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Coinfections of Two Strains of NDM-1- and OXA-232-Coproducing *Klebsiella pneumoniae* in a Kidney Transplant Patient

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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 here a fatal case of carbapenem-resistant *Klebsiella pneumoniae* (CRKP) infections in a renal transplant patient without a travel history in the prior year, from whom 2 genetically different CRKP (sequence type 14 [ST14] and ST2497) strains carrying the same plasmids and antimicrobial resistance genes, including bla_{NDM-1}, $bla_{OXA-232}$, $bla_{CTX-M-15}$, *armA*, and *tet*(D), were isolated from blood and the abdominal cavity. The isolates were susceptible to colistin, tigecycline, eravacycline, and cefiderocol, which was used to treat the CRKP in combination with ceftazidime-avibactam and polymyxin B and resulted in bacterial clearance. Despite the aggressive treatment, the patient died of ischemic colitis and multiorgan failure.

KEYWORDS carbapenem resistance, CRKP, NDM-1, OXA-232, ST14, ST2497, carbapenemase coproduction, cefiderocol

Carbapenem-resistant *Klebsiella pneumoniae* (CRKP) is an urgent and global threat to hospitalized patients. CRKP strains commonly carry carbapenemase-encoding genes, such as bla_{KPC}, $bla_{OXA-48\ group}$, and bla_{NDM}, accompanied by many other resistance genes that render almost all available antibiotics ineffective (1). Globally, coproduction of multiple types of carbapenemases in CRKP is on the rise and found to be associated with high-level resistance to carbapenems (2, 3). Recently, there has been a surge of NDM- and OXA-48 group-coproducing CRKP strains in several countries of endemicity. In particular, cases have been documented in Italy (4), India (5), Malaysia (6), and South Korea (7). In the Arabian Peninsula, up to 20% of CRKP strains were found to coproduce NDM and the OXA-48 group enzymes (8). Coproduction of NDM-1 and OXA-232 was first documented in the United States in 2014 from a patient that had traveled from India (9). In our institution, we have identified 1 or 2 cases of CRKP coproducing NDM and OXA-48 group enzymes each year since 2016 (unpublished data). Here, we document the case of a kidney transplant patient whose posttransplant clinical course was complicated by infections with two strains of extensively drug-resistant CRKP coproducing NDM-1 and OXA-232. Combination therapy with multiple antibiotics was used in the treatment.

CASE PRESENTATION

A 68-year-old female of Filipino descent with end-stage renal disease secondary to diabetes who had been on hemodialysis for 8 years presented to the UCLA Medical Center for a deceased-donor renal transplant (DDRT). She had not traveled for a year prior to her transplant. Based on DonorNet (https://unos.org), the donor was a 50-year-

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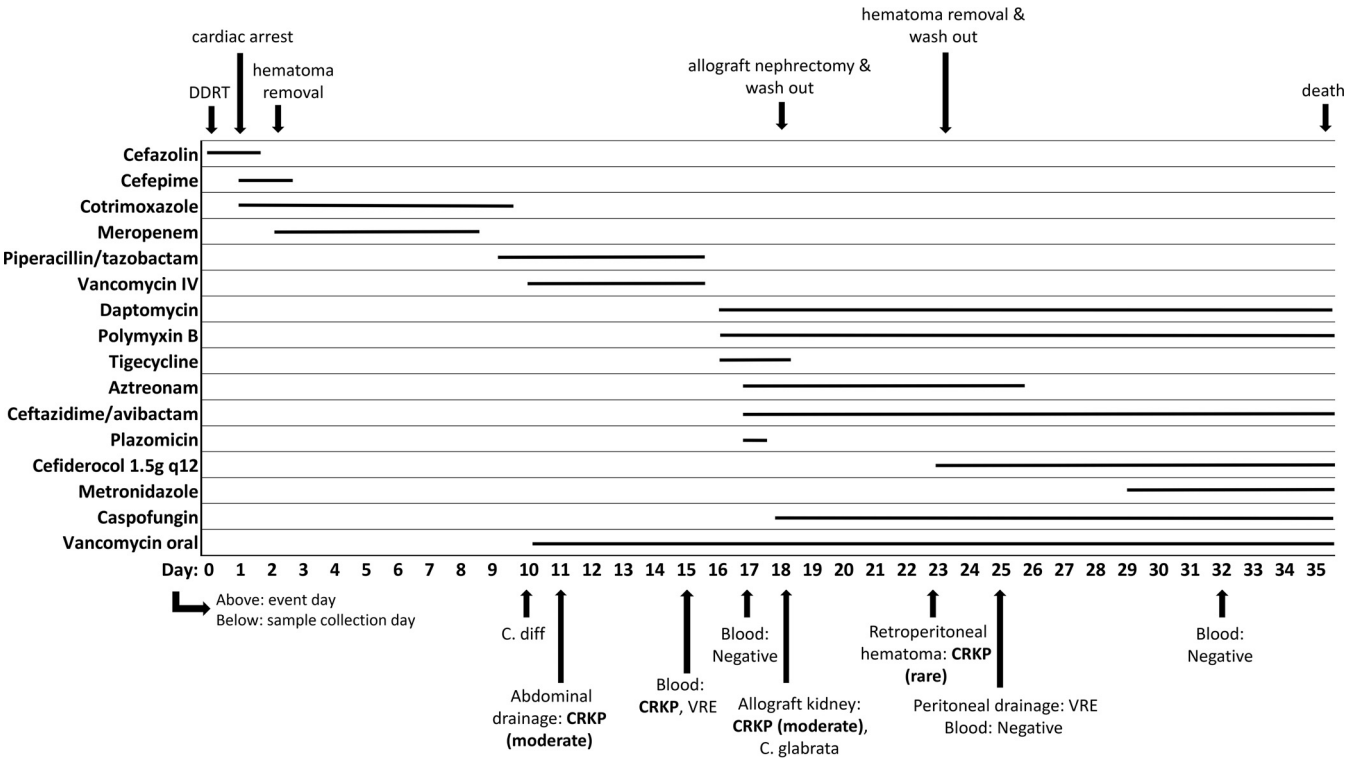

FIG 1 Timeline of the major clinical events, treatment, and microbiological findings. (Note that the number of days indicated for the microbiological findings were all based on sample collection times.)

old male with no significant past medical or travel history who passed away due to a stroke. The patient's postoperative course was complicated by cardiac arrest with pulseless electronic activity, requiring initiation of extracorporeal membrane oxygenation and continuous renal replacement therapy. An exploratory laparotomy was performed, with removal of hematoma surrounding the kidney allograft and placement of abdominal drains. CRKP was initially isolated from peritoneal drain cultures as part of an evaluation for leukocytosis. Carbapenemase genotype testing by CARBA-R (Cepheid, Sunnyvale, CA) routinely performed in the clinical laboratory indicated that the CRKP isolate was positive for both NDM-1 and OXA-48 group enzymes. CRKP was subsequently recovered from a blood culture, which showed the same phenotypic antimicrobial resistance pattern and the carbapenemase genotype pattern as the prior isolate. Due to a persistent right retroperitoneal hematoma likely infected with the CRKP strain, which would be difficult to treat medically alone, the patient underwent allograft nephrectomy and abdominal washout. Although the allograft did not appear grossly infected, the explant bacterial culture grew a moderate amount of CRKP organisms and pathology showed focal abscess formation, perinephric hemorrhage, and diffuse acute tubular necrosis. Five days later, a repeat hematoma removal and abdominal washout were performed, and only a small amount of CRKP organisms grew from the hematoma fluid (Fig. 1). These CRKP cells were susceptible to tigecycline and colistin but resistant to all other drugs, including the third- and fourth-generation cephalosporins, aztreonam, piperacillin-tazobactam, ceftolozane-tazobactam, ceftazidime-avibactam, ertapenem, imipenem, meropenem, meropenem-vaborbactam, amikacin, gentamicin, tobramycin, ciprofloxacin, levofloxacin, moxifloxacin, tetracycline, omadacycline, and minocycline. Intraoperative cultures were also positive for *Candida glabrata*, and blood cultures were positive for vancomycin-resistant *Enterococcus faecium* (VRE).

CHALLENGE QUESTION

This double-carbapenemase-producing CRKP strain posed a big challenge for treatment. Several novel antibiotics, including plazomicin, eravacycline, and cefiderocol, were considered. Both phenotypic susceptibility tests (Table 1) and whole-genome sequencing (WGS) were performed to provide more information to help guide better selection of these new drugs. WGS showed that the CRKP strain carries $bla_{OXA-232}$, bla_{NDM-1}, $bla_{CTX-M-15}$, *armA*, and *tet*(D). Based on these genotypic results, which of the following drugs, in addition to colistin or polymyxin B, may be considered to treat the CRKP strain?

A. Plazomicin
B. Eravacycline
C. Meropenem-vaborbactam
D. Ceftazidime-avibactam plus aztreonam
E. Cefiderocol
F. B, D, or E

TREATMENT AND OUTCOME

During her clinical course, treatment options were extremely limited, and phenotypic testing (disk diffusion) was carried out on several novel antibiotics, including plazomicin, omadacycline, eravacycline, and cefiderocol, to explore any alternative treatment options. All the isolates were resistant to plazomicin and omadacycline, but all cells were susceptible to eravacycline and cefiderocol (Table 1). The patient was initially treated with polymyxin B and tigecycline based on the phenotypic drug susceptibility results. This was subsequently changed to polymyxin B, ceftazidime-avibactam, and aztreonam based on the CARBA-R results (positive for both NDM-1 and the OXA-48 group enzymes) and a case report of successful treatment of an NDM- plus OXA-48 group-coproducing CRKP strain with ceftazidime-avibactam and aztreonam (10). Two days after the first positive blood culture that grew CRKP, the second blood culture turned negative (hospital day 17) (Fig. 1), but the tissues from the allograft nephrectomy the next day still grew a moderate amount of CRKP organisms. Plazomicin was added for 1 day but discontinued when the disk diffusion test revealed drug resistance (Table 1), which is consistent with the *armA* gene being detected by WGS 1 week later, since it confers high-level resistance to aminoglycosides, including plazomicin (11). Meropenem-vaborbactam was not chosen because it is not effective against OXA-48 group producers (12). We did not choose eravacycline due to its borderline susceptibility results (Table 1) and a lack of understanding of the effect of the tetracycline efflux gene *tet*(D) to the drug (see Table S1 in the supplemental material). Thus, the answer to the challenge question is E. After receiving the emergency use approval from the FDA, cefiderocol (1.5 g every 12 h [q12], without renal dosage adjustment) was administered for a total of 12 days, starting on the same day on which the repeat abdominal washout was performed (hospital day 23). During the course of cefiderocol treatment, aztreonam was discontinued after the first 2 days, but ceftazidime-avibactam and polymyxin B were continued throughout. This regimen (polymyxin B plus ceftazidime-avibactam plus cefiderocol) was decided due to our experience using ceftazidime-avibactam and polymyxin B to treat common carbapenem-resistant *Enterobacteriaceae* (CRE) infections in transplant patients, as well as our concern about using monotherapy, given our lack of experience with cefiderocol. Since our lab does not routinely perform the synergistic testing of ceftazidime-avibactam plus aztreonam, we did not have conclusive evidence to support continuing aztreonam treatment after cefiderocol became available. It is prudent to state, however, that the initial regimen (polymyxin B plus ceftazidime-avibactam plus aztreonam) might be as effective if continued, given multiple studies showing *in vitro* synergistic effects of ceftazidime-avibactam plus aztreonam on NDM- and OXA-48 group-coproducing *Enterobacteriaceae* species (13, 14). Subsequent blood cultures (hospital days 25 and 32) and peritoneal fluid culture (hospital day 25) were all negative for CRKP after cefiderocol was started, and sepsis physiology was improved, as demonstrated by the patient's

TABLE 1 Drug susceptibility profiles of plazomicin, omadacycline, eravacycline, tigecycline, and cefiderocol

Drug	AST method[a]	Zone sizes (mm) (interpretation) for *Enterobacteriaceae* or reference[b]	Blood isolate		Abdominal isolates from:					
					Abdominal drainage		Kidney allograft		Hematoma	
			Zone size or MIC	Interpretation	Zone size or MIC	Interpretation	Zone size or MIC	Interpretation	Zone size or MIC	Interpretation
Cefiderocol	DD	≤15 (resistant), 16–19 (intermediate), ≥20 (susceptible)	22 mm	Susceptible	21 mm	Susceptible	22 mm	Susceptible	22 mm	Susceptible
Eravacycline	DD	≥15 (susceptible)	15 mm	Susceptible	15 mm	Susceptible	15 mm	Susceptible	15 mm	Susceptible
Omadacycline	DD	≤15 (resistant), 16–17 (intermediate), ≥18 (susceptible)	16 mm	Intermediate	16 mm	Intermediate	15 mm	Resistant	15 mm	Resistant
Plazomicin	DD	≤13 (resistant), 14-15 (intermediate), ≥16 (susceptible)	6 mm	Resistant	6 mm	Resistant	6 mm	Resistant	6 mm	Resistant
Amikacin	BMD	21	>32 μg/ml	Resistant	>32 μg/ml	Resistant	>32 μg/ml	Resistant	>32 μg/ml	Resistant
Aztreonam	BMD	21	>32 μg/ml	Resistant	>32 μg/ml	Resistant	>32 μg/ml	Resistant	>32 μg/ml	Resistant
Cefazolin	BMD	21	>32 μg/ml	Resistant	>32 μg/ml	Resistant	>32 μg/ml	Resistant	>32 μg/ml	Resistant
Cefepime	BMD	21	>32 μg/ml	Resistant	>32 μg/ml	Resistant	>32 μg/ml	Resistant	>32 μg/ml	Resistant
Ceftazidime	BMD	21	>32 μg/ml	Resistant	>32 μg/ml	Resistant	>32 μg/ml	Resistant	>32 μg/ml	Resistant
Ceftazidime-avibactam	BMD	21	>32 μg/ml	Resistant	>32 μg/ml	Resistant	>32 μg/ml	Resistant	>32 μg/ml	Resistant
Ceftriaxone	BMD	21	>32 μg/ml	Resistant	>32 μg/ml	Resistant	>32 μg/ml	Resistant	>32 μg/ml	Resistant
Ciprofloxacin	BMD	21	>2 μg/ml	Resistant	>2 μg/ml	Resistant	>2 μg/ml	Resistant	>2 μg/ml	Resistant
Colistin	BMD	21	≤2 μg/ml	Wild type	≤2 μg/ml	Wild type	≤2 μg/ml	Wild-type	≤2 μg/ml	Wild type
Ertapenem	BMD	21	>4 μg/ml	Resistant	>4 μg/ml	Resistant	>4 μg/ml	Resistant	>4 μg/ml	Resistant
Gentamicin	BMD	21	>16 μg/ml	Resistant	>16 μg/ml	Resistant	>16 μg/ml	Resistant	>16 μg/ml	Resistant
Imipenem	BMD	21	>16 μg/ml	Resistant	>16 μg/ml	Resistant	>16 μg/ml	Resistant	>16 μg/ml	Resistant
Levofloxacin	BMD	21	>8 μg/ml	Resistant	>8 μg/ml	Resistant	>8 μg/ml	Resistant	>8 μg/ml	Resistant
Meropenem	BMD	21	>16 μg/ml	Resistant	>16 μg/ml	Resistant	>16 μg/ml	Resistant	>16 μg/ml	Resistant
Meropenem-vaborbactam	BMD	21	>32 μg/ml	Resistant	>32 μg/ml	Resistant	>32 μg/ml	Resistant	>32 μg/ml	Resistant
Minocycline	BMD	21	>16 μg/ml	Resistant	>16 μg/ml	Resistant	>16 μg/ml	Resistant	>16 μg/ml	Resistant
Piperacillin-tazobactam	BMD	21	128 μg/ml	Resistant	128 μg/ml	Resistant	128 μg/ml	Resistant	128 μg/ml	Resistant
Tigecycline	BMD	21	1 μg/ml	Susceptible	1 μg/ml	Susceptible	1 μg/ml	Susceptible	1 μg/ml	Susceptible
Tobramycin	BMD	21	>16 μg/ml	Resistant	>16 μg/ml	Resistant	>16 μg/ml	Resistant	>16 μg/ml	Resistant
Trimethoprim-sulfamethoxazole	BMD	21	>4/80 μg/ml	Resistant	>4/80 μg/ml	Resistant	>4/80 μg/ml	Resistant	>4/80 μg/ml	Resistant

[a]AST, antimicrobial susceptibility testing; DD, disk diffusion; BMD, broth microdilution.
[b]21, breakpoints were based on CLSI document M100 (21).

decreased vasopressor requirement and stable blood pressure. In addition to CRKP infection, the patient developed VRE bacteremia, *Candida glabrata* infection, and *Clostridium difficile*-associated diarrhea, which were treated with daptomycin, caspofungin, and oral vancomycin, respectively. Despite the aggressive treatment, the patient developed ischemic colitis with ongoing bloody stools and sepsis physiology, and the decision was made with the family to withdraw care.

WGS was performed using both MiSeq (Illumina, San Diego, CA) and MinION (Nanopore, UK) on one blood isolate and three abdominal isolates. The largest contig (chromosome) and 3 smaller contigs (plasmids) from the MinION sequence assembly were manually corrected and polished by the raw MiSeq sequences using Geneious (Biomatters, New Zealand). Center of Genomic Epidemiology tools, including ResFinder (for resistance genes), PlasmidFinder (for plasmids), and KmerFinder (for closely related strain), were also used. The single nucleotide polymorphism (SNP)-based and Kmer-based phylogenetic tree analysis was done by using CLCbio (Qiagen, Germany). The results revealed that there were two different CRKP strains: a sequence type 14 (ST14) blood isolate and novel ST2497 isolates (all 3 abdominal isolates were from an abdominal drainage specimen, allograft from a kidney, and a hematoma, with fewer than 3 SNP differences in their chromosomes) that possessed nearly identical plasmids and antimicrobial resistant gene profiles (Table S1). Interestingly, all 3 of these SNPs caused amino acid changes in an SOS response-associated peptidase (SRAP) gene that is related to adaptive mutagenesis under stress conditions (15). Both bacterial strains (of ST14 and ST2497) possessed three plasmids, including a colKP3-type plasmid (6.1 kb) carrying $bla_{\text{OXA-232}}$, an IncFIB (Mar)/IncHI1B-type plasmid (297.8 kb) carrying $bla_{\text{NDM-1}}$ and other resistance genes, such as $bla_{\text{CTX-M-15}}$, *armA*, and *tet*(D), and an IncFIB(pQil)-type plasmid (57.2 kb) carrying *catA1* (Table S1). Interestingly, both the $bla_{\text{NDM-1}}$-carrying plasmids and the $bla_{\text{OXA-232}}$ carrying plasmids in our isolates are genetically related (>94% coverage and >99% identity) to plasmid1 (GenBank accession number CP006799) and plasmid4 (accession number CP006802) in the first documented NDM-1- and OXA-232-coproducing CRKP strain PittNDM01 (accession number CP006798) in the United States in 2014 (16), indicating that these 2 plasmids have been circulating for at least 5 years without major changes. Chromosomally, both strains possess the fluoroquinolone and the fosfomycin resistance genes *oqxB*, *oqxA*, and *fosA*, but the ST14 isolate contained a penicillinase gene, $bla_{\text{SHV-28}}$, while the ST2497 isolates had a different penicillinase gene, $bla_{\text{SHV-182}}$. Phylogenetic analysis of the isolates showed that the ST14 isolate from the blood was closely related to strain KP67 (accession number AP018753.1), which also carries the $bla_{\text{NDM-1}}$ gene that originated from Bangkok, Thailand (17), with 99.8% genome coverage and 98.7% pairwise identity, while the ST2497 isolates were genetically close to another strain, CRK0298 (accession number CP034039) originally identified from a body fluid in Ohio in 2015 with 95.1% genome coverage and 99.5% pairwise identity. However, no further information is available regarding the Ohio strain.

Our report highlighted the emergence of a highly drug-resistant NDM-1- and OXA-232-coproducing CRKP strain within the United States. Alarmingly, they were found in a patient without a history of travel within the prior year and contributed directly to her death. There was no clear source of these CRKP strains, and no other genetically related CRKP strains have been isolated after this case at our center. Donor cultures were negative for CRKP and other Gram-negative organisms. Therefore, we hypothesize that the patient was an asymptomatic carrier prior to hospital admission and transplantation. One possibility is that the patient acquired the CRKP colonization due to distant travel history to an area of endemicity, such as Southeast Asia. Another possibility is that the CRKP strain came from a dialysis center to which the patient had been, since dialysis may be a risk factor for nosocomial transmission of CRE (18). The third possibility is that she might have acquired the CRKP strain from a close family member or a visitor who had recently traveled from a country of endemicity, but that information is unavailable.

To our knowledge, this is also the first case report of the use of cefiderocol, a

siderophore cephalosporin with activity against carbapenem-resistant and Gram-negative bacilli, for treating the double-carbapenemase-producing CRKP strain in the United States. As a conjugate between cephalosporin and a siderophore, which forms a chelating complex with iron ("Trojan Horse") to utilize the bacterial iron transport system to penetrate the outer membrane of bacteria, cefiderocol has potent *in vitro* antimicrobial activity against multidrug-resistant (MDR) *Enterobacteriaceae*, including carbapenemase producers (19). The role of cefiderocol in this case, however, was complicated by multiple combination regimens prior to its administration. Besides polymyxin B and ceftazidime-avibactam, which were administered throughout, tigecycline (3 days) and aztreonam (10 days) were used. It is also unclear whether there is a synergistic effect of cefiderocol plus ceftazidime-avibactam, which were added empirically only based on our clinical experience.

Interestingly, we identified a novel CRKP strain (ST2497) that carries identical plasmids shared by another more common CRKP strain (ST14) in the same patient from different anatomical sites. The identical plasmids in the 2 different CRKP strains may be due to a recent horizontal gene transfer event, but it is hard to prove this hypothesis due to limited isolates being available for study. In addition, the intrahost CRKP genetic heterogeneity (multiple sequence types or multiple lineages of the same sequence type) that was observed in this case and discovered by previous studies (20) highlight the limitations of using susceptibility patterns or single-isolate sequencing in an outbreak investigation. Only with sequencing all isolates were we able to determine that multiple strains of CRKP were responsible for the severe disease seen in this patient. This report also demonstrates the potential clinical application of WGS, as the timely receipt of information (ideally within 3 days) regarding both bacterial resistance gene profiles and high-definition strain typing may lead to more-guided decision-making for antibiotic treatment and more-accurate risk assessments for infection prevention.

SUPPLEMENTAL MATERIAL

Supplemental material is available online only.

SUPPLEMENTAL FILE 1, PDF file, 0.1 MB.

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We declare no conflict of interest.

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