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ID TEACHING CASES

Meropenem-Vaborbactam as Salvage Therapy for Ceftazidime-Avibactam-, Cefiderocol-Resistant ST-512 *Klebsiella pneumoniae*–Producing KPC-31, a D179Y Variant of KPC-3

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A 68-year-old man had recurrent bacteremia by *Klebsiella pneumoniae* carbapenemase (KPC)–producing *K. pneumoniae* resistant to ceftazidime-avibactam and cefiderocol. The sequencing of a target region showed that it harbored a KPC-3 variant enzyme (D179Y; KPC-31), which confers resistance to ceftazidime-avibactam and restores meropenem susceptibility. The patient was successfully treated with meropenem-vaborbactam.

Keywords. ceftazidime-avibactam resistant; *Klebsiella pneumoniae*; KPC; KPC-3; meropenem-vaborbactam.

Among multidrug-resistant (MDR) organisms, carbapenem-resistant Enterobacterales (CRE) represent a great challenge due to their global spread and limited treatment options. *Klebsiella pneumoniae* carbapenemase (KPC) is the predominant carbapenemase detected among CRE, and KPC-producing Enterobacterales are endemic in several countries, including the United States, Israel, Latin American countries, and Southern Europe [1]. Before the approval of novel β-lactam/β-lactamase inhibitors, treatment of CRE infection consisted of combination therapy with "agents of last resort," such as polymyxins, which are associated with high rates of adverse events. The advent of ceftazidime-avibactam (CZA) changed the therapeutic approach to infections caused by CRE [2]. Compared with colistin-containing regimens, CZA is associated with reduced risk of 30-day mortality or nephrotoxicity in critically ill patients with KPC-producing Enterobacterales [3, 4]. Remarkably, current guidelines recommend CZA as the preferred treatment in patients with CRE infections [5]. However, CZA, as well as meropenem-vaborbactam (MVB) and imipenem-relebactam (I-R), are not active against metallo-β-lactamase (MBL)–producing strains [2, 6], and other treatment options should be considered. Aztreonam-avibactam (ATM-AVI) and cefiderocol are usually in vitro active against MBL-producing Enterobacterales, and preliminary clinical experience is encouraging [2, 7–9].

Resistance to CZA is increasingly reported in KPC-producing strains [10–12]. Although it is due to several mechanisms, including alterations of Ompk35 and Ompk36 porins [10, 11], β-lactamase-related mutations are the most common causes of CZA resistance [10].

Here we report the clinical use of MVB as salvage therapy for a CZA and cefiderocol-resistant KPC-producing *K. pneumoniae* infection in a critically ill patient.

CASE PRESENTATION

A 68-year-old man was admitted to the Azienda Ospedaliera Universitaria Pisana in June 2020 and underwent hip replacement surgery (defined as day 1) due to osteoarthritis. His medical history was significant for hypertension and chronic ischemic cardiomyopathy. He was a past smoker and obese (body mass index 34 kg/m^2). According to standard of care at our institution, rectal swabs were performed at admission and periodically during the hospital stay. At admission, the rectal swab culture was negative. A rectal swab taken on day 4 postsurgery, however, led to the detection of a KPC-producing *K. pneumoniae* (KPC-Kp).

On day 7, he developed fever, hypotension, and dysuria. Considering the presence of intestinal colonization by KPC-Kp and the presence of septic shock, empirical treatment with CZA 2.5 g administered intravenously (iv) over 2 hours every 8 hours was started. A KPC-producing *K. pneumoniae* was detected from blood and urine specimens by matrix-assisted laser desorption/ionization–time of flight mass spectrometry (MALDI Biotyper, Bruker Daltonics, Billerica, MA, USA). The KPC-encoding gene was detected by polymerase chain reaction using the GeneXpert System (Cepheid, Sunnyvale, CA, USA). Routine susceptibility testing was performed according to the laboratory protocol using the SensiTitre system (Thermo Fisher Scientific, Cleveland, OH, USA). Cefiderocol antimicrobial susceptibility testing (AST) was initially assessed by SensiTitre lyophilized broth microdilution (BMD) panel (Thermo Fisher Scientific, Cleveland, OH, USA) and confirmed using iron-depleted cation-adjusted Mueller-Hinton broth (ID-CAMHB)

Received 2 February 2021; editorial decision 17 March 2021; accepted 18 March 2021.

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Open Forum Infectious Diseases®2021

DOI: 10.1093/ofid/ofab141

at a final iron concentration of ≤0.03 μg/mL [13]. Minimum inhibitory concentrations (MICs) were classified according to breakpoints established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST).

The KPC-Kp strain was susceptible to colistin, fosfomycin, tigecycline, CZA (MIC, 1 mg/L), MVB (MIC, 0.125 mg/L), and cefiderocol (MIC, 2 mg/L) (Table 1). The minimum bactericidal concentration (MBC) of cefiderocol was 4 mg/L (ID-CAMHB).

Blood cultures obtained on day 7 were negative. Clinical conditions rapidly improved, and CZA was discontinued after 14 days of treatment. A delayed healing of the surgical wound was noted. On day 28 (7 days after CZA discontinuation), the patient had fever and worsening clinical conditions. Renal function worsened, with an estimated glomerular filtration rate of 46 mL/min/1.73 m^2. A swab from the wound was obtained, and blood cultures were collected. Rapid testing of the blood cultures identified again KPC-producing *K. pneumoniae*, and CZA 1.25 g iv every 8 hours was promptly restarted. Blood and wound cultures grew a new carbapenem-resistant *K. pneumoniae* displaying resistance to CZA (MIC, >8 mg/L) and cefiderocol (MIC, 16 mg/L and 8 mg/L using ID-CAMHB and Sensititre BMD, respectively), but with restored susceptibility to meropenem (MIC, 2 mg/L) (Table 1). The strain remained susceptible to MVB (MIC, 0.125 mg/L). Cefiderocol MBC was 16 mg/L using ID-CAMHB.

Table 1. Antibiotic Susceptibility of the Clinical Isolates of KPC-Producing *K. pneumoniae* (First KPC-3 and Recurrent KPC-31-D179Y Isolate)

	First Isolate KPC-3	Recurrent Isolate KPC-31, D179Y
	MIC, mg/L (Interpretation)	
Amoxicillin/clavulanate	>16 (R)	>16 (R)
Piperacillin/tazobactam	>128 (R)	>128 (R)
Ceftriaxone	>4 (R)	>4 (R)
Ceftazidime	>128 (R)	>128 (R)
Cefepime	>32 (R)	>32 (R)
Ertapenem	>1 (R)	>1 (R)
Imipenem	>16 (R)	<0.25 (S)
Meropenem	>64 (R)	2 (S)
Fosfomycin	<16 (S)	>128 (R)
Amikacin	>16 (R)	>16 (R)
Gentamicin	4 (I)	4 (I)
Ciprofloxacin	>2 (R)	>2 (R)
Tigecycline	0.5 (S)	0.5 (S)
Colistin	0.5 (S)	0.5 (S)
Ceftazidime-avibactam	1 (S)	>8 (R)
Cefiderocol	2 (S)[a]	16 (R)[a]
	2 (S)[b]	8 (R)[b]
Meropenem-vaborbactam	0.125 (S)	0.125 (S)

Abbreviations: KPC, *Klebsiella pneumoniae* carbapenemase; MIC, minimum inhibitory concentration; R, resistant; S, susceptible.

[a]Iron-depleted Mueller Hinton broth.

[b]Broth microdilution (Sensititre).

CZA was discontinued. To evaluate the mechanism of CZA resistance, a polymerase chain reaction and Sanger sequencing of the complete gene and promoter were performed on both urine and blood *K. pneumoniae* isolates. The analysis revealed that the first CZA-susceptible KPC-*Klebsiella pneumoniae* isolate carried the bla_{KPC-3} gene. The second CZA-resistant strain carried the bla_{KPC-31} gene. This latter isolate of *Klebsiella pneumoniae* harbored a KPC-3 variant enzyme with a tyrosine for aspartic acid substitution at Ambler amino acid position 179 (D179Y; KPC-31, accession number MAPH01000113), which is known to confer CZA resistance and restore carbapenem susceptibility [11, 12, 14, 15]. Both strains were assigned to Sequence Type 512 by multilocus sequence typing (performed according to the Institute Pasteur scheme; https://bigsdb.pasteur.fr/).

At this time, clinicians faced a clinical dilemma about the most appropriate treatment of this patient considering that (1) the CZA-resistant KPC-producing isolate was in vitro resistant to cefiderocol; (2) there were concerns about the use of colistin due to high risk of nephrotoxicity; (3) it was not clear whether it would be better to use MEM or combinations of MVB.

We decided to start MVB 1/1 g iv every 8 hours. Clinical conditions improved, with decrease and normalization of inflammatory markers (C-reactive protein and procalcitonin) and healing of the surgical wound. The patient completed a 14-day course of MVB and was discharged. The patient completed a follow-up of 6 months, and no relapse occurred.

Patient Consent

This study was conducted according to the principles stated in the Declaration of Helsinki, and it conforms to standards currently applied in our country. The compassionate use of MVB in this patient was approved by the Comitato Etico Area Vasta Nord Ovest (Tuscany, Italy). The patient's written consent was obtained.

DISCUSSION

Our case highlights 2 key considerations in the management of KPC-producing *Klebsiella pneumoniae* bacteremia: (1) the development of treatment-emergent CZA resistance after CZA therapy and (2) the challenging therapeutic option against CZA-resistant KPC-Kp.

The occurrence of CZA resistance in a patient with KPC-Kp infection treated with CZA may have different explanations, including the failure of CZA monotherapy and the use of inadequate dosages of this antibiotic. The use of CZA as monotherapy or in combination with other in vitro active drugs is debated, and a recent network meta-analysis did not detect differences in mortality rates between patients receiving CZA combination therapy or monotherapy [16]. Instead, it is not exactly known whether combination therapy might prevent the

selection of CZA resistance. Time–kill kinetics showed that combining imipenem with CZA prevents the emergence of a resistant CZA subpopulation in KPC-3-producing *Klebsiella pneumoniae* [17]. Moreover, an animal model of *G. mellonella* infected with mutant KPC-3^{D179Y}-producing *K. pneumoniae* confirmed that combination therapy was significantly more effective than CZA monotherapy [17]. These experimental studies suggest that selection of CZA-resistant variants of KPC-Kp may be prevented by using CZA combined with other antibiotics such as carbapenems. Although we recently showed that recommended dosages of CZA appeared to be adequate to meet time-dependent pharmacokinetic targets [18], we cannot exclude in our case a CZA underdosing that finally favored the selection of a CZA-resistant strain.

Treatment of CZA-resistant KPC-producing *Klebsiella pneumoniae* is challenging for clinicians. During recent decades, colistin has resurged, assuming its role as salvage therapy for otherwise untreatable multidrug-resistant gram-negative bacilli. However, nephrotoxicity remains a concerning adverse effect of this old drug. Among critically ill patients with bloodstream infections caused by CRE, colistin-containing regimens were associated with high risk of 30-day mortality or nephrotoxicity [3, 4, 8]. Interestingly, KPC-31-producing *Klebsiella pneumoniae* isolates have a restoration of carbapenem susceptibility, suggesting the potential therapeutic usefulness of these drugs [12, 19]. The use of carbapenem monotherapy in patients with KPC-Kp with restored susceptibility to meropenem remains debated. As previously reported in the CZA-resistant KPC-3 variant, sublethal meropenem concentrations may select in vitro meropenem-resistant variants [20]. Double carbapenem therapy demonstrated activity against colistin-resistant KPC-producing *K. pneumoniae* [21], but it has not been evaluated in patients with infections due to CZA-resistant KPC variants. Clinical data addressing this question are lacking, and further studies are warranted to clarify this clinical unmet need.

Other new beta-lactam/beta-lactamase inhibitors such as I-R and MVB may represent an alternative option in patients with CZA-resistant KPC-producing *K. pneumoniae*. In our case, the CZA-resistant strain was fully susceptible to MVB, and we observed a significant reduction of meropenem MIC (from 2 to 0.125 mg/L) after the addition of vaborbactam. This seems to suggest an enhanced activity of vaborbactam against KPC-31. Data about MVB are limited. MVB therapy has been evaluated in 16 critically ill patients with KPC- *Klebsiella pneumoniae* infections [22]. One of the isolates produced KPC-31, and this strain was resistant to CZA. Notably, MVB therapy of KPC-31 *Klebsiella pneumoniae* infection was associated with recurrent infection by an MVB-nonsusceptible strain (the initial MVB MIC was 0.12 μg/mL, while the MIC of the subsequent recurrent isolate was 8 μg/mL). Whole-genome sequencing analysis identified an IS5 insertion in the ompK36 promoter of the recurrent isolate that was not present at baseline and that might explain the increase in the MIC values to MVB. The bla_{KPC} on an IncFIA pBK30683-like plasmid that encoded KPC-31 was unchanged, suggesting that the MVB nonsusceptibility was independent from production of mutant KPC-31 carbapenemase [22]. All these observations support the choice to treat our patient with MVB.

Finally, it should be noted that the KPC-producing *K. pneumoniae* isolated in our patient was resistant to cefiderocol. To the best of our knowledge, resistance to cefiderocol has been not described in KPC–*Klebsiella pneumoniae*. A recent study showed that out of 51 KPC-3-producing carbapenem-resistant *Klebsiella pneumoniae* strains, all were susceptible to cefiderocol, even if resistant to CZA [23]. Further studies investigating the resistance mechanism to cefiderocol in KPC-producing *Klebsiella pneumoniae* are needed.

In conclusion, the spread of *Klebsiella pneumoniae* harboring KPC-3 variant enzymes, such as KPC-31, that confer resistance to CZA should be carefully monitored. As these variants are associated with restoration of meropenem susceptibility, MVB—instead of meropenem alone—may be a therapeutic option.

Acknowledgments

Financial support. This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Potential conflicts of interest. M.F. received grants and/or speaker honoraria from MSD, Angelini, Shionogi, Pfizer, Menarini, and Nordic Pharma. F.M. has participated in advisory boards and/or received speaker honoraria from Angelini, Correvio, Merck Sharp & Dohme (MSD), Nordic Pharma, Pfizer, Astellas, Gilead, Bristol-Myers Squibb (BMS), Janssen, ViiV, bioMérieux, Biotest, Becton Dickinson, Pfizer, and Shionogi. Declared conflicts of interest are outside the submitted work and did not affect the scientific objectivity of this study. The other authors have none to declare. 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.

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