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Managing All the Genotypic Knowledge: Approach to a Septic Patient Colonized by Different *Enterobacteriales* with Unique Carbapenemases

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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. Two expert clinicians then provide a commentary on the case.

ABSTRACT The recent development of new antimicrobials active against carbapenemase-producing *Enterobacteriales* (CPE) has brought new hope for the treatment of infections due to these organisms. However, the evolving epidemiology of bacteria with carbapenemases may complicate management, as providers are faced with treating patients colonized by bacteria producing multiple carbapenemases. Here, we present the clinical course and treatment of *Raoultella planticola* bacteremia in a cirrhotic patient known to be colonized with both bla_{KPC}- and bla_{OXA-48}-carrying organisms.

KEYWORDS OXA-48, *Raoultella planticola*, carbapenem-resistant *Enterobacteriales* (CRE), carbapenemase-producing *Enterobacteriales* (CPE), ceftazidime-avibactam

Since the first recovery of an organism producing *Klebsiella pneumoniae* carbapenemase (KPC) from a patient in 1996, a variety of clinically relevant carbapenemases in *Enterobacteriales* have been disseminating. KPC-producing bacteria have now been extensively reported worldwide, and a familiar tale has unfolded for several other carbapenemases—identification in a hospital, regional outbreaks, reports of travel-associated cases in distant locations, and finally endemicity across disparate regions of the world. OXA-48-producing *K. pneumoniae* was first identified in Istanbul in 2001; by 2012, OXA-48 producers had spread throughout Turkey, the Middle East, and North Africa, with sporadic identification in many European countries (1). The first clinical cases of infection due to OXA-48-producing *K. pneumoniae* in the United States were identified at our institution in 2012 without evidence of further transmission (2). Between June 2010 and September 2014, the CDC received eight carbapenemase-producing *Enterobacteriales* (CPE) isolates harboring bla_{OXA-48} (3).

Meanwhile, the geographical distributions of different carbapenemases are increasingly converging; in India, $bla_{OXA-181}$ is commonly associated with bla_{NDM-1} and bla_{VIM-5}, and a hospital in Taiwan has experienced nosocomial spread of *K. pneumoniae* coproducing KPC and OXA-48 (4, 5). OXA-48 producers can be challenging to detect, as

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OXA-48 exhibits poor hydrolysis of extended-spectrum cephalosporins; thus, elevated MICs for these antibiotics are not observed in the absence of additional beta-lactamases (6). OXA-48 also has greater activity against imipenem than other carbapenems, so screening methods that rely on carbapenems other than imipenem may miss OXA-48 producers (6). Furthermore, OXA-48 is not inhibited by traditional beta-lactamase inhibitors, including clavulanic acid, tazobactam, and sulbactam (6). Clinical evidence regarding treatment is limited—OXA-48 producers have not been included in recent trials assessing performance of the novel beta-lactamase inhibitors, which may be helpful but remain clinically untested (5). We report a case in which the simultaneous potential for KPC-producing and OXA-48-producing organisms complicated the choice of empirical treatment, a situation which may become more common for clinicians, as nosocomial risk factors for CPE often overlap and the molecular epidemiology of CPE continues to evolve.

CASE PRESENTATION

A 35-year-old male with cirrhosis was transferred to our institution from a hospital in West Virginia for management of severe anemia and decompensated cirrhosis. He received vancomycin and piperacillin-tazobactam due to reported fever on presentation, which was discontinued on admission. Routine perirectal screening for CPE, processed per usual practice in the clinical microbiology lab (7), was negative on admission to the medical intensive care unit (MICU). His anemia responded to transfusions without evidence of ongoing gastrointestinal bleeding. He was transferred to the floor unit the next day. Another perirectal screen on hospital day 4 showed colonization with *Klebsiella oxytoca* positive for bla_{KPC} and *Pantoea* species positive for $bla_{OXA\text{-}48\text{-}like}$ by PCR. On hospital day 8, he became febrile, tachycardic, and tachypneic; he was started on piperacillin-tazobactam with clinical improvement. Two sets of blood cultures were obtained and subsequently grew pan-susceptible *Escherichia coli*. Work-up did not reveal any clear source of infection. He was continued on piperacillin-tazobactam treatment with a plan for a 14-day course. On hospital day 10, he returned to the MICU for hemorrhagic shock and refractory anemia due to hemoperitoneum. He required continuous renal replacement therapy (CRRT) and had multiple central venous catheters placed. On hospital day 18, he again became febrile and tachycardic, and his antibiotic regimen was changed to vancomycin, meropenem (1 g every 8 h), and micafungin. Blood cultures became positive for Gram-negative rods on day 1 of growth in both bottles. On hospital day 19, the infectious disease team was consulted for management of Gram-negative rod bacteremia. At the time, the patient was known to be colonized by multiple species of CPE producing both KPC and OXA-48-like carbapenemases based on routine perirectal CPE screening.

CHALLENGE QUESTION

What is the best choice to include in empirical antibiotic therapy of Gram-negative rod bacteremia that developed during treatment with piperacillin-tazobactam in a patient known to be colonized with both KPC-producing CPE and OXA-48-like-producing CPE?

A. Colistin
B. Meropenem-vaborbactam
C. Ceftazidime-avibactam
D. Ceftolozane-tazobactam

TREATMENT AND OUTCOME

Meropenem was initially continued due to marked clinical improvement within the first 24 h of treatment. Work-up for a source of the bacteremia was unrevealing. Computed tomography (CT) of the abdomen demonstrated cholelithiasis without cholecystitis. Diagnostic paracentesis demonstrated a white blood cell count of 6,000/μl with 87% neutrophils; however, this was confounded by hemoperitoneum. The Gram stain and culture of fluid remained negative. On hospital day 21, the

TABLE 1 Features of clinical isolates, *E. coli* J53, and transconjugants[a]

Characteristic	Value for characteristic or MIC (μg/ml) (susceptibility test result)					
	CAVP427	**J53pCAVP427**	**CAVP428**	**CAVP433**	**J53pCAVP433**	**J53**
Species[b]	*Pantoea* spp.	*E. coli*	*K. oxytoca*	*R. planticola*	*E. coli*	*E. coli*
Source	Perirectal		Perirectal	Blood		
Susceptibility testing[c]						
AMK	≤8 (S)	≤8 (S)	≤8 (S)	≤8 (S)	≤8 (S)	≤4 (S)
AMX	>16 (R)	>16 (R)	>16 (R)	>16 (R)	>16 (R)	≤8 (S)
SAM	>16 (R)	>16 (R)	>16 (R)	>16 (R)	>16 (R)	
ATM	16 (R)	>16 (R)	8 (I)	>16 (R)	16 (R)	≤8 (S)
CRO	>32 (R)	>32 (R)	4 (R)	>32 (R)	>32 (R)	
FEP	>16 (R)	16 (R)	≤2 (S)	>16 (R)	8 (R)	≤2 (S)
TZP	>128 (R)	>128 (R)	64 (I)	>128 (R)	>128 (R)	
CAZ	8 (I)	8 (I)	8 (I)	16 (R)	4 (S)	≤1 (S)
CZA	≤2 (S)	≤2 (S)	≤2 (S)	≤2 (S)	≤2 (S)	
CIP	≤0.5 (S)	1 (S)	≤0.5 (S)	2 (S)	1 (S)	≤1 (S)
ETP	4 (R)	2 (R)	≤0.25 (S)	>8 (R)	2 (R)	≤0.5 (S)
MEM						
Sensititre	2 (I)	1 (S)	≤0.5 (S)	>8 (R)	1 (S)	≤0.25 (S)
Diam[d]	20 (I)	NA	23 (S)	6 (R)	NA	NA
MVB[d]	21 (S)	23 (S)	28 (S)	6 (R)	22 (S)	NA
GEN	≤2 (S)	≤2 (S)	≤2 (S)	≤2 (S)	≤2 (S)	≤1 (S)
TOB	≤2 (S)	≤2 (S)	≤2 (S)	≤2 (S)	≤2 (S)	≤1 (S)
SXT	≤2 (S)	≤2 (S)	≤2 (S)	≤2 (S)	≤2 (S)	≤2/38 (S)
TGC	≤1 (S)	≤1 (S)	≤1 (S)	4 (I)	≤1 (S)	≤0.5 (S)
Gene(s) of resistance[e]	*aph(6)-Id*, *aph(3'')-Ib*, bla_{OXA-48}, $bla_{CTX-M-9}$, *qnrB1*, *tet*(A)	bla_{OXA-48}, $bla_{CTX-M-9}$	bla_{KPC}	*aph(6)-Id*, *aph(3'')-Ib*, bla_{PLA2a}, bla_{OXA-48}, $bla_{CTX-M-9}$, *qnrB1*, *fosA*, *tet*(A)	bla_{OXA-48}, $bla_{CTX-M-9}$	

[a]Features of clinical isolates (CAVP427, CAVP428, and CAVP433), *E. coli* J53, and transconjugants (J53pCAVP427 and J53pCAVP433).
[b]Species identification was conducted using matrix-assisted laser desorption ionization-time of flight mass spectrometry (Biomerieux, Durham, North Carolina).
[c]MICs (in micrograms per milliliter) were determined using Sensititre panels and interpreted under Clinical and Laboratory Standards Institute (CLSI) M100-Ed28. In the absence of established CLSI breakpoints (i.e., for MVB and TGC), FDA breakpoints were used. Susceptibility result abbreviations: S, susceptible; R, resistant; I, intermediate; NA, not available. Drug abbreviations: AMK, amikacin; AMX, amoxicillin; SAM, ampicillin-sulbactam; ATM, aztreonam; CRO, ceftriaxone; FEP, cefepime; TZP, piperacillin-tazobactam; CAZ, ceftazidime; CZA, ceftazidime-avibactam; CIP, ciprofloxacin; ETP, ertapenem; MEM, meropenem; MVB, meropenem-vaborbactam; GEN, gentamicin; TOB, tobramycin; SXT, trimethoprim-sulfamethoxazole; TGC, tigecycline.
[d]Diameters (in millimeters) of inhibition by disk diffusion.
[e]Genes of resistance were determined by WGS and Resfinder for isolates CAVP427 and CAVP433. PCR for bla_{OXA-48} and $bla_{CTX-M-9}$ was performed on all isolates.

Gram-negative rods were identified to the species level as *Raoultella planticola* resistant to carbapenems and extended-spectrum cephalosporins, and the isolate was positive for $bla_{OXA-48-like}$ by PCR (GeneXpert, Cepheid) (see Table 1 for full antibiotic susceptibility testing [AST] results). His antibiotic regimen was changed to ceftazidime-avibactam and metronidazole, and he was treated for 14 days. Repeat blood cultures on hospital days 21 and 26 were negative. His treatment course was complicated by another MICU readmission for intubation and CRRT due to worsening kidney injury and respiratory failure (during CRRT, the blood flow rate was 250 ml/min and ceftazidime-avibactam was dosed at 2.5 g every 8 h). He was transferred back to the floor unit on hospital day 39 but returned to the MICU on hospital day 43 due to hypotension that limited hemodialysis. Shortly after transfer, the patient and his family decided to pursue comfort measures only, and he died within hours.

The advent of combination antibiotics containing novel beta-lactamase inhibitors (BLI) has expanded treatment options for CPE infections; however, these agents are not created equal, and physicians should be familiar with the treatment implications of common carbapenemases. Avibactam is a novel diazabicyclooctane non-beta-lactam BLI that has demonstrated inhibition of class A and C beta-lactamases as well as class D OXA-48 carbapenemase (5). Thus, ceftazidime-avibactam may be a treatment option for both KPC- and OXA-48-producing CPE. Unfortunately, the development of ceftazidime-avibactam resistance among KPC producers during therapy has already been reported (8). Meropenem-vaborbactam has enhanced potency against KPC producers *in vitro* and has been tested in a randomized clinical trial in CPE; thus, some

providers may prefer meropenem-vaborbactam for infections due to KPC producers (9). However, vaborbactam does not inhibit the activity of OXA-48 (5). While this patient did not survive the hospitalization, ceftazidime-avibactam monotherapy appeared to successfully treat his infection due to OXA-48-producing *R. planticola* based on his initial clinical improvement and negative follow-up blood cultures. Retrospective studies have suggested that combination therapy is superior to monotherapy in the treatment of infections due to OXA-48 producers; however, these data are largely from the era before the newer beta-lactam/BLI combinations (5). Whether ceftazidime-avibactam monotherapy is adequate for treatment of OXA-48 producers is not firmly established; however, a recent retrospective review found a 62.5% clinical cure rate in patients treated with ceftazidime-avibactam and found no difference in clinical cure or 90-day mortality between patients receiving it as monotherapy versus combination therapy (10).

This patient had no history of international travel, and based on the institution's previous experience with wastewater reservoirs for KPC-producing organisms, there was concern for an environmental source for his infection (11). Environmental sampling of the MICU and floor rooms the patient inhabited was performed as previously described (11), and PCR for bla_{KPC} and bla_{OXA-48} was performed for all isolates that were phenotypically positive for carbapenemase production by modified carbapenemase inactivation method (12). No environmental isolates producing OXA-48 were found, and screening of patients exposed to the same units revealed no additional bla_{OXA-48} colonized patients. As there had not been a case at our institution since 2012 and this patient had exposure to multiple other hospitals prior to admission, bla_{OXA-48} is most likely circulating in hospitals in the region and was missed by the initial admission screening.

The genetic contexts for bla_{KPC} and bla_{OXA-48} are unique. Most reports of bla_{OXA-48} involve a single broad-host-range plasmid, while bla_{KPC} in our institution has been characterized by transmission where the most consistent genetic element is the Tn*4401* transposon which carries bla_{KPC}. Further characterization of the patient's isolates was performed in the research laboratory. Whole-genome sequencing (WGS) (Illumina MiSeq) of the OXA-48 producing CPE isolates from the patient (CAVP427 and CAVP433) was performed. Using WGS data, known genes of resistance were identified using Resfinder, and both isolates also harbored $bla_{CTX-M-9}$ (Table 1) (13). Plasmid transfer from isolates CAVP427 and CAVP433 was performed via filter mating with *E. coli* J53 Rif^r; the resulting transconjugants underwent PCR and AST. There was significant overlap in the resistance genes of isolates CAVP427 and CAVP433 based on WGS. PCR analysis of J53p427 and J53p433 revealed transfer of both bla_{OXA-48} and $bla_{CTX-M-9}$, suggesting that the genes encoding both enzymes may be colocated on the same plasmid (14). While the first reports of OXA-48-producing *Enterobacteriales* involved a broad-host-range plasmid without other resistance genes, variant plasmids harboring $bla_{CTX-M-14}$ and $bla_{CTX-M-15}$, in addition to bla_{OXA-48}, have since been described (3, 15). The possibility that plasmids harboring both bla_{OXA-48} and bla_{CTX-M} genes are circulating in the United States is alarming. While OXA-48 lacks the ability to efficiently hydrolyze extended-spectrum cephalosporins, in combination with a beta-lactamase like CTX-M-9, it confers resistance to all beta-lactam antibiotics.

R. planticola as the pathogen in this case also merits attention. Primarily an environmental bacterial species, it has been increasingly recognized as a (rare) human pathogen (16). A retrospective analysis of clinical *R. planticola* isolates from a Turkish hospital from 2011 to 2015 identified three carbapenem-resistant isolates, and all harbored $bla_{OXA-48-like}$ (16). Per our literature review, this is the only previous report of infection due to OXA-48-producing *R. planticola*. Even more interesting is the preceding colonization of this patient with OXA-48-producing *Pantoea* sp., which in combination with the results of our mating experiments suggests *in vivo* transfer of bla_{OXA-48} and $bla_{CTX-M-9}$ between these rare organisms. Of note, another group recently highlighted the role of horizontal gene transmission in the spread of bla_{OXA-48} among *Enterobacteriales* in their report of six patients colonized with OXA-48-producing *Kluyvera* sp.; in two patients, *Kluyvera* coexisted with

other OXA-48-producing species, including *Raoultella ornithinolytica*, *K. pneumoniae*, and *E. coli* (17). Given the role of the hospital wastewater in transmission and perpetuation of resistant Gram-negative bacteria, carbapenemase gene exchange by environmental organisms with pathogenic potential is concerning.

Multiple aspects of this case are unusual: OXA-48-producing bacteria in a patient in the United States without international exposure, cocolonization with KPC and OXA-48 producers, OXA-48 production by *R. planticola*, and likely colocation of $bla_{\text{CTX-M-9}}$ and $bla_{\text{OXA-48}}$ on a single plasmid. The intersection of all these rarities in a single patient speaks to the dynamic nature of resistant Gram-negative bacteria; unfortunately, as microbes with carbapenemases continue to disseminate, this may be encountered more frequently. Awareness of the changing epidemiology of these organisms, understanding of the molecular mechanisms of resistance, and knowledge of the limitations of various antibiotic agents is crucial to preserving the activity of our newest treatment options for these challenging infections.

Data availability. NCBI records for the two isolates sequenced in association with this paper can be found under BioSample no. SAMN12138073 and SAMN12138074 (BioProject PRJNA246471).

COMMENTARY

The case presented by Park and colleagues highlights many of the challenges encountered by clinicians dealing with multidrug-resistant organisms (MDROs). In particular, barriers to effective care highlighted in this case include (i) rapid initial identification of a resistant organism, (ii) accurate interpretation of genotypic and phenotypic data by the clinician, and (iii) selecting an optimal antimicrobial regimen in the presence of multiple resistance determinants. Unfortunately, it is highly likely that scenarios as the one described herein will become increasingly common across many health care settings in the near future. Hence, it is more important than ever for clinicians to comprehend the relevance of understanding the mechanisms of resistance and mode of action of our antimicrobial ammunition and to use this knowledge to guide therapeutic decisions.

Identifying when a patient is colonized with a MDRO, while an important first step, can often be a challenge for the clinical microbiology lab. Selection of screening criteria and methodology is constrained by labor and cost, and some resistance mechanisms may be more difficult to detect. As the authors astutely point out, the catalytic activity of OXA-48-like carbapenemases often results in subtle changes in the activity of carbapenems and extended-spectrum cephalosporins, many of which remain fully susceptible *in vitro*. Moreover, routine phenotypic screening is less sensitive for these enzymes, making OXA-48 a particularly insidious threat (1). Rapid molecular diagnostics are an emerging tool for the clinician, and they can provide more timely detection of common resistance mechanisms. However, some limitations of these assays include fixed panels, which may miss newly emerging mechanisms and false-negative results when organisms are present below the limits of detection. In this case, it is noteworthy that while initial screening did not detect resistance determinants, a subsequent screening (4 days later) identified both bla_{KPC} and $bla_{\text{OXA-48}}$. The fact that no evidence of $bla_{\text{OXA-48}}$ was observed in the hospital environment or in other patients is intriguing and might point toward the possibility of an initial false-negative result.

Emerging genotypic testing often provides important clues regarding the potential approach to MDROs, but it requires the treating physician to understand the information and act accordingly. In this case, colonization with MDROs was identified on hospital day 4; however, infectious disease (ID) specialists were not involved until hospital day 19 despite two febrile episodes with documented bacteremia. The choice of empirical antimicrobials active against Gram-negative pathogens for each of these episodes, piperacillin-tazobactam and meropenem, would not be expected to have reliable efficacy against isolates harboring bla_{KPC} or $bla_{\text{OXA-48}}$. Studies investigating the use of rapid diagnostics demonstrate that reporting results alone is often insufficient to make significant changes to prescriber behavior. Indeed, having an active antimicrobial

stewardship component to guide clinicians is associated with institution of (or de-escalation to) effective therapy (18). Instituting a timely and effective empirical regimen can be a challenge in patients colonized with MDROs and highlights the growing need to educate primary providers on resistance and when to seek help. Retrospective studies of staphylococcal bacteremia and severe MDRO infections have demonstrated that consulting ID specialists is associated with better outcomes and decreased mortality (19, 20). In this particular case, consultation with ID specialists earlier in the hospital stay may have influenced the selection of therapy to manage the first episode of bacteremia, caused by a pan-susceptible *E. coli*. Careful selection of both empirical and definitive antibiotics is critical, since it is well established that selective pressure plays an important role in the emergence of resistant organisms.

Managing the results of genotypic testing is especially important with the introduction of new antibiotics, particularly the novel β-lactamase inhibitors. These compounds have important differences in their spectrum of inhibition, and understanding the resistance mechanism of an infecting isolate allows for targeted use. For example, boronic acid inhibitors such as vaborbactam are excellent inhibitors of KPC enzymes, but their activity against OXA-48-like enzymes is unreliable (21). In contrast, the diazabicyclooctane avibactam displays broad inhibition against most Ambler class A and C serine β-lactamases, and it also inhibits select class D enzymes, such as OXA-48-like carbapenemases (but not other OXA-type enzymes) (22). In this case, ceftazidime-avibactam was used successfully, despite the ultimate death of the patient, and would have been the advisable empirical therapy in a patient known to be colonized with organisms harboring bla_{KPC} and bla_{OXA-48}.

This case illustrates the increasingly complex scenario faced by many clinicians dealing with MDROs, the role of rapid molecular testing for resistance determinants, and the importance of interpreting and acting upon these results. Finally, it highlights the often silent presence of MDROs harboring OXA-48-like enzymes, a particularly worrisome menace.

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