IDCases 36 (2024) e01946

Contents lists available at ScienceDirect

IDCases

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

Case report

Novel case of combination antibiotic therapy for treatment of a complicated polymicrobial urinary tract infection with one organism harboring a metallo-β-lactamase (MBL) in a pregnant patient

S. Ruddy [a,b], M. Bapna [a,b], K. Karnik [a,b], L. Yung [a,b,c], G. Rodriguez [b,d], C. Urban [a,b,c,*], J. Yoon [a,b,c], N. Prasad [a,b,c], S. Segal-Maurer [a,b,c], G. Turett [a,b]

[a] Department of Medicine, NewYork-Presbyterian Queens, 56-45 Main St, Flushing, NY 11355, United States of America
[b] The Dr. James J. Rahal, Jr. Division of Infectious Diseases, NewYork-Presbyterian Queens, 56-45 Main St, Flushing, NY 11355, United States of America
[c] Weill Cornell Medicine, Cornell University, New York, NY 10065, United States of America
[d] Columbia University School of Nursing, New York, NY, 10032, United States of America

ARTICLE INFO

Keywords:
Metallo-beta-lactamase (MBL)
Stenotrophomonas maltophilia
Ceftazidime-avibactam
Pregnancy
Therapy

ABSTRACT

Carbapenem resistance due to metallo-beta-lactamases (MBLs) is a global phenomenon and an important challenge for antibiotic therapy (Boyd et al., 2020 [1]). While previous reports have demonstrated both *in vitro* and *in vivo* synergy using the combination of ceftazidime-avibactam and aztreonam against *Stenotrophomonas maltophilia*, an MBL-harboring organism, this treatment strategy has not been reported during pregnancy (Mojic et al., 2017 [2], [3], Mojica et al., 2016 [4], Alexander et al., 2020 [5]). We describe a 33-year-old pregnant female with polymicrobial, bilateral pyelonephritis caused by *Stenotrophomonas maltophilia* and other gram-negative bacteria. The organisms were eradicated with the combination of ceftazidime-avibactam and aztreonam followed by successful delivery with no observed adverse effects in either mother or child post-partum.

Introduction

Carbapenem resistance due to metallo-beta-lactamases (MBLs) is a global phenomenon and detection of such enzymes requires molecular techniques [1]. *Stenotrophomonas maltophilia* (*S. maltophilia*) is an aerobic, gram-negative bacillus which poses therapeutic challenges due to its innate mechanisms of resistance. *S. maltophilia* possesses an MBL (designated L1) that hydrolyzes most beta-lactam agents, except the monobactam, aztreonam (AZM), as well as a second non-MBL serine based beta-lactamase designated L2 that hydrolyzes aztreonam and is inhibited by clavulanic acid. Hence, no single beta-lactam antibiotic can effectively treat such infections (with possible exception of cefiderocol) [1,4–7]. We report a case that demonstrates a safe and successful treatment of acute pyelonephritis in a pregnant female caused by polymicrobial infection including *S. maltophilia* using a novel combination strategy of multiple beta-lactam agents.

Case presentation

A 33-year-old female presented at 33 weeks of gestation to our Emergency Department in Flushing, Queens, complaining of four days of worsening bilateral flank pain, nausea, vomiting, chills, fevers, and malodorous urine. She had a history of nephrolithiasis requiring temporary use of ureteral stents in the past. She underwent placement of a right percutaneous nephrostomy tube (PCNT) 1 month prior to admission which was exchanged two weeks prior to presentation. On admission, the patient was febrile and demonstrated suprapubic and bilateral costovertebral angle tenderness (CVAT) on physical examination. An abdominal computerized tomography scan revealed left hydronephrosis. Her labs were significant for an elevated white blood cell count of 10.95 K/μL with 85 % neutrophils, 1 % bands, 5 % lymphocytes, and 4 % monocytes. She was anemic with a hemoglobin of 9.5 g/dL and hematocrit of 28.8 %. Her creatinine was normal at 0.55 mg/dL. A clinical diagnosis of bilateral pyelonephritis was made. Urinalysis demonstrated gross pyuria and urine culture from PCNT grew five different organisms including a carbapenem-resistant *S. maltophilia, Enterobacter cloacae* complex, a pan-susceptible *Escherichia coli* (*E. coli*), *Lactobacillus* species, and another gram-negative bacillus that could not be identified. Based on review of available susceptibilities (Table 1) and the known pregnancy safety concerns of fluoroquinolones, the patient

* Correspondence to: NewYork-Presbyterian Queens, Division of Infectious Diseases, 56-45 Main St, N-011, Flushing, NY 11355, United States of America.
E-mail address: cmurban@nyp.org (C. Urban).

https://doi.org/10.1016/j.idcr.2024.e01946
Received 4 October 2023; Received in revised form 23 February 2024; Accepted 14 April 2024
Available online 15 April 2024

Table 1
Organisms identified from the urine before treatment, and minimum inhibitory concentration of tested antibiotics using the VITEK 2 system (BioMerieux, Les Pennes-Mirabeau, France).

	Stenotrophomonas maltophilia		*Escherichia coli*		*Enterobacter cloacae* complex	
Antibiotic	MIC	Int.	MIC	Int.	MIC	Int.
Amikacin	-	-	≤ 2	S	≤ 2	S
Aztreonam	-	-	≤ 1	S	≤ 1	S
Cefazolin	-	-	≤ 4	S	≥ 64	R
Cefepime	-	-	≤ 1	S	≤ 1	S
Cefoxitin	-	-	≤ 4	S	≥ 64	R
Ceftazidime	-	-	≤ 1	S	≤ 1	S
Ceftriaxone	-	-	≤ 1	S	≤ 1	S
Ertapenem	-	-	≤ 0.5	S	≤ 0.5	S
Gentamicin	-	-	≤ 1	S	≤ 1	S
Levofloxacin	1	S	≤ 0.12	S	≤ 0.12	S
Meropenem	-	-	≤ 0.25	S	≤ 0.25	S
Tobramycin	-	-	≤ 1	S	-	-
TMP-SMX	> 320	R	≤ 20	S	≤ 20	S
AMP-SUL	-	-	≤ 2	S	-	-
Tetracycline	-	-	≤ 1	S	≤ 1	S
PIP-TAZ	-	-	≤ 4	S	≤ 4	S
Tigecycline	-	-	-	-	1	S

MIC = minimum inhibitory concentration in μg/mL; Int. = interpretation; S = susceptible; R = resistant; - = antibiotic not tested; TMP-SMX = trimethoprim-sulfamethoxazole; AMP-SUL = ampicillin-sulbactam; PIP-TAZ = piperacillin-tazobactam.

was treated with a combination of aztreonam 2 g every 8 h, ceftazidime-avibactam (CZA) 2.5 g every 8 h, and ampicillin 2 g every 6 h.

Throughout the treatment course, she remained afebrile and her pyuria resolved. She underwent a right PCNT exchange on the third day of antimicrobial therapy. The patient's urine was sterilized after five days of triple antibiotic therapy. She underwent induction and delivered a healthy baby *via* non-spontaneous vaginal delivery while remaining on the above antibiotic regimen. Her right PCNT was removed two days following delivery and antibiotics were discontinued one day after PCNT removal. In total, the patient received twelve days of aztreonam, thirteen days of ceftazidime-avibactam, and eight days of ampicillin. She remained symptom-free and was discharged from the hospital without further antibiotic treatment. A timeline of antibiotic administration and events is provided (Fig. 1).

Discussion

Acute pyelonephritis is one of the most common indications for antepartum hospitalizations and is often easily treated with standard therapies leading to excellent outcomes [8,9]. The antimicrobial safety profile for the mother and fetus is of utmost importance when choosing an antimicrobial agent for the treatment of UTIs and pyelonephritis in pregnancy. Due to increasing frequency of antimicrobial resistance encountered in many bacterial species, cephalosporins are considered first-line therapy for urinary tract infections in pregnancy in many settings [8]. Cephalosporins achieve therapeutic renal parenchymal and urinary concentrations, have effective spectrums of coverage for common uropathogens, and are considered safe for use in pregnancy. Dilemmas exist when confronted with a pregnant patient infected with antimicrobial resistant bacteria as potential antibiotic options are contraindicated or have limited clinical data to support their use in pregnancy. Many *S. maltophilia* isolates may be susceptible to trimethoprim-sulfamethoxazole (TMP-SMX), quinolones, and later generation tetracycline derivatives (including tigecycline, minocycline, and eravacycline) but treatment of infections in the setting of resistance to these agents as seen in our case poses therapeutic challenges [10,11].

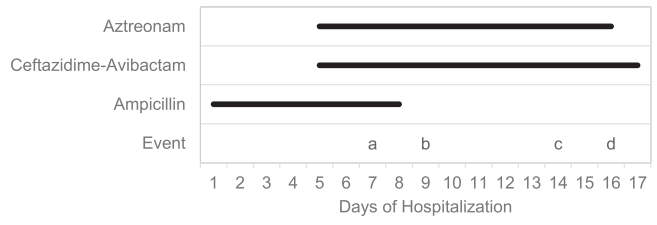

Fig. 1. Timeline of events and antibiotic administration. Events: a = PCNT exchanged; b = urine cultures sterilized; c = vaginal delivery; d = PCNT removal.

Ceftazidime-avibactam (CZA), a beta-lactam-beta-lactamase inhibitor combination that is stable to hydrolysis by Class A and C beta-lactamases, as well as OXA-48, was approved by the FDA for the treatment of complicated urinary tract infection, including pyelonephritis, in the adult and pediatric patient populations [12]. Registrational trials of CZA included successful treatment of a pregnant woman with complicated urinary infection caused by *Klebsiella pneumoniae* possessing a *Klebsiella pneumoniae* carbapenemase (KPC) [13,16]. It is important to note that there is limited data describing reproductive toxicology studies with CZA in pregnancy, as female patients recruited in these trials were required to have a negative pregnancy test as entry criteria. However, ceftazidime and avibactam were not teratogenic in rat studies and no reported safety concerns were raised when avibactam was tested in rabbits [12].

Cefiderocol is a novel siderophore cephalosporin antibiotic with broad coverage against difficult-to-treat Gram-negative bacteria, including those resistant to carbapenems, with reports claiming that the L1 MBL does not hydrolyze cefiderocol [14,15]. *In vitro* and *in vivo* data demonstrated that cefiderocol is efficacious in patients with *S. maltophilia* infections, including pulmonary and skin/soft tissue infections [6,7]. However, data on the use of cefiderocol during pregnancy in humans is currently not available and we chose not to administer this to our patent due to safety considerations.

To our knowledge, this is the first case documenting the safe and efficacious administration of CZA plus aztreonam to treat polymicrobial pyelonephritis in a pregnant female. The reasoning for the use of CZA plus aztreonam, given the limited experience with its use in pregnancy and the lack of existing literature documenting its safety on the fetus, was to ensure antimicrobial activity against *S. maltophilia* in addition to the other bacteria identified in her urinary specimen. We based our choice on the hydrolytic profile of both L1 and L2 in *S. maltophilia*, the avibactam in CZA serving to inhibit L2 allowing aztreonam to retain sensitivity, bypassing L1, and reaching its target [2,3]. The initial use of ampicillin for the treatment of *Lactobacillus* species isolated was based on the patient's level of clinical acuity but discontinued after several days due to concerns for possible antagonism associated with administration of dual beta-lactam agents as well as concerns for potential increased risk of adverse events in including seizure activity. Antimicrobial treatment was successfully administered until delivery (with documented sterilization of urinary specimens and clinical resolution of pyelonephritis symptoms). The patient tolerated the treatment without any adverse side effects and mother and baby continue to do well at one-year of follow-up.

In conclusion, this case highlights the use of CZA in combination with other beta-lactam antibiotics to treat pyelonephritis in a pregnant female caused by MDR organisms including *S. maltophilia,* suggesting this as a novel, safe, and effective therapeutic option.

CRediT authorship contribution statement

Carl Urban: Writing – review & editing. **George Rodriguez:** Formal analysis. **Lok Yung:** Formal analysis. **Krupa Karnik:** Formal analysis. **Monica Bapna:** Investigation. **Samantha Ruddy:** Investigation. **Glenn Turett:** Writing – review & editing. **Sorana Segal-Maurer:** Writing – review & editing. **Nishant Prasad:** Writing – review & editing. **James Yoon:** Formal analysis.

Funding

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

Ethical approval

All authors have agreed for authorship, read and approved the manuscript, and given consent for publication of the manuscript.

Consent

Consent to publish was not obtained since the case report does not contain any personal identifiers.

Author statement

Attached please find our revised manuscript (IDCR-d-23-00515) entitled “Novel case of combination antibiotic therapy for treatment of a complicated polymicrobial urinary tract infection with one organism harboring a metallo-β-Lactamase (MBL) in a pregnant patient” This manuscript is a previously unpublished work and all authors participated in the study and have agreed to the content of the manuscript. Thank you for your consideration of this manuscript.

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] Boyd SE, Livermore DM, Hooper DC, Hope WW. Metallo-β-lactamases: structure, function, epidemiology, treatment options, and the development pipeline. Antimicrob Agents Chemother 2020;64(10) [e00397-20].

[2] Mojica MF, Papp-Wallace KM, Taracila MA, Barnes MD, Rutter JD, Jacobs MR, et al. Avibactam restores the susceptibility of clinical isolates of *Stenotrophomonas maltophilia* to aztreonam. Antimicrob Agents Chemother 2017;61(10) [e00777-17].

[3] Sader HS, Duncan LR, Arends SJR, Carvalhaes CG, Castanheira M. Antimicrobial activity of aztreonam-avibactam and comparator agents when tested against a large collection of contemporary *Stenotrophomonas maltophilia* isolates from medical centers worldwide. Antimicrob Agents Chemother 2020;64(11) [e01433-20].

[4] Mojica MF, Ouellette CP, Leber A, Becknell MB, Ardura MI, Perez F, et al. Successful treatment of bloodstream infection due to metallo-β-lactamase-producing *Stenotrophomonas maltophilia* in a renal transplant patient. Antimicrob Agents Chemother 2016;60(9):5130–4.

[5] Alexander J, Carr A, Minor SB, Navas D. Dual therapy with aztreonam & ceftazidime/avibactam against multi-drug resistant *Stenotrophomonas maltophilia* on tricuspid valve endocarditis. Open Forum Infect Dis 2020;7(Suppl. 1):S798.

[6] Biagi M, Vialichka A, Jurkovic M, Wu T, Shajee A, Lee M, et al. Activity of cefiderocol alone and in combination with levofloxacin, minocycline, polymyxin B, or trimethoprim-sulfamethoxazole against multidrug-resistant *Stenotrophomonas maltophilia*. Antimicrob Agents Chemother 2020;64(9) [e00559-20].

[7] Nakamura R, Ito-Horiyama T, Takemura M, Toba S, Matsumoto S, Ikehara T, et al. *In vivo* pharmacodynamic study of cefiderocol, a novel parenteral siderophore cephalosporin, in murine thigh and lung infection models. Antimicrob Agents Chemother 2019;63(9) [e02031-18].

[8] Jolley JA, Wing DA. Pyelonephritis in pregnancy: an update on treatment options for optimal outcomes. Drugs 2010;70(13):1643–55.

[9] Hibbard L, Thrupp L, Summeril S, Smale M, Adams R. Treatment of pyelonephritis in pregnancy. Am J Obstet Gynecol 1967;98(5):609–15.

[10] Mojica MF, Humphries R, Lipuma JJ, Mathers AJ, Rao GG, Shelburne SA, et al. Clinical challenges treating *Stenotrophomonas maltophilia* infections: an update. JAC Antimicrob Resist 2022;4(3):1–19.

[11] Gibb J, Wong DW. Antimicrobial treatment strategies for *Stenotrophomonas maltophilia*: a focus on novel therapies. Antibiotics 2021;10(10):1226.

[12] Forest Pharmaceuticals, AVYCAZ (Ceftazidime and Avibactam) for Injection, for intravenous use (Reference ID 3949759, Forest Pharmaceuticals, 2016); ⟨www.accessdata.fda.gov/drugsatfda_docs/label/2016/206494s002lbl.pdf⟩.

[13] Khatri A, Naeger Murphy N, Wiest P, Osborn M, Garber K, Hecker M, et al. Community-acquired pyelonephritis in pregnancy caused by KPC-producing *Klebsiella pneumoniae*. Antimicrob Agents Chemother 2015;59(8):4375–8.

[14] Yamano Y. *In vitro* activity of cefiderocol against a broad range of clinically important Gram-negative bacteria. Clin Infect Dis 2019;69(Suppl. 7):S544–51.

[15] Nakamura R, Oota M, Matsumoto S, Sato T, Yamano Y. *In vitro* activity and *in vivo* efficacy of cefiderocol against *Stenotrophomonas maltophilia*. Antimicrob Agents Chemother 2021;65(4):18 [e01436-20].

[16] Broderick C, Lebedevs T. Treating carbapenemase-producing *Enterobacterales* urosepsis with ceftazidime/avibactam in pregnancy. Int J Antimicrob Agents 2023; 62:106903.