IDCases 37 (2024) e02020

Contents lists available at ScienceDirect

IDCases

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

Case report

Treatment of a challenging NDM and OXA-48-producing *Klebsiella pneumoniae* causing skin and soft tissue infection and exhibiting resistance to the combination of Ceftazidime-Avibactam and Aztreonam: A case report

Thamer A. Almangour [a,*], Ghaida A. Aldajani [b], Ali Alhijji [c], Aynaa Alsharidi [c]

[a] Department of Clinical Pharmacy, College of Pharmacy, King Saud University, P.O. Box 2457, Riyadh 11451, Saudi Arabia
[b] Clinical Pharmacy Services, King Saud University Medical City, King Saud University, Riyadh, Saudi Arabia
[c] Division of Infectious Diseases, Department of Medicine, College of Medicine, King Saud University, Riyadh 11461, Saudi Arabia

ARTICLE INFO

Keywords:
NDM
OXA-48
Klebsiella pneumoniae
Skin and Soft Tissue Infection
Ceftazidime-Avibactam
Aztreonam

ABSTRACT

Carbapenem-resistant Enterobacterales (CRE) pose a significant public health concern. CRE could be carbapenamse producers or non-producers. In the Kingdom of Saudi Arabia, bla_{OXA-48} and bla_{NDM} represent the majority of carbapenemase isolates. There are very limited treatment options for carbapenemase-producing CRE caused by bla_{NDM}. Ceftazidime-avibactam plus aztreonam (CZA-ATM) or cefiderocol as monotherapy are considered the treatment of choice for these infections. Here, we report a case of a 70-year-old man presented with surgical site infection of above knee amputation stump. The cultures revealed carbapenem-resistant *Klebsiella pneumoniae* positive for bla_{NDM} and bla_{OXA-48} resistant to CZA-ATM therapy and intermediate susceptibility to tigecycline. He was started on CZA-ATM both adjusted for renal function, and high dose tigecycline with daily wound dressing and irrigation. By day 20 of the antibiotic regimens, he had clinical and microbiological cure based on repeated wound cultures. This case identifies a rare incidence of CRE skin and soft tissue infection positive for bla_{NDM} and bla_{OXA-48} resistant to CZA-ATM in a background of limited targeted options, but successfully treated with CZA-ATM and high-dose tigecycline. Such therapeutic approach might be useful in few circumstances when no other antibiotic options are available to treat extensively drug-resistant *Klebsiella pneumoniae*.

Background

As antimicrobial resistance rises, resistance in Gram-negative microorganisms creates a serious therapeutic challenge. Carbapenem-resistant Enterobacterales (CRE) pose a significant public health concern. In 2017, the World Health Organization published a priority pathogens list for research and development of new antibiotics in which CRE were listed as a critical priority [1].

CRE could be carbapenamse producers or non-producers [2]. The most well know of the 2 types are the carbapenemase producers in which CRE acquire the carbapenemase gene. Unlike the United States in which bla_{KPC} is the most predominant carbapenemase gene, in the Kingdom of Saudi Arabia, bla_{OXA-48} is the most common gene followed by bla_{NDM} [3,4]. In the Kingdom, bla_{OXA-48} and bla_{NDM} represent 70–82 % and 7–17 % of carbapenemase isolates, respectively [3,5]. Noteworthy, the first case of *Klebsiella pneumoniae* carbapenemase (KPC)-producing Enterobacterales in Saudi Arabia was reported from our center in 2020 [6].

There are very limited treatment options for carbapenemase-producing CRE caused by $bla_{NDM.}$ The preferred treatment options are ceftazidime-avibactam plus aztreonam (CZA-ATM) or cefiderocol as monotherapy. Aztreonam (ATM) is active against strains that produce bla_{NDM}. However, this gene is usually co-produced with serine β-lactamase including ESBLs, AmpC, KPCs, or OXA-48-like carbapenemases, which hydrolyze ATM. This requires the addition of avibactam which remains effective at inhibiting the activity of these latter β-lactamases enabling ATM to overcome the hydrolysis from these enzymes and to safely reach its site of activity (penicillin binding protein 3 [PBP3]) [2]. Tigecycline is an alternative option for the treatment of CRE infections not including bloodstream or urinary tract independent of the presence or type of carbapenemases [2].

Data regarding the percent of New Delhi Metallo β-Lactamase (NDM)-producing isolates susceptible to the combination of CZA-ATM are not available. In addition, there are very limited data regarding

* Corresponding author.
E-mail address: talmangour@ksu.edu.sa (T.A. Almangour).

https://doi.org/10.1016/j.idcr.2024.e02020
Received 31 May 2024; Received in revised form 7 June 2024; Accepted 30 June 2024
Available online 2 July 2024

NDM-producing isolates exhibiting resistance to such regimen. Here, we report a successful treatment outcome of patient with skin and soft tissue infection due to Oxacillinase-48 (OXA-48) and NDM-producing CRE resistant to CZA-ATM treated with combination regimen including high-dose tigecycline. The IRB approval was granted for this case (E24–8653).

Case presentation

A 70-year-old man who is known to have hypertension being managed with lisinopril 20 mg daily, type 2 diabetes mellitus being managed with metformin 850 mg twice daily, and two previous strokes for which he is on aspirin 81 mg, clopidogrel 75 mg daily, and atorvastatin 40 mg daily. He was diagnosed to have right critical limb ischemia in 2023 and underwent above knee amputation, which was performed at another medical center in the Western Province. Two weeks later, he presented to the vascular surgery clinic at our center with purulent discharge from the surgical site of the amputation stump when he was admitted for stump infection management.

The wound culture results revealed *Klebsiella pneumoniae* positive for NDM and OXA-48 genes, as well as *Acinetobacter baumannii* (Table 1). Laboratory studies showed mild leukocytosis with a white blood cell count of 13.34 $\times$ 10^9 /L and hyperglycemia of 12.2 mmol/L. The hemoglobin A1c (HbA1c) was 10.6 %. C-reactive protein (CRP) was 3.76 mg/L. Rest of chemistry profile was unremarkable. Magnetic resonance imaging revealed no evidence of osteomyelitis or drainable collections.

Treatment was initiated with intravenous colistin, with a loading dose of 9 million units followed by maintenance dose of 5 million units every 12 h. Local debridement was performed for source control. Six days later, he developed acute kidney injury, with a serum creatinine level of 265 μmol/L (baseline 62 μmol/L). Colistin and all nephrotoxic medications were discontinued.

Afterward, he developed fever with a temperature of 38 °C, and repeated tissue culture revealed *Klebsiella pneumoniae* positive for NDM and OXA-48 genes, as well as *Pseudomonas aeruginosa* (Table 2).

Microbiology laboratory data

Wound specimens were transported to the microbiology laboratory and underwent a Gram-stain procedure. Samples were then inoculated in 5 % sheep blood agar, chocolate agar, and MacConkey agar plates and stored in the incubator at 37 °C for 18–24 h. After the growth was observed, identification and antimicrobial susceptibility testing to commonly used antibiotics were performed using automated systems: MicroScan WalkAway 96 plus (Beckman Coulter, Inc., Brea, CA, USA). The automated systems identified the microorganisms with the percentage of assurance and susceptibility to 15–20 antimicrobials (susceptible, intermediate, or resistant). The susceptibility of these microorganisms to colistin was tested using commercial broth microdilution [(ComASP™ Colistin (Liofilchem® srl, Roseto degli Abruzzi, Italy)]. GeneXpert (Xpert® Carba-R; Cepheid, Sunnyvale, CA, USA) was used to detect carbapenemase production and differentiate bla_{KPC}, bla_{NDM}, bla_{VIM}, bla_{IMP}, and bla_{OXA-48} genes.

In vitro susceptibility testing was performed on the isolate to evaluate the synergy of CZA-ATM using an E-test fixed ratio method. This involved applying a standardized inoculum on a Mueller-Hinton agar plate, followed by the application of an ATM E-test strip. The plate was then incubated at room temperature for 5 min to 1 h to allow for diffusion, after which the ATM E-test strip was removed. Then, a second E-test strip of ceftazidime/avibactam (CZA) was positioned exactly over the imprint of the first E-test strip. The inhibition zone and minimum inhibitory concentration (MIC) were recorded after 18–20 h of incubation. ATM in the presence of CZA showed no synergic effect with a MIC of $>$ 16 μg/ml.

Antimicrobial therapy was switched to CZA 0.94 g IV every 12 h, ATM IV 2 g every 12 h (both adjusted for renal function), and high dose tigecycline 200 mg once followed by 100 mg IV every 12 h with daily wound dressing and irrigation. He received a total of 20 days of this combination therapy. Repeated wound cultures were done on day 12 and day 16 while on the later antibiotic regimen and returned back negative. The wound had granulated well and was clean with no discharge or inflammatory signs. As the patient remained vitally stable and laboratory results were unremarkable, antibiotics were discontinued and he was discharged home.

Discussion

Here, we report a rare case of skin and soft tissue infection due to NDM-producing CRE resistant to CZA-ATM and with intermediate susceptibility to tigecycline and colistin treated with combination regimen including CZA-ATM and high-dose tigecycline. Colistin was initially used and discontinued due to the incidence of acute kidney injury. Due to its good penetration and the FDA approval for skin infections, tigecycline was used in this case. The successful outcome could be explained by the use of high dose tigecycline and the fact that the infection did not extend to the bone or bloodstream. Although a meta-analysis of 15 clinical trials showed that tigecycline is associated with higher rate of mortality compared to alternative regimens [7], subsequent data showed that mortality difference diminished when high dose tigecycline is used (200 mg IV as a single dose followed 100 mg IV every 12 h) [8]. Other possibilities for successful treatment with CZA-ATM could be

Table 1
Antimicrobial susceptibility results from wound culture according to clinical and laboratory standards institute (CLSI).

	Klebsiella pneumoniae						*Acinetobacter baumanii*					
Drug	MIC Int	MIC Dil	E-test Int	E-test Dil	MB int	MB Dil	MIC Int	MIC Dil	E-test Int	E-test Dil	MB Int	MB Dil
Amikacin	S	< =16					R	> 32				
Ampicillin	R	> 16					R	> 16				
Ampicillin\sulbactam	R	> 16/8					R	> 16/8				
Aztreonam	R	> 16										
Cefepime	R	> 16					R	> 16				
Ceftazidime	R	> 16					R	> 16				
Ceftazidime\Avibactam			R	256								
Ciprofloxacin	R	> 2					R	> 2				
Colistin					I	0.5					I	0.5
Gentamicin	S	< =4					R	> 8				
Imipenem	R	> 8	R	32			R	> 8	R	32		
Meropenem	R	> 8	R	32			R	> 8	R	32		
Tigecycline	I	4					S	2				
Tobramycin	S	< =4					R	> 8				
Trimethoprim\Sulfa	R	> 4/76										

Abbreviations: Dil: dilution; Int: interpretation; MIC, minimum inhibitory concentration; MB, Microbroth; susceptible; R, resistant; I, intermediate.

Table 2
Antimicrobial susceptibility results from tissue culture according to clinical and laboratory standards institute (CLSI).

	Klebsiella pneumoniae						*Pseudomonas aeruginosa*					
Drug	MIC Int	MIC Dil	E-test Int	E-test Dil	MB int	MB Dil	MIC Int	MIC Dil	E-test Int	E-test Dil	MB Int	MB Dil
Amikacin	S	< =16					S	< =16				
Amoxicillin\Clavulanate	R	> 16/8										
Ampicillin	R	> 16										
Aztreonam							S	8				
Cefepime	R	> 16					S	8				
Cefoxitin	R	> 16										
Ceftazidime	R	> 16					S	8				
Cefuroxime	R	> 16										
Ciprofloxacin	R	> 2					R	> 2				
Colistin					I	< = 0.25					I	0.5
Gentamicin	S	< =4					S	< =4				
Imipenem	R	> 8	R	32					R	32		
Levofloxacin	R	> 4					R	> 4				
Meropenem	R	> 8	R	32					R	16		
Piperacillin\Tazobactam	R	> 64					S	16/4				
Tobramycin	S	< =4					S	< =4				
Tigecycline	I	4										
Trimethoprim\Sulfa	R	> 4/76										

Abbreviations: Dil: dilution; Int: interpretation; MIC, minimum inhibitory concentration; MB, Microbroth; S, susceptible; R, resistant; I, intermediate.

discordance between MICs measured in vitro and the in vivo activity of CZA against NDMs [9–11].

The selection of this regimen was due to several reasons. First, there is very limited available option in this case. Second, the speculation that CZA-ATM may retain activity against NDM-producing CRE although Avibactam-ATM testing may not be active. This is may be due to that ceftazidime targets more PBP, which hypothetically may serve as a "decoy" that is inactivated by serine β-lactamases coexpressed with NDM enzymes, allowing more amounts of ATM to reach PBP3 [12]. Third, beside the *Klebsiella pneumoniae*, the wound culture revealed *Pseudomonas aeruginosa* susceptible to CZA and ATM which support the decision of resuming CZA-ATM despite the lack of synergy against Klebsiella isolate. Lastly, although the isolate was resistant to the combination regimen, CLSI does not currently endorse a particular approach to test in vitro activity with this combination which may question the reliability of the results. Noteworthy, if susceptibility is demonstrated in the in vitro testing, cefiderocol would be the most appropriate option in this case. However, this agent is not currently available in the Kingdom and not yet approved by the Saudi FDA.

Resistance to CZA-ATM is mostly due to presence of bla_{NDM} genes in conjunction with modified PBP3, the specific site of activity of ATM through a 4–amino acid insertion [13,14]. In addition, the resistance could be due to the presence of a bla_{CMY} gene [15]. Resistance to ATM-AVI (and, by extension, CZA-ATM) was reported in other countries [12,16]. However, to our knowledge, no data was published in Saudi Arabia.

In conclusion, although whole-genome sequencing to identify the resistance mechanism was not conducted, this case identifies a rare incidence of NDM-producing CRE causing skin and soft tissue infection resistant to CZA-ATM but successfully treated with CZA-ATM and high-dose tigecycline. Considering the current global challenges to treat antimicrobial-resistant bacteria, we thought that our experience with this patient could highlight the possible positive clinical and microbiological outcomes by applying such salvage approach when the circumstances indicate.

Ethics approval

this case report has been approved by the IRB at King Saud University Medical City, Riyadh, Saudi Arabia, project number E-24–8653.

Transparency declarations

The authors declare that they have no conflict of interest.

Consent

This case report has been approved by the IRB at King Saud University Medical City, Riyadh, Saudi Arabia, project number E-24–8653. The procedure does not pose "more than minimal risk to the human participant" per the assessment by the IRB.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

Thamer A Almangour: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Investigation, Data curation, Conceptualization. **Ghaida A Aldajani:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Investigation, Data curation, Conceptualization. **Ali Alhijji:** Writing – review & editing, Visualization, Validation, Investigation. **Aynaa Alsharidi:** Writing – review & editing, Visualization, Validation, Investigation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] WHO. World Health Organization. Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics. 2017. Available at: ⟨https://www.who.int/news/item/27–02-2017-who-publishes-list-of-bacteria-for-which-new-antibiotics-are-urgently-needed⟩. Accessed 05 April 2024.

[2] Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van Duin D, Clancy CJ. Infectious diseases society of America 2023 guidance on the treatment of antimicrobial resistant gram-negative infections. Clin Infect Dis: Publ Infect Dis Soc Am 2023.

[3] Alraddadi BM, Heaphy ELG, Aljishi Y, Ahmed W, Eljaaly K, Al-Turkistani HH, et al. Molecular epidemiology and outcome of carbapenem-resistant enterobacterales in Saudi Arabia. BMC Infect Dis 2022;22(1):542.
[4] Almangour TA, Ghonem L, Aljabri A, Alruwaili A, Al Musawa M, Damfu N, et al. Ceftazidime-avibactam versus colistin for the treatment of infections due to carbapenem-resistant enterobacterales: a multicenter cohort study. Infect Drug Resist 2022;15:211–21.
[5] Al-Zahrani IA, Alsiri BA. The emergence of carbapenem-resistant Klebsiella pneumoniae isolates producing OXA-48 and NDM in the Southern (Asir) province, Saudi Arabia. Saudi Med J 2018;39(1):23–30.
[6] Alghoribi MF, Binkhamis K, Alswaji AA, Alhijji A, Alsharidi A, Balkhy HH, et al. Genomic analysis of the first KPC-producing Klebsiella pneumoniae isolated from a patient in Riyadh: a new public health concern in Saudi Arabia. J Infect Public Health 2020;13(4):647–50.
[7] Yahav D, Lador A, Paul M, Leibovici L. Efficacy and safety of tigecycline: a systematic review and meta-analysis. J Antimicrob Chemother 2011;66(9):1963–71.
[8] Zha L, Pan L, Guo J, French N, Villanueva EV, Tefsen B. Effectiveness and safety of high dose tigecycline for the treatment of severe infections: a systematic review and meta-analysis. Adv Ther 2020;37(3):1049–64.
[9] Asempa TE, Abdelraouf K, Nicolau DP. Metallo-β-lactamase resistance in Enterobacteriaceae is an artefact of currently utilized antimicrobial susceptibility testing methods. J Antimicrob Chemother 2020;75(4):997–1005.
[10] MacVane SH, Crandon JL, Nichols WW, Nicolau DP. 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(11):7007–9.
[11] Simon M, Gerlach RG, Pfeifer Y, Pfennigwerth N, Gatermann SG, Schröder A, et al. Increased zinc levels facilitate phenotypic detection of ceftazidime-avibactam resistance in metallo-β-lactamase-producing Gram-negative bacteria. Front Microbiol 2022;13:977330.
[12] Simner PJ, Bergman Y, Conzemius R, Jacobs E, Tekle T, Beisken S, et al. An NDM-producing escherichia coli clinical isolate exhibiting resistance to cefiderocol and the combination of ceftazidime-avibactam and aztreonam: another step toward pan-β-lactam resistance. Open Forum Infect Dis 2023;10(7):ofad276.
[13] Ma K, Feng Y, McNally A, Zong Z. Struggle To survive: the choir of target alteration, hydrolyzing enzyme, and plasmid expression as a novel aztreonam-avibactam resistance mechanism. mSystems 2020;5(6).
[14] Alm RA, Johnstone MR, Lahiri SD. Characterization of Escherichia coli NDM isolates with decreased susceptibility to aztreonam/avibactam: role of a novel insertion in PBP3. J Antimicrob Chemother 2015;70(5):1420–8.
[15] Niu S, Wei J, Zou C, Chavda KD, Lv J, Zhang H, et al. In vitro selection of aztreonam/avibactam resistance in dual-carbapenemase-producing Klebsiella pneumoniae. J Antimicrob Chemother 2020;75(3):559–65.
[16] Periasamy H, Joshi P, Palwe S, Shrivastava R, Bhagwat S, Patel M. High prevalence of Escherichia coli clinical isolates in India harbouring four amino acid inserts in PBP3 adversely impacting activity of aztreonam/avibactam. J Antimicrob Chemother 2020;75(6):1650–1.