IDCases 21 (2020) e00816

Contents lists available at ScienceDirect

IDCases

journal homepage: www.elsevier.com/locate/idcr

Case report

# A New Delhi metallo-β-lactamase (NDM)-positive isolate of *Klebsiella pneumoniae* causing catheter-related bloodstream infection in an ambulatory hemodialysis patient

Kevin H. Toomer[a,b,*], Daniela de Lima Corvino[a], Katie A. McCrink[c], Jose Armando Gonzales Zamora[a]

[a] Infectious Diseases Division, Department of Medicine, University of Miami Miller School of Medicine, Miami, FL, USA
[b] Department of Microbiology and Immunology, University of Miami Miller School of Medicine, Miami, FL, USA
[c] Department of Pharmacy, Jackson Memorial Hospital, Miami, FL, USA

ARTICLE INFO

*Article history:*
Received 26 January 2020
Accepted 9 May 2020

*Keywords:*
Carbapenemases
New Delhi metallo-β-lactamase
*Klebsiella pneumoniae*
Catheter-related infection
Hemodialysis

ABSTRACT

The New Delhi metallo-β-lactamase (NDM) is a mediator of broad antimicrobial resistance among the *Enterobacteriaceae* and other gram-negative pathogens that cause opportunistic and nosocomial infections. In the decade since its discovery, NDM has spread worldwide and represents an increasing threat to public health. NDM is capable of hydrolyzing nearly all known β-lactam antibiotics, including the carbapenems, and due to its zinc ion-dependent catalytic mechanism is unaffected by available β-lactamase inhibitors. We report a case of catheter-related bloodstream infection caused by a pan-resistant, NDM-positive isolate of *Klebsiella pneumoniae* in an ambulatory end-stage renal disease patient started on hemodialysis approximately 8 weeks prior. The absence of any recent hospitalization indicates that the infection was likely acquired from a hemodialysis center in the United States. This case demonstrates the increasing prevalence of antimicrobial resistance mechanisms in ambulatory as well as inpatient healthcare settings, and highlights the particular risk of the outpatient hemodialysis facility as an optimal environment for colonization with multidrug- and pandrug-resistant pathogens.


## Introduction

Expression of the β-lactamase enzymes known as carbapenemases has become widespread among clinically important *Enterobacteriaceae* and non-enteric gram-negative bacilli (*Pseudomonas* spp. and *Acinetobacter baumannii*), driving increasing rates of antibiotic resistance in nosocomial and opportunistic infections. Carbapenemases typically possess a broad spectrum of substrate activity, with capacity to hydrolyze not only carbapenems but one or more other classes of β-lactam antimicrobials in widespread clinical use (penicillins, cephalosporins, and monobactams) [1]. These enzymes tend to be encoded on plasmids and other mobile genetic elements, allowing their expression to propagate rapidly to new locations and between discrete gram-negative species in healthcare settings [1,2].

The present case of New Delhi metallo-β-lactamase (NDM)-positive *Klebsiella pneumoniae* bacteremia in an ambulatory patient with no history of recent hospitalization highlights the role of outpatient hemodialysis centers as favorable sites for colonization with emerging multidrug- and pandrug-resistant pathogens [3]. In evaluating possible routes of exposure to resistant pathogens, it is important to assess patients' prior contact with ambulatory healthcare facilities as well as inpatient hospital admissions. Clinicians must maintain a high index of suspicion for bacteremia in any hemodialysis patient with corresponding symptoms.

## Case

A 53-year-old male with end-stage renal disease on hemodialysis (HD) presented to the emergency department (ED) at Jackson Memorial Hospital with a 2-day history of nausea, vomiting, fever, and chills. He stated that during his last appointment at his outpatient HD center 2 days ago, a nurse noted local erythema and discharge at his port site and advised him to go to the ED. However, he delayed presenting until his constitutional symptoms became intolerable. At the time of admission, he had been receiving outpatient HD for approximately 8 weeks. HD was performed

* Corresponding author at: Infectious Diseases Division, Department of Medicine, University of Miami Miller School of Medicine, Miami, FL, USA.
*E-mail address:* khtoomer@med.miami.edu (K.H. Toomer).

https://doi.org/10.1016/j.idcr.2020.e00816

through a right-sided tunneled central venous catheter (CVC), which had been replaced 2 weeks prior at the same site due to catheter obstruction. Past medical history included type 2 diabetes mellitus for 28 years, currently controlled on insulin, and longstanding hypertension. His only outpatient medication was subcutaneous insulin (basal and bolus). He lives in South Florida with his wife and two children, and denied sick household contacts. He is employed as a construction worker. He reported that he often sweats profusely due to working outdoors and was not compliant with CVC cleaning instructions following catheter replacement. The patient is originally from Nicaragua but has lived in the United States for 30 years and denied recent travel abroad.

On physical exam, the patient was febrile to 103.3F. Laboratory studies revealed mild leukocytosis of 11,300 WBC/μL (88.1% segmented neutrophils). Glucose was 283 mg/dL, BUN/Cr was 57/6.57, with no significant electrolyte disturbances. Erythema was noted surrounding the catheter site, but no local fluctuance, discharge, or tenderness to palpation was evident. The patient was treated empirically with intravenous (IV) vancomycin (dosing guided by therapeutic drug monitoring) and cefepime (1 g q24h) pending blood culture results. 1 of 2 admission blood cultures was positive for gram-negative rods, found to be *K. pneumoniae* on speciation. This isolate was found to be resistant to nearly all antimicrobials in the initial MIC screening panel performed by VITEK 2, which included first-, second-, third- and fourth-generation cephalosporins, aminoglycosides, fluoroquinolones, carbapenems, and β-lactam/β-lactamase inhibitor combinations. The only initially tested agents to which the isolate was susceptible were tetracycline and tigecycline (Table 1). These results became available on Day 2 of hospitalization, at which time Infectious Diseases was consulted and the patient was placed on contact isolation. Antibiotic therapy was escalated with addition of IV ceftazidime/avibactam (0.94 g q24h) pending additional susceptibility testing. Vancomycin and cefepime were discontinued at this time, and tunneled CVC was removed. Following catheter removal, the patient remained comfortable and afebrile, with no leukocytosis or symptom recurrence. Culture of catheter tip and concurrent blood cultures were negative.

On Day 4 of hospitalization, carbapenemase genotypic testing by Xpert® Carba-R (Cepheid, CA, USA) showed that the *K. pneumoniae* isolate carried the $bla_{NDM}$ gene. Additional testing by microdilution and Etest revealed marked resistance to ceftazidime/avibactam (MIC ≥ 256 μg/mL) and meropenem/vaborbactam (MIC ≥ 256 μg/mL), as well as resistance to colistin (MIC ≥ 4 μg/mL), polymyxin B (MIC ≥ 4 μg/mL), and fosfomycin (MIC = 384 μg/mL). The patient was placed on enhanced contact precautions and test results were reported to the Florida Department of Health. Antimicrobial therapy was escalated further with the addition of IV aztreonam (500 mg q6h), selected due to its unique resistance to hydrolysis by MBLs, and IV tigecycline (100 mg q12h). As the patient had no acute indications for HD, the decision was made by Nephrology to give patient a line holiday prior to placement of new left-sided catheter. Day 4 blood cultures were also negative. The patient had no subjective symptoms, and vitals and complete blood count (CBC) remained within normal limits. Combination testing of in vitro susceptibility was performed on the isolate to evaluate for antimicrobial synergy. MIC values of aztreonam and ceftazidime/avibactam alone were ≥4 μg/mL and ≥256 μg/mL, respectively (Table 1). However, MIC of aztreonam in the presence of ceftazidime/avibactam was ≥1.0 μg/mL, and MIC of ceftazidime/avibactam in the presence of aztreonam was ≥32 μg/mL. From these data, the Fractional Inhibitory Concentration (FIC) of the aztreonam + ceftazidime/avibactam combination was calculated as 0.375. A value ≤0.5 is consistent with the presence of synergy, justifying the continuation of this regimen.

A left-sided CVC was placed on Day 8 of hospitalization. Blood cultures obtained on Day 3 and Day 4 of hospitalization remained negative. Resumption of HD was well-tolerated, and the patient remained clinically asymptomatic on IV antimicrobial regimen of aztreonam, ceftazidime/avibactam, and tigecycline. Erythema at the previous site of right-sided catheter insertion was resolved by this time, and no tenderness was noted on serial physical

**Table 1**
Antimicrobial resistance testing of *Klebsiella pneumoniae* isolate from admission blood culture.

| | **MIC interp** | MIC dilution (μg/mL) | E dilution (μg/mL) | E interp | PCR Results |
|---|---|---|---|---|---|
| **Amikacin** | **R** | | | | |
| **Ampicillin/sulbactam** | **R** | | | | |
| **Aztreonam** | **R** | ≥4 | | | |
| **Cefazolin (urine)** | **R** | | | | |
| **Cefazolin (non urine)** | **R** | | | | |
| **Cefepime** | **R** | | | | |
| **Cefoxitin** | **R** | | | | |
| **Ceftazidime** | **R** | | | | |
| **Ceftriaxone** | **R** | | | | |
| **Gentamicin** | **R** | | | | |
| **Levofloxacin** | **R** | | | | |
| **Meropenem** | **R** | ≥8 | ≥32 | R | |
| **Piperacillin/tazobactam** | **R** | | | | |
| **Trimethoprim/sulfamethoxazole** | **R** | | | | |
| **Tetracycline** | **S** | | | | |
| **Tigecycline** | **S** | | | | |
| **Tobramycin** | **R** | | | | |
| Colistin | R | ≥4 | | | |
| Fosfomycin | R | = 384 | | | |
| Polymyxin B | R | ≥4 | | | |
| Ceftazidime/avibactam | | | ≥256 | R | |
| Meropenem/vaborbactam | | | ≥256 | R | |
| Carbapenemase PCR-IMP | | | | | Not detected |
| Carbapenemase PCR-KPC | | | | | Not detected |
| Carbapenemase PCR-NDM | | | | | Detected |
| Carbapenemase PCR-OXA-48 | | | | | Not detected |
| Carbapenemase PCR-VIM | | | | | Not detected |

Note: Characters in bold indicate initial MIC screening results obtained on hospitalization Day 2. Normal typeface indicates results of subsequent reflex testing.

examinations. Two sets of negative repeat blood cultures and absence of clinical evidence of sepsis or skin and soft tissue infection (SSTI) indicated that step down in antimicrobial therapy was warranted. Tigecycline was discontinued on Day 8 of hospitalization. IV antibiotic therapy with aztreonam and ceftazidime/avibactam was continued for 10 days from first negative blood culture, in accordance with 2009 IDSA clinical practice guidelines for management of intravascular catheter-related bloodstream infection (CRBSI) [4]. The patient was discharged home, with arranged home health care follow-up to ensure completion of IV antibiotic course. The patient was also scheduled for outpatient nephrology follow-up and resumption of HD on MWF schedule. Counseling was provided on importance of thorough CVC cleaning and dressing changes.

## Discussion

Carbapenemases and other β-lactamase enzymes represent a predominant mechanism of antimicrobial resistance among gram-negative bacterial pathogens [5]. Their propagation has spurred a revival in the use of the older antimicrobials fosfomycin, colistin, and polymyxin B as agents of last resort, despite limited efficacy and significant adverse effects [6]. Carbapenemases of the metallo-β-lactamase (MBL) class represent a particular therapeutic challenge. In addition to broad-spectrum activity against nearly all β-lactam antimicrobials, MBLs utilize a distinct, zinc ion-based catalytic mechanism which renders them immune to available β-lactamase inhibitors. Their high degree of structural and biochemical variation, with sequence identity of less than 20% across subclasses [7], has frustrated drug development. Although human trials are ongoing [2,8], no targeted MBL inhibitor has yet been approved for clinical use. The New Delhi metallo-β-lactamase (NDM) exemplifies the capacity of locally endemic carbapenemases to achieve global dispersion with alarming speed. Initial case reports of NDM-positive infections in the West were confined to Indian-born patients or those who had received medical care in India, a pattern consistent with dissemination from a regional source. However, since its initial characterization in 2009, NDM has become established worldwide, with 24 variants identified in >60 species across 11 bacterial families as of January 2019 [2].

At present, NDM variants are most abundantly expressed among the *Enterobacteriaceae*. *K. pneumoniae* is the most commonly implicated species, accounting for slightly more than 50% of positive isolates, followed by *Escherichia coli* and the *Enterobacter cloacae* complex. NDM-positive *Pseudomonas* spp. and *Acinetobacter baumannii* isolates are also encountered with increasing frequency [2]. The rapid proliferation of NDM reflects the prevalence of horizontal gene transfer among gram-negative bacterial pathogens. Due in large part to this copious genetic exchange, carbapenemases typically coexist with other antimicrobial resistance mechanisms, further hindering therapeutic strategies. For instance, aztreonam, the only monobactam in clinical use, is uniquely stable to hydrolysis by MBLs. However, it is poorly suited for use as a single agent to treat MBL-positive organisms, as it remains vulnerable to hydrolysis by the active-site serine β-lactamases that such pathogens co-express [2]. The absence of targeted pharmacotherapy for these resistant pathogens forces clinicians to improvise treatment regimens from a limited armamentarium of antibiotics, without the benefit of large-scale clinical trials to guide decision-making. Pending the introduction of new antimicrobials, synergistic combinations that exploit the unique MBL resistance of aztreonam by pairing with available β-lactamase inhibitors represent a crucial strategy [9–11], as exemplified by an aztreonam/avibactam combination currently in clinical development [2]. Other emerging agents with evidence of clinical efficacy include the siderophore cephalosporin cefiderocol [12], currently in Phase III trials, and the semi-synthetic aminoglycoside plazomicin [13,14], approved by the FDA in June 2018. Eravacycline, a novel synthetic tetracycline-class antimicrobial, has shown broad in vitro activity against carbapenem-resistant organisms including MBL producers, but clinical data are still lacking [6,15].

While surveillance and research on carbapenemase-expressing pathogens has emphasized their role in nosocomial infections, the NDM-positive *K. pneumoniae* isolate in this case appears to have been acquired in an outpatient HD facility. Given the inherent risk factors in this patient population and abundant opportunities for cross-contamination between patients, staff, and environmental surfaces, HD facilities are likely to represent a major dissemination route for multidrug-resistant organisms, including carbapenem-resistant *Enterobacteriaceae* [3]. The high rate of access-related bloodstream infections in HD centers is compounded by incomplete staff adherence to established infection prevention guidelines [16], as well as frequent antibiotic misuse, with as many as 30% of antimicrobial doses administered in this setting deemed inappropriate [17]. Data are currently insufficient to assess overall colonization rates among end-stage renal disease patients, or to develop evidence-based infection prevention strategies specific to outpatient HD facilities [3].

Our patient's rapid and uneventful recovery contrasts with preliminary evidence associating end-stage renal disease with poor outcomes in the setting of carbapenem-resistant *Enterobacteriaceae* infection [18,19]. It is likely that this favorable clinical course is attributable to the prompt identification and removal of the infected CVC. Rigorous clinical and laboratory surveillance is imperative to quickly identify and localize infection in high-risk patient categories (e.g., maintenance HD or other indwelling vascular access, frequent inpatient or outpatient healthcare exposures, comorbidities such as type 2 diabetes mellitus). In the setting of limited therapeutic options, efficiency of diagnosis and management, with an emphasis on rapid source control, will be critical to improving outcomes. It should also be noted that a pathogen's broad spectrum of resistance identified on laboratory testing does not necessarily correlate with clinical virulence. Many documented NDM-positive infections have had favorable outcomes despite treatment with antibiotics against which the infecting pathogen exhibited in vitro resistance [2,20]. Although tested susceptibilities should be used to guide therapy whenever possible, this evidence must be interpreted with caution in the case of new and emerging resistance mediators, where data correlating laboratory and clinical results are sparse. Operating within a landscape of limited therapeutic options and scientific uncertainties, physicians will be required to make nuanced and individualized treatment choices in order to manage these burgeoning threats.

## Conclusions

Outpatient HD facilities are important dissemination sites for emerging multidrug- and pandrug-resistant bacterial pathogens, including MBL-positive organisms. High clinical suspicion for these infections is warranted in all HD patients, including those without a history of inpatient hospitalization. Given the lack of effective pharmacotherapy, treatment should emphasize prompt, aggressive source control measures.

## Author Contributions

K.H.T., D.D.C., and K.A.M. were involved in direct patient care. K. H.T wrote the manuscript. J.A.G.Z. edited the manuscript and provided critical revision. All the authors have discussed, read and approved the final manuscript.

## Funding

This research received no external funding.

## Informed Consent

Informed consent was obtained from the patient for publication of this case report.

## Declaration of Competing Interest

No potential conflict of interest was reported by the authors.

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