followed by 1.5 mg/kg/dose every 12 h). Gentamicin (5 mg/kg/dose i.v. every 24 h) was added on day 70 when blood cultures remained positive despite dual Gram-negative therapy.

Due to irreversible vascular compromise of the hepatic artery, a decision was made to list the patient for liver retransplantation, pending clearance of persistent *K. pneumoniae* infection. Blood cultures were briefly rendered negative by combination therapy with polymyxin B, tigecycline, and gentamicin. However, renal tubular toxicity emerged with an increase in serum creatinine from 0.67 to 2.37 mg/dl, hypomagnesemia (1.3 mg/dl), and hypokalemia (2.6 mg/dl). Despite temporary bacteremia clear-

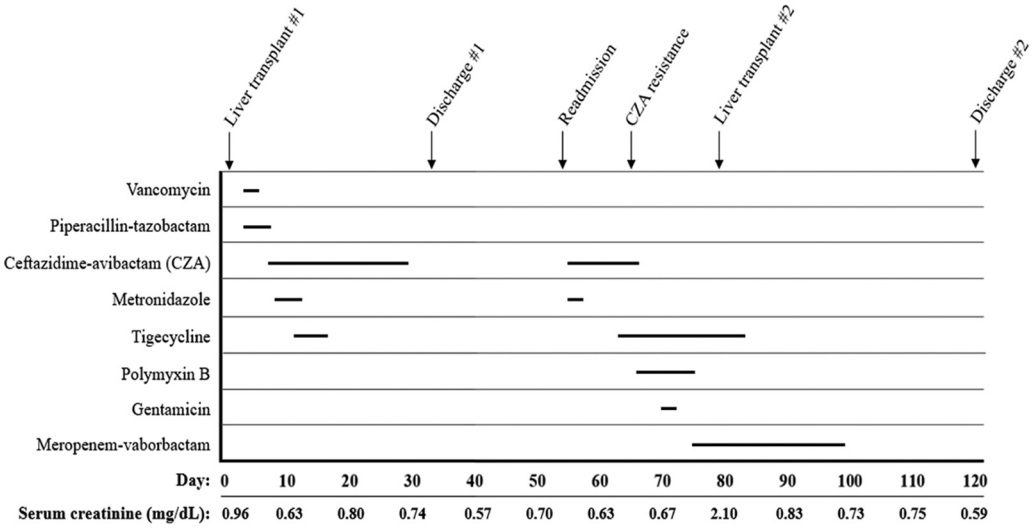

FIG 1 Summary of clinical case and timing of antibiotic exposures.

ance, *K. pneumoniae* (meropenem MIC 8 μg/ml, ceftazidime-avibactam MIC >256 μg/ml, polymyxin B MIC 2 μg/ml, tigecycline MIC $\leq$ 2 μg/ml, gentamicin MIC $\leq$ 2 μg/ml) was again recovered from abscess fluid, suggesting residual infection.

Retransplantation and renal failure have each been independently associated with poor outcomes posttransplantation. The ongoing toxicity from the patient's antimicrobial regimen, therefore, was critically important. However, persistent multidrug-resistant infection was also a relative contraindication to retransplantation. These dynamics created a challenging clinical dilemma, in which a seemingly unresolvable conflict existed between potentially fatal organ failure syndromes and continued infection on a toxic, failing antibiotic regimen.

CHALLENGE QUESTION

Which mechanism best explains the evolution of ceftazidime-avibactam resistance with retained susceptibility to meropenem-vaborbactam?

A. Production of an OXA-48-like β-lactamase.
B. Downregulation of OprD porin expression.
C. Production of a mutant KPC β-lactamase.
D. Production of a VIM metallo-β-lactamase.
E. Upregulation of OprD porin expression.

TREATMENT AND OUTCOME

The *K. pneumoniae* isolate was tested for meropenem-vaborbactam susceptibility as part of a reflex laboratory protocol for CRE (disk diffusion and research use only Etest; bioMérieux Inc., Durham, NC). The meropenem-vaborbactam MIC was reported as susceptible with an MIC of 2 μg/ml and a zone diameter of 19 mm (FDA susceptibility breakpoints of $\leq$4 μg/ml and $\geq$17 mm [14]), which supported a decision to discontinue polymyxin B and gentamicin in favor of renal-adjusted meropenem-vaborbactam (4 g i.v. over 3 h every 12 h) on day 75. All subsequent cultures remained negative, and renal function gradually improved, allowing successful liver retransplantation on day 79. The patient completed a 25-day course of meropenem-vaborbactam (dose increased to 4 g i.v. over 3 h every 8 h) that extended 3 weeks from the date of retransplantation. All abdominal drains were removed with resolution of fluid collections on postoperative imaging. The patient's renal function fully recovered to baseline, and he was discharged infection free on day 119. His full treatment course and *K. pneumoniae* blood culture susceptibility trends are summarized in Fig. 1 and Table 1, respectively.

To evaluate the mechanism of ceftazidime-avibactam resistance, the *K. pneumoniae*

TABLE 1 Antibiotic susceptibility of the patient's multidrug-resistant *K. pneumoniae* blood isolates

Antibiotic	MIC, μg/ml (interpretation)[a]			
	Day 5	Day 54	Day 62	Day 68
Ampicillin-sulbactam	≥32 (R)	≥32 (R)	≥32 (R)	≥32 (R)
Cefazolin	≥64 (R)	≥64 (R)	≥64 (R)	≥64 (R)
Ceftriaxone	≥64 (R)	≥64 (R)	≥64 (R)	≥64 (R)
Cefepime	≥64 (R)	≥64 (R)	≥64 (R)	≥64 (R)
Ceftazidime-avibactam	4 (S)	4 (S)	128 (R)	>256 (R)[b]
Piperacillin-tazobactam	≥128 (R)	≥128 (R)	128 (R)	16 (S)
Ertapenem	≥8 (R)	≥8 (R)	>8 (R)	≥8 (R)
Meropenem	≥16 (R)	≥16 (R)	2 (I)	4 (R)[c]
Ciprofloxacin	≥4 (R)	≥4 (R)	≥4 (R)	≥4 (R)
Gentamicin	≤1 (S)	≤1 (S)	≤1 (S)	≤1 (S)
Polymyxin B[d]	>4 (NI)	2 (NI)	1 (NI)	1 (NI)
Tigecycline	≤1 (S)	0.5 (S)	≤1 (S)	≤1 (S)
TMP-SMX[e]	≥4/76 (R)	≥4/76 (R)	≥4/76 (R)	≥4/76 (R)
Meropenem-vaborbactam	NP	NP	NP	2 (S)[b]

[a]S, susceptible; I, intermediate; R, resistant; NI, not interpretable; NP, not performed.
[b]Analysis was performed by disk diffusion and Etest at Cleveland Clinic; MICs determined by broth microdilution at JMI Laboratories were >32 μg/ml for ceftazidime-avibactam and 2 μg/ml for meropenem-vaborbactam.
[c]Confirmed by broth microdilution at JMI Laboratories.
[d]Polymyxin B MICs were determined by the use of a Sensititre GNX2F tray previously validated by comparing to CLSI broth macrodilution.
[e]TMP-SMX, trimethoprim-sulfamethoxazole.

blood isolate (day 68; Table 1) was submitted to whole-genome sequencing using the Nextera XT library construction protocol and an index kit (Illumina, San Diego, CA, USA) following the manufacturer's instructions and was sequenced on a MiSeq sequencer (Illumina) with a target coverage of 30×. FASTQ format files for each sample set were assembled independently using *de novo* assembler SPAdes 3.9.0 (1) with K-values of 21, 33, 55, 77, and 99 and careful mode on to reduce the number of mismatches, producing a FASTA format file of contiguous sequences with the best N50 value. In-house software using the target assembled sequences as queries to align against numerous resistance determinants from the NCBI Bacterial Antimicrobial Resistance Reference Gene Database (https://www.ncbi.nlm.nih.gov/bioproject/PRJNA313047) was used to search for resistance genes. Potential matches were generated with the criteria of >94% identity and 40% minimum coverage length. Outer membrane protein sequences were compared to sequences deposited under GenBank accession numbers YP002239423.1, YP002237369.1, and YP002238854.1 for OmpK35, OmpK36, and OmpK37, respectively.

The isolate carried a gene encoding a mutated KPC-2, in addition to TEM-1, SHV-11, and SHV-12, and disruptions (frameshifts or >2 amino acid insertions/deletions) in OmpK35, OmpK36, and OmpK37. The mutant bla_{KPC-2} detected in the patient's clinical isolate, named KPC-33 (GenBank accession no. NG056170), featured a tyrosine for aspartic acid substitution at Ambler amino acid position 179 (D179Y) within the KPC Ω-loop compared to the wild type. This alteration is known to codify resistance to ceftazidime-avibactam (15, 16).

Treatment-emergent ceftazidime-avibactam resistance has been previously described in the setting of KPC-producing *K. pneumoniae* infection. Resistance typically occurs after 10 to 19 days of drug exposure and often manifests during treatment of recurrent infection (10–12). The patient described in this case was intermittently exposed to 33 days of ceftazidime-avibactam and also had an episode of recurrent bloodstream infection before phenotypic resistance was documented (Fig. 1). It is likely that the patient's persistent focus of intra-abdominal infection was a contributing factor in the emergence of mutant bla_{KPC-2} subpopulations. Ceftazidime-avibactam monotherapy may have also contributed to the development of resistance. To date, approximately 58% (7/12) of ceftazidime-avibactam microbiologic failures have been associated with administration as monotherapy (10–12). Furthermore, the patient in this case

underwent solid-organ transplantation, which has been identified in 42% (5/12) of documented ceftazidime-avibactam microbiologic failures (10–12). Solid-organ transplant recipients are frequently subjected to broad-spectrum antimicrobials, lengthy hospital admissions, and periods of heightened immunosuppression, all of which may add to the likelihood of treatment-emergent resistance. Lastly, the case patient's initial infection was pneumonia, which has been recently identified as an independent predictor of ceftazidime-avibactam microbiologic failure (17). Although some associations are speculative and based on a limited sample size, risk factors for ceftazidime-avibactam treatment failure merit further study as additional reports are compiled.

The case patient's *K. pneumoniae* isolate was found to harbor a D179Y mutant bla_{KPC-2} gene, which has been previously described in detail (15, 16). When other resistance determinants are excluded, D179Y mutation has been attributed to a ≥16-fold ceftazidime-avibactam MIC increase, which aligns with our observations (≥64-fold increase) (9, 15, 16). It is postulated that KPC Ω-loop substitution results in stabilizing interactions (e.g., hydrogen bonds) that prolong ceftazidime binding at the active site, thus preventing the inhibitory activity of avibactam (15, 16, 18). Interestingly, the D179Y mutation has also been shown to confer a significant reduction in meropenem MIC (9, 15, 16, 19), a feature which was demonstrated in the patient's day 68 isolate (Table 1). Further, the addition of 8 μg/ml of vaborbactam altered the meropenem MIC of this isolate only slightly (from 4 to 2 μg/ml). These findings support the notion of bla_{KPC} mutants conferring ceftazidime-avibactam resistance function as extended-spectrum β-lactamases with reduced carbapenem hydrolytic activity (19). However, the mechanism and stability of enhanced carbapenem susceptibility have not been fully elucidated.

To our knowledge, this is the first reported clinical case of meropenem-vaborbactam used as salvage therapy for ceftazidime-avibactam-resistant *K. pneumoniae* infection. Meropenem-vaborbactam is the first FDA-approved carbapenem/β-lactamase-inhibitor combination with potent activity against KPC-producing isolates. *In vitro* susceptibility analyses found that 99.5% of KPC-producing *Enterobacterales* isolates were inhibited at the FDA susceptibility breakpoint concentration of 4/8 μg/ml (20). Meropenem and vaborbactam concentrations obtained readily from dosing regimens used in clinical trials (4 g i.v. over 3 h every 8 h) are expected to suppress resistant mutant emergence with a frequency of 10^{-9} in most KPC-producing *K. pneumoniae* bacteria (21). Furthermore, no single KPC mutation has been shown to confer resistance to meropenem-vaborbactam (21), suggesting a higher overall barrier to resistance compared to ceftazidime-avibactam.

Clinical experience using meropenem-vaborbactam for the treatment of CRE is limited. The TANGO 1 randomized trial, which led to the approved indication of complicated urinary tract infection, was not designed to evaluate the use of meropenem-vaborbactam for CRE (22). The TANGO 2 randomized, open-label trial (presented in abstract form to date) compared meropenem-vaborbactam monotherapy to the best available therapy for CRE infection and included 20 patients with bloodstream infection. At test-of-cure follow-up, meropenem-vaborbactam-treated patients experienced a higher rate of clinical cure than those receiving best available therapy (57.1% versus 26.7%) (difference, +30.4%; 95% confidence interval [CI], 1.6% to 59.4%) (23). Favorable clinical cure rates were also noted in a subset of immunocompromised patients from the same trial (70% versus 0%) (difference, +70%; 95% CI, 26.9% to 93.3%) (24). However, only one patient assigned to the best available therapy received ceftazidime-avibactam, precluding a direct comparison.

After prior therapies failed due to resistance and toxicity, meropenem-vaborbactam salvage therapy contributed to a positive clinical outcome and created a safe bridge to retransplantation for a patient with persistent KPC-producing *K. pneumoniae* infection. Since a robust head-to-head comparison between ceftazidime-avibactam and meropenem-vaborbactam is unlikely in the foreseeable future, case descriptions may inform decisions regarding when to administer these agents. Although additional studies are needed to validate the optimal approach to treatment of KPC-producing *Enterobacte-*

rales infection, meropenem-vaborbactam appears to be a formidable addition to the CRE armamentarium.

COMMENTARY

The central concern regarding the continued dissemination of carbapenemase-producing *Enterobacteriaceae* (CPE) across the globe is a severely limited ability to treat patients with invasive infections with these highly resistant organisms. Thankfully, novel β-lactamase inhibitors paired with existing agents have become available as therapeutic advances to combat CPE. However, because of the desperate need for effective agents, both meropenem-vaborbactam and ceftazidime-avibactam were appropriately fast-tracked through phase III clinical trials, often with little treatment data with respect to the specific resistance mechanisms that the agents were designed to target (22, 25, 26). This approach raises the need for observational descriptions of real-world clinical use. The authors of the present work describe an interesting and important case of a patient who had a carbapenemase (KPC)-producing *Klebsiella pneumoniae* infection which was successfully treated with meropenem-vaborbactam after development of resistance to ceftazidime/avibactam and previously failure of older agents.

Traditionally, little specific clinical attention has been given to the treatment of infections with β-lactamase inhibitors (which have been most frequently paired with various penicillins) due to the comparable spectra of β-lactamase inhibitors such as clavulanic acid, sulbactam (other than the *Acinetobacter baumannii* complex), and tazobactam. The deployment of the novel and distinct β-lactamase inhibitors, which preferentially target specific β-lactamases, and increasing molecular information from clinical laboratories about the presence of specific carbapenemases underscore that a deep understanding of the similarities and differences between these compounds will be important for clinicians in selecting definitive or empirical therapy to treat these infections.

As pointed out by the authors, avibactam is a β-lactamase inhibitor with spectra of activity against some β-lactamases from classes A, C, and D. Avibactam was the first β-lactamase inhibitor with clinically meaningful activity (specifically against KPC-producing organisms) to come to the U.S. market. Soon after ceftazidime-avibactam's release, however, there were descriptions of resistance, most frequently mediated by a specific mutation in bla_{KPC-3} (leading to a D179Y substitution), resulting in resistance to inhibition but decreased meropenem hydrolysis. Here, the authors report that the D179Y substitution can also occur in bla_{KPC-2}, with a similar effect on meropenem affinity.

There is less clinical experience with meropenem-vaborbactam, but vaborbactam has a very strong affinity for KPC but, unlike avibactam, does not have potent class D carbapenemase inhibition. As the authors point out, vaborbactam is predicted to have a higher barrier for development of resistance with current dosing strategies and it is too early to determine if this combination will become the primary therapy for KPC-producing organisms. Interestingly, in the initial randomized phase III open label trial of meropenem-vaborbactam targeting inpatients with serious CRE infections (pneumonia, bacteremia, complicated urinary tract infection, or intra-abdominal infection), no evidence of resistance was observed among 25 patients receiving meropenem-vaborbactam (although one isolate had a 4-fold increase from 0.25 to 1 μg/ml). On the other hand, among the four patients treated with ceftazidime-avibactam, resistance emerged in one case (an intra-abdominal infection) and the infecting isolate harbored a mutation in bla_{KPC-2} (22, 27). Here, the authors do a nice job of describing the clinical scenarios in which ceftazidime-avibactam resistance can emerge. Essentially, ceftazidime-avibactam resistance has often occurred in high-burden infections such as pneumonia or in patients who are at high risk for relapse (10). As this case illustrates, the patient treated with ceftazidime-avibactam was at high risk for resistance, as is the case for many patients who develop infections with carbapenem-producing *Enterobacteriaceae*.

Finally, this case illustrates the point that even combination therapy with older agents such as colistin is often ineffective, resulting in toxicity, and should be avoided whenever possible. With recent publications evaluating colistin, it appears that the therapeutic window may be very narrow, with little to no benefit and a high degree of toxicity when effective dosing strategies are used (28, 29). A retrospective comparison of colistin-based combinations with ceftazidime-avibactam found lower 30-day mortality and overall improved outcomes with less renal toxicity in patients treated with ceftazidime-avibactam (8). Clinicians, microbiologists, and pharmacists need to become comfortable with the use of newer agents even with the gaps in the existing data, making sure the agents are available for use and that susceptibility testing is performed in a timely manner.

In summary, this case illustrates some of the potential challenges in the contemporary management of CPE. Use of novel β-lactamase inhibitors needs to be carried out thoughtfully with knowledge of the differences between the agents and their paired β-lactam and with a complete understanding of the molecular mechanisms of resistance involved, as there are still a number of uncertainties. Thus, reports such as the one presented here are extremely important to help clinicians manage life-threatening infections caused by carbapenemase-producing organisms.

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