CASE REPORT

Two for the price of one: emerging carbapenemases in a returning traveller to New York City

Jaimie Mittal,¹ Wendy A Szymczak,¹ Yi Guo,¹ Michael H Levi,¹ Liang Chen,² Barry N Kreiswirth,² Paul F Riska,¹ Priya Nori¹

¹Albert Einstein College of Medicine and Montefiore Medical Center, Bronx, New York, USA

²Public Health Research Institute Center, NJMS-Rutgers University, Newark, New Jersey, USA

Correspondence to

Dr Jaimie Mittal, jaimie.mittal@outlook.com

Accepted 29 June 2018

SUMMARY

We report a case of a complex orthopaedic infection in a patient returning to New York City from Bangladesh where he was involved in a serious motor vehicle accident. He developed extensive osteomyelitis with a carbapenem-resistant *Klebsiella pneumoniae*. The isolate was unique due to the coexistence of New Delhi metallo- β -lactamase-1 and Oxacillinase type-181 carbapenemases, which are relatively uncommon in North America and were presumably acquired in Bangladesh. Herein, we explore challenges associated with management of carbapenem-resistant Enterobacteriaceae infections, including limited available data on effective antimicrobial therapy. We also highlight the added value of rapid diagnostic technology in guiding clinical management. Ultimately, the patient required both aggressive surgical management and combination therapy with aztreonam and ceftazidime-avibactam for true source control and favourable clinical outcome.

BACKGROUND

The Centres for Disease Control and Prevention (CDC) classify carbapenem-resistant Enterobacteriaceae (CRE) as an urgent threat in terms of clinical and economic impact, increasing incidence and transmissibility.¹ The CDC estimates as many as 9000 cases of CRE occur annually in the USA.¹ CRE infections are associated with higher mortality and poor outcomes due to diagnostic delays, their resistance to usual empiric antibiotic therapy and unfavourable host factors.²

Antibiotic resistance in CRE can be mediated by carbapenemase production (CP-CRE) or by other mechanisms, such as extended spectrum β -lactamase (ESBL) or AmpC β -lactamase production in conjunction with a porin mutation (non-CP-CRE). Specific resistance mechanisms may have prognostic implications and affect clinical management.² A recent study suggested that the odds of death at day 14 for patients with significant CP-CRE infection was four times greater than that of patients infected with non-CP-CRE.³

Herein we report a case of upper extremity osteomyelitis due to a novel CP-CRE isolate containing two carbapenemases (New Delhi metallo- β -lactamase-1 (NDM-1) and Oxacillinase type-181 (OXA-181)) likely acquired in Bangladesh. Clinical decision making was aided by rapid diagnostic technology. The patient ultimately required surgical

intervention and aztreonam and ceftazidime-avibactam combination therapy to achieve a positive clinical outcome.

CASE PRESENTATION

A 42-year-old man without significant medical history presented to our hospital in Bronx, New York, USA with progressive right arm pain following a serious motor vehicle accident, which occurred while visiting his home country of Bangladesh. During the accident, he sustained a degloving injury of his right forearm with an open elbow fracture. He was hospitalised for 2 months in Bangladesh and required several surgical procedures for fracture repair and wound closure. He received imipenem and colistin for up to 2 months while hospitalised, then an unknown oral regimen on discharge which he completed 3 weeks prior to his presentation at our hospital.

On examination, the patient's elbow was fixed at 90°, and there were two, 5 cm areas of breakdown in his skin graft. The olecranon was exposed. Wound cultures were obtained, and intravenous vancomycin and cefazolin were initiated. The patient received a washout and external fixation on hospital day 1 and was switched to tigecycline and meropenem postoperatively by our infectious diseases consult service, given the concern for a multidrug-resistant organism acquired abroad. Hospital records from Bangladesh revealed two organisms isolated from separate cultures: a CRE *Klebsiella pneumoniae* susceptible only to colistin and tigecycline and *Pseudomonas aeruginosa* susceptible to quinolones, ceftazidime and the carbapenems.

K. pneumoniae was again recovered from surgical specimens obtained at our hospital. Susceptibility testing revealed resistance to nearly all antibiotics, therefore we suspected a CP-CRE containing NDM-1 given the patient's travel location (table 1). Using a multiplex PCR assay (Cepheid, Xpert Carba-R) capable of detecting five classes of carbapenemases (blaKPC, blaNDM, blaVIM, blaOXA-48 and blaIMP), the isolate was found to harbour genes encoding both NDM and OXA-48 group enzymes. Additional synergy testing was performed to identify potential combination therapies for treatment. Though limited, there has been some reports of improved outcomes with combination regimens.⁴ Synergy testing was performed by crossing E-tests (Biomérieux) perpendicularly at the minimum inhibitory concentration (MIC) of each agent.⁵

© BMJ Publishing Group Limited [year]. No commercial re-use. See rights and permissions. Published by BMJ.

To cite: Mittal J, Szymczak WA, Guo Y, et al. *BMJ Case Rep* Published Online First: [please include Day Month Year]. doi:10.1136/bcr-2018-225440

Table 1 Susceptibility testing results of the *Klebsiella pneumoniae* isolate

Antibiotic tested	Interpretation (MIC (µg/mL))
Amikacin	Resistant (>32)
Ampicillin	Resistant (>16)
Ampicillin-sulbactam	Resistant (>16/8)
Aztreonam	Resistant (64)
Cefazolin	Resistant (>16)
Cefoxitin	Resistant (>16)
Ceftriaxone	Resistant (>32)
Cefepime	Resistant
Ceftazidime-avibactam	Resistant (>256)*
Ciprofloxacin	Resistant (>2)
Gentamicin	Resistant (>8)
Meropenem	Resistant (>8)
Piperacillin-tazobactam	Resistant (64/4)
Polymyxin B	(0.05)*
Tigecycline	Intermediate (3.0)
Tobramycin	Resistant (>8)
Trimethoprim-sulfamethoxazole	Resistant (>2/38)
Chloramphenicol	Resistant
Meropenem-vaborbactam	Resistant*

*Testing done for research purposes only.
MIC, minimum inhibitory concentration.

The MIC of each agent when tested alone and in combination were then used to calculate the Fractional Inhibitory Concentration Index and an Index of ≤ 0.5 was considered synergistic.⁶ Synergy was observed only for ceftazidime-avibactam plus aztreonam with a reduction in the aztreonam MIC from 64 µg/mL to 4 µg/mL suggesting in vitro susceptibility (table 2, figure 1). Subsequent next generation sequencing analyses (SRA accession: SRP105805) defined the carbapenemases as blaNDM-1 and blaOXA-181, a variant of blaOXA-48. The isolate was also found to contain genes encoding the β -lactamases blaTEM-1b, blaSHV-28 and blaOXA-9 and the ESBL blaCTX-M-15.

The patient required multiple modifications of his antimicrobial regimen as outlined in figure 2. Due to concurrent infection with *Rhizopus* species, which was recovered from bone cultures, the patient was additionally started on liposomal amphotericin B. Though his wound was healing, the patient developed renal dysfunction and mild nausea after 2 weeks of therapy. He was transitioned to a combination of ceftazidime-avibactam 2.5 g every 8 hours plus aztreonam 2 g every 8 hours and oral posaconazole. Once renal function improved on cessation of amphotericin, he was rechallenged with polymyxin B on hospital day 22, intended for 6 more weeks. Unfortunately, the patient was readmitted 5 days later with nausea, vomiting and new onset dizziness attributed

Table 2 Synergy testing results

Antibiotic tested	Interpretation (FIC Index)*
Ceftazidime-avibactam+aztreonam	Synergy (0.11)
Tigecycline+meropenem	Indifference (2)
Meropenem+polymyxin B	Indifference (2)
Polymyxin B+tigecycline	Indifference (4)
Aztreonam+ampicillin-sulbactam	Indifference (2)

*FIC, Fractional inhibitory concentration (FIC Index=Drug A MIC in combination/Drug A MIC alone +Drug B MIC in combination/Drug B MIC alone). Testing performed for research purposes only.

MIC, minimum inhibitory concentration.

Figure 1 Ceftazidime-avibactam+aztreonam synergy testing results.

to polymyxin B. Ceftazidime-avibactam and aztreonam were resumed for the remaining 32 days of therapy, and posaconazole was continued for a total of 6 months until December 2017. After completion of antimicrobials, he underwent a repeat washout and revision of his external fixator. Repeat operative bacterial and fungal cultures were negative. He received external fixator removal several months later and the wound has fully healed. Unfortunately, the patient's right arm remains functionally limited, with decreased range of motion at the elbow and significant loss of fine motor function in his hand. He is currently undergoing intensive physical and occupational therapy to help regain function.

DISCUSSION

New York City is considered an epicentre of CRE within the USA. The most common CRE types isolated in the USA are class A, *K. pneumoniae* carbapenemases.⁷ NDM-1 is a metallo- β -lactamase (MBL) endemic to South Asia, which is infrequently encountered in the USA. However, the prevalence of NDM-1 in developed nations is increasing due to international travel.⁸ OXA-181, a derivative of OXA-48 with a substitution of four amino acids, was first reported in India,⁹ and subsequently reported in Southeast Asia, Eastern Europe and Australia.^{4,9} In a 2016 review by Lee *et al* exploring the global emergence and epidemiology of these multidrug-resistant organisms, the frequency of OXA-48 group enzymes in *K. pneumoniae* was found to be very low in North America.⁴

Coexistence of NDM-1 and OXA-181 group enzymes has been reported in cases from Southeast Asia, Turkey, Australia and parts of Africa.^{4,9-12} Between 2010 and 2015, 52 Enterobacteriaceae isolates from the USA containing OXA-48 group carbapenemases were reported to CDC, and 5 of the isolates were found to harbour coexisting NDM and OXA-48 group enzymes.¹³ Among the clinical cases reviewed, most patients had travelled internationally and some required hospitalisation while abroad. India was the most frequent destination reported.¹³ This supports the hypothesis that our patient likely acquired his infection after his accident and extended hospitalisation in Bangladesh.

Molecular assays for determining the mechanism of carbapenem resistance are mainly used for epidemiological investigations.¹⁴ However, the rapid molecular detection of genes encoding NDM and OXA-48 group carbapenemases in our patient's isolate prompted additional synergy testing. This highlights the importance of readily available, specialised diagnostic testing in clinical microbiology laboratories. In our patient, polymyxin B was

Figure 2 Timeline of events during the patient's course of antibiotic therapy. NDM-1, New Delhi metallo- β -lactamase-1; OXA-48, Oxacillinase type-48.

initially used but was poorly tolerated and ultimately stopped. Patients infected with CRE are often subject to initial ineffective or poorly tolerated regimens 'of last resort'. There are also limited data on use of agents such as polymyxin B for long-term treatment of osteomyelitis.¹⁵

Evidence for treatment of challenging CRE infections often stems from case reports and in vitro studies.² We used synergy testing results and studies supporting aztreonam plus ceftazidime-avibactam combination therapy to guide our clinical management.^{16–20} The serine carbapenemase inhibitor, avibactam, is ineffective against MBLs; however, aztreonam has in vitro activity against the MBLs.²¹ The potent activity of this combination may be mediated by the preservation of aztreonam activity by avibactam. Although aztreonam is not hydrolysed by NDM-1, our isolate contained the ESBL blaCTX-M-15 which likely contributed to aztreonam resistance in the absence of avibactam.²² Unlike other β -lactamase inhibitors (eg, tazobactam, sulbactam and clavulanic acid), avibactam has activity against both ESBL and carbapenemases.⁴ This is consistent with the findings from synergy testing of our isolate as we saw no added benefit to the combination of aztreonam and ampicillin-sulbactam. The use of aztreonam and ceftazidime-avibactam combination therapy was recently described in a case series from Spain involving 10 patients during a hospital outbreak of an NDM-1, OXA-48 and CTX-M-15 producing *K. pneumoniae*. Patients had infections including complicated bacteraemia, urinary tract infection, pneumonia or cholangitis.²³ Using this antibiotic combination, six patients had clearance of their infection, which was defined as clearance of their cultures, lack of recurrence in 30 days or sustained resolution of signs and symptoms of infection. Three patients expired though unrelated to their infections, and one relapsed by day 30. Of the six patients with initial clearance of infection, two had recurrences in 90 days thought to be due to structural anomalies at the site of infection. Of these two patients, one had a complicated urinary tract infection and the other had cholangitis in a transplanted liver. Although this case series was limited in number, no adverse reactions were seen when aztreonam plus ceftazidime-avibactam drug combination was used.

Data on use of this combination specifically for treatment of bone and joint infections are limited. We encountered an additional case using aztreonam plus ceftazidime-avibactam to treat a prosthetic hip arthroplasty infection.¹⁵ This patient also acquired a traumatic fracture requiring orthopaedic surgery complicated by infection while travelling abroad. She returned to the USA with a surgical site infection requiring multiple revision surgeries and antimicrobial regimens including colistin, which precipitated renal toxicity. She was eventually switched to a combination of aztreonam plus ceftazidime-avibactam based on results of in vitro testing. At 6 months post-treatment, her hip joint was reimplanted and repeat surgical cultures remained negative.

Our case lends further support for the combination of aztreonam plus ceftazidime-avibactam for complex bone and joint infections with CRE, especially if in vitro synergy is demonstrated. Both cases also emphasise the need for targeted antimicrobial therapy in conjunction with surgical management to maximise the potential for cure.

Learning points

- ▶ Infections with carbapenem-resistant Enterobacteriaceae (CRE) are challenging to manage as they often require prolonged courses of potentially toxic antibiotics.
- ▶ There are minimal clinical data on effective regimens for treatment of osteomyelitis due to CRE.
- ▶ Rapid molecular diagnostics and synergy testing are valuable resources to assist with the management of patients with CRE infections.
- ▶ Healthcare providers in developed nations should be cognisant of the risk of CRE infections due to international travel.
- ▶ Complicated osteomyelitis often requires a combination of surgical management and targeted antimicrobials for maximally favourable outcomes.

Contributors JM, WAS, YG and MHL were actively involved in acquisition of data for the case, drafting the article, producing the figures and collecting and interpreting background research including cases and relevant papers. WAS and MHL were also involved with and performed the synergy testing on the isolate and provided assistance with getting testing performed by the NYSDOH. LC and BNK performed genome sequencing of our isolates, and they were part of drafting, researching and editing this manuscript. Finally, PFR and PN were also integral to the conception of the case, drafting and editing and assisted with background research. They were also the leaders of our group and coordinated our efforts and testing of the isolates. All the authors approve of this final version and agree to be held accountable and ensure that all questions regarding accuracy or integrity of the article are investigated and resolved promptly.

Funding This work was in part supported by the following grants from the National Institute of Allergy and Infectious Diseases R01AI090155, R21AI135250 and R21AI117338.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Antibiotic resistance threats in the United States. 2013 <https://www.cdc.gov/drugresistance/threat-report-2013/index.html>.
- 2 Temkin E, Adler A, Lerner A, et al. Carbapenem-resistant Enterobacteriaceae: biology, epidemiology, and management. *Ann N Y Acad Sci* 2014;1323:22–42.
- 3 Tamma PD, Goodman KE, Harris AD, et al. Comparing the Outcomes of Patients With Carbapenemase-Producing and Non-Carbapenemase-Producing Carbapenem-Resistant Enterobacteriaceae Bacteremia. *Clin Infect Dis* 2017;64:257–64.
- 4 Lee CR, Lee JH, Park KS, et al. Global Dissemination of Carbapenemase-Producing *Klebsiella pneumoniae*: Epidemiology, Genetic Context, Treatment Options, and Detection Methods. *Front Microbiol* 2016;7:895.
- 5 Doern CD. When does 2 plus 2 equal 5? A review of antimicrobial synergy testing. *J Clin Microbiol* 2014;52:4124–8.
- 6 Hall MJ, Middleton RF, Westmacott D. The fractional inhibitory concentration (FIC) index as a measure of synergy. *J Antimicrob Chemother* 1983;11:427–33.
- 7 Satlin MJ, Chen L, Patel G, et al. Multicenter Clinical and Molecular Epidemiological Analysis of Bacteremia Due to Carbapenem-Resistant Enterobacteriaceae (CRE) in the CRE Epicenter of the United States. *Antimicrob Agents Chemother* 2017;61:e02349–16.
- 8 van der Bij AK, Pitout JD. The role of international travel in the worldwide spread of multiresistant Enterobacteriaceae. *J Antimicrob Chemother* 2012;67:2090–100.
- 9 Castanheira M, Deshpande LM, Mathai D, et al. Early dissemination of NDM-1- and OXA-181-producing Enterobacteriaceae in Indian hospitals: report from the SENTRY Antimicrobial Surveillance Program, 2006–2007. *Antimicrob Agents Chemother* 2011;55:1274–8.
- 10 Cho SY, Huh HJ, Baek JY, et al. *Klebsiella pneumoniae* co-producing NDM-5 and OXA-181 carbapenemases, South Korea. *Emerg Infect Dis* 2015;21:1088–9.
- 11 Uwaezuoke NS, Kieffer N, Iregbu KC, et al. First report of OXA-181 and NDM-1 from a clinical *Klebsiella pneumoniae* isolate from Nigeria. *Int J Infect Dis* 2017;61:1–2.
- 12 Shanthi M, Sekar U, K A, Bramhne HG, et al. OXA-181 Beta Lactamase is not a Major Mediator of Carbapenem Resistance in Enterobacteriaceae. *J Clin Diagn Res* 2013;7:1986–8.
- 13 Lyman M, Walters M, Lonsway D, et al. Notes from the Field: Carbapenem-resistant Enterobacteriaceae Producing OXA-48-like Carbapenemases—United States, 2010–2015. *MMWR Morb Mortal Wkly Rep* 2015;64:1315–6.
- 14 CLSI. *Performance Standards for Antimicrobial Susceptibility Testing*. 27th edn. Wayne, PA: Clinical and Laboratory Standards Institute, 2017.
- 15 Tascini C, Gemignani G, Palumbo F, et al. Clinical and microbiological efficacy of colistin therapy alone or in combination as treatment for multidrug resistant *Pseudomonas aeruginosa* diabetic foot infections with or without osteomyelitis. *J Chemother* 2006;18:648–51.
- 16 Marshall S, Hujer AM, Rojas LJ, et al. Can Ceftazidime-Avibactam and Aztreonam Overcome β -Lactam Resistance Conferred by Metallo- β -Lactamases in Enterobacteriaceae? *Antimicrob Agents Chemother* 2017;61:e02243–16.
- 17 MacVane SH, Crandon JL, Nichols WW, et al. Unexpected *in vivo* activity of ceftazidime alone and in combination with avibactam against New Delhi metallo- β -lactamase-producing Enterobacteriaceae in a murine thigh infection model. *Antimicrob Agents Chemother* 2014;58:7007–9.
- 18 Wang X, Zhang F, Zhao C, et al. *In vitro* activities of ceftazidime-avibactam and aztreonam-avibactam against 372 Gram-negative bacilli collected in 2011 and 2012 from 11 teaching hospitals in China. *Antimicrob Agents Chemother* 2014;58:1774–8.
- 19 Karlowsky JA, Kazmierczak KM, de Jonge BLM, et al. *In Vitro* Activity of Aztreonam-Avibactam against Enterobacteriaceae and *Pseudomonas aeruginosa* Isolated by Clinical Laboratories in 40 Countries from 2012 to 2015. *Antimicrob Agents Chemother* 2017;61:e00472–17.
- 20 Jayol A, Nordmann P, Poirel L, et al. Ceftazidime/avibactam alone or in combination with aztreonam against colistin-resistant and carbapenemase-producing *Klebsiella pneumoniae*. *J Antimicrob Chemother* 2018;73:542–4.
- 21 Abboud MI, Damblon C, Brem J, et al. Interaction of Avibactam with Class B Metallo- β -Lactamases. *Antimicrob Agents Chemother* 2016;60:5655–62.
- 22 de Jonge BL, Karlowsky JA, Kazmierczak KM, et al. *In Vitro* Susceptibility to Ceftazidime-Avibactam of Carbapenem-Nonsusceptible Enterobacteriaceae Isolates Collected during the INFORM Global Surveillance Study (2012 to 2014). *Antimicrob Agents Chemother* 2016;60:3163–9.
- 23 Shaw E, Rombauts A, Tubau F, et al. Clinical outcomes after combination treatment with ceftazidime/avibactam and aztreonam for NDM-1/OXA-48/CTX-M-15-producing *Klebsiella pneumoniae* infection. *J Antimicrob Chemother* 2018;73:1104–6.

Copyright 2018 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- Submit as many cases as you like
- Enjoy fast sympathetic peer review and rapid publication of accepted articles
- Access all the published articles
- Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow