European Journal of Clinical Microbiology & Infectious Diseases
https://doi.org/10.1007/s10096-024-04791-1

BRIEF REPORT

Successful treatment of sino-pulmonary infection & skull base osteomyelitis caused by New Delhi metallo-β-lactamase-producing *Pseudomonas aeruginosa* in a renal transplant recipient by using an investigational antibiotic cefepime/zidebactam (WCK 5222)

Rajeev Soman[1,2] · Rasika Sirsat[3] · Ayesha Sunavala[4] · Neha Punatar[3] · Jugal Mehta[3] · Camilla Rodrigues[5] · Balaji Veeraraghavan[6]

Received: 8 December 2023 / Accepted: 21 February 2024

Abstract
A case of sino-pulmonary infection with skull base osteomyelitis due to XDR-*Pseudomonas aeruginosa* in renal transplant recipient was successfully treated with investigational antibiotic, cefepime/zidebactam (WCK 5222). This case highlights challenges in managing XDR-pseudomonal infection where source control was infeasible, antibiotic options were extremely limited and individualized dose adjustments were needed.

Keywords New Delhi metallo-β-lactamase (NDM) · *Pseudomonas aeruginosa* · Cefepime/Zidebactam · Osteomyelitis · β-lactam enhancer-action

Case presentation

The case pertains to a 62-year-old male with a long history of diabetes, hypertension and chronic kidney disease on maintenance hemodialysis who underwent ABO incompatible living related kidney transplantation elsewhere in November 2022. The patient received immunosuppressive therapy consisting of rituximab and four sessions of plasma exchange in the pre-transplant phase. Anti-thymocyte globulin and methylprednisolone were the induction agents in the post-transplant phase followed by an immunosuppressive oral regimen of cyclosporine, mycophenolate mofetil and prednisolone.

One-month post-transplant, he was admitted to the same institution for fever and cough. A left upper zone pulmonary cavitary lesion (Fig. 1a) was detected with high-resolution computerized tomography (CT). Bronchoalveolar lavage (BAL) fluid as well as biopsy from lung lesion yielded *Pseudomonas aeruginosa*. Employing the broth micro-dilution method, the isolate was found to be resistant to carbapenems, aminoglycosides, fluoroquinolones and was intermediate to colistin as per Clinical & Laboratory Standards Institute (CLSI) interpretive criteria. Moreover, in vitro synergy between the off-label combination, ceftazidime/avibactam and aztreonam was negative as assessed by determining the broth micro-dilution MIC of aztreonam and ceftazidime (1:1 ratio) in the presence of a fixed concentration of avibactam (4 mg/L). MIC of fosfomycin, determined by ETEST, was 16 mg/L and the Xpert® Carba-R test flagged the presence of New Delhi metallo-β-lactamase (NDM). The patient was treated with a combination of intravenous polymyxin B (7.5 lac units, q12h) and fosfomycin (4gm, q12h) for 6 weeks period leading to transient clinical recovery. However, his serum creatinine levels showed

✉ Neha Punatar
shahnehashines@gmail.com

1 Department of Infectious Diseases, Jupiter Hospital, Pune, India

2 Courtesy Visiting Consultant, P. D. Hinduja National Hospital & Medical Research Centre, Mumbai, India

3 Department of Nephrology, P. D. Hinduja National Hospital & Medical Research Centre, Mumbai, India

4 Department of Infectious Diseases, P. D. Hinduja National Hospital & Medical Research Centre, Mumbai, India

5 Department of Microbiology, P. D. Hinduja National Hospital & Medical Research Centre, Mumbai, India

6 Department of Microbiology, Christian Medical College, Vellore, India

Published online: 28 February 2024

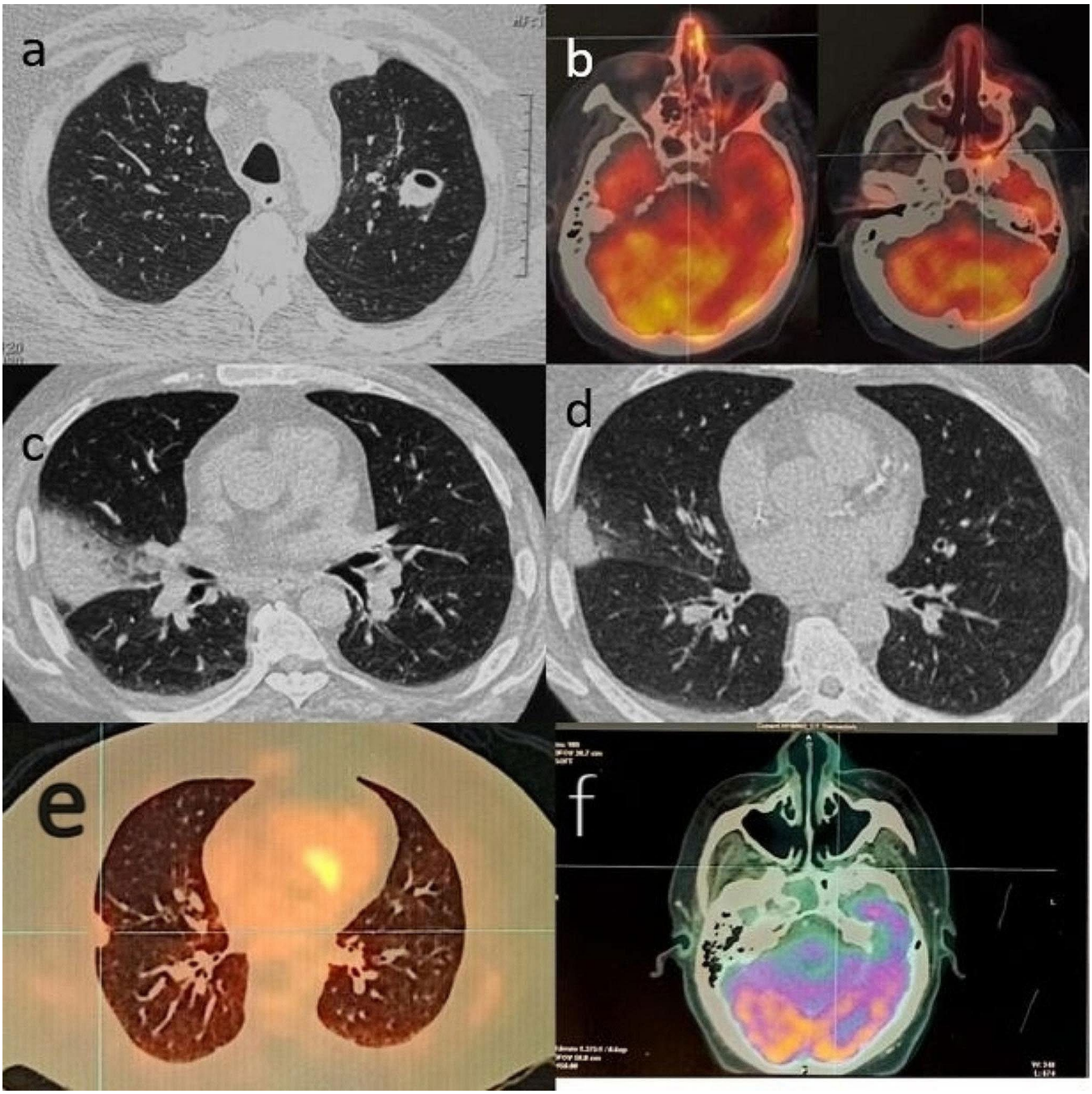

Fig. 1 Images before (**a-c**) and after (**d-f**) treatment with cefepime/zidebactam. (**a**) CT image of lung showing cavitary nodule in left lung. (**b**) PET-scan image of facial region showing FDG uptake in the nasal & sphenopalatine region indicating rhino-sinusitis & skull base osteomyelitis. (**c**) Right sided lobar consolidation in the lung indicative of pneumonia before initiation of cefepime/zidebactam. (**d**) CT of lung at the end of cefepime/zidebactam treatment showing significant resolution of pneumonia. (**e**) PET scan done 2 months after the end of cefepime/zidebactam treatment showed near complete resolution of right sided lobar consolidation. (**f**) PET scan done 2 months after the end of cefepime/zidebactam treatment showed complete resolution of skull base osteomyelitis

a rising trend suggesting rejection of renal graft which was managed with pulse steroid therapy in May 2023.

The patient was admitted to our institution in second week of June 2023 with severe headache. A CT paranasal sinus and PET scan were done which showed signs of rhino-sinusitis and central skull base osteomyelitis (Fig. 1b). The sample collected from the maxillary sinus grew *P. aeruginosa* with a very similar antibiogram, However, the ETEST MIC of fosfomycin had increased to > 1024 mg/L. Therefore, he was put on intravenous polymyxin B monotherapy (7.5 million units, q12h) as no other option was available. Despite this, he clinically worsened with the development

of respiratory distress. CT chest showed a right-sided lobar pneumonia (Fig. 1c), presumably due to aspiration of infected material carrying *P. aeruginosa* from the sinuses. The infecting pathogen recovered from the maxillary sinus (second isolate) was an extensively-drug-resistant (XDR), NDM-producing *P. aeruginosa* which had failed initial prolonged treatment with polymyxin B and fosfomycin. The presence of bla_{NDM} gene and associated resistance mechanisms were confirmed by whole genome sequencing. The purified DNA was sequenced using Hiseq Illumina 4000 platform (short-read sequencing 2×150 bp). The core genome alignment, variant calling of SNPs and small insertions/deletions (indels) were performed using the Snippy v4.6 program.

Bearing in mind, the patient's compromised renal function, co-morbidities and acquired fosfomycin resistance, novel antibiotic options with potential coverage of NDM-producing *P. aeruginosa* were considered such as cefiderocol, combination of aztreonam plus ceftazidime/avibactam, cefepime/taniborbactam and cefepime/zidebactam.

Treatment and outcome

We opted for cefepime/zidebactam (WCK 5222) under compassionate use and requested for susceptibility testing of the pathogen for this antibiotic at Christian Medical College, Vellore. The broth micro-dilution MIC of cefepime/zidebactam was 16 mg/L which was below its PK/PD-based investigational susceptible breakpoint of 32 mg/L [1]. Detailed whole-genome-sequencing analyses confirmed presence of several mutations in genes encoding Penicillin Binding Protein 3 (PBP3), outer membrane proteins (OprD), efflux pumps and AmpC, a typical representation of molecular epidemiology in high-resistance regions.

With due permission from the regulatory authority, cefepime/zidebactam monotherapy was initiated on July 13, 2023 replacing polymyxin B. A dose of cefepime 2 g/zidebactam 1 g, 90-min infusion, q12h (standard regimen is cefepime 2 g/zidebactam 1 g, q8h), was initiated considering an eGFR of 30mL/min. Though the recommended adjusted dose for this degree of renal impairment is cefepime 1 g/zidebactam 0.5 g, q48h, a higher initial dose was opted for in view of the site of infection known for poor drug penetration, the propensity of *P. aeruginosa* to form biofilms, inability to undertake source control and immunocompromised status of the patient, all needing high drug exposures to ensure therapeutic efficacy. Within 48 h of treatment initiation, facial swelling and pain substantially reduced. However, by day 3, the patient developed drowsiness and significant azotemia, hemodialysis was initiated and immunosuppressive therapy withdrawn.

Therapeutic drug monitoring (TDM) using Liquid Chromatography with tandem mass spectrometry (LC-MS-MS), was used to guide individualized dosing of cefepime/zidebactam for this patient. Based on the determined exposure profile of cefepime, the doses were readjusted to cefepime 1 g/zidebactam 0.5 g, q48h (after each hemodialysis) to maintain a trough level less than 20 mg/L. A week later, the patient developed an influenza-like illness. Multiplex PCR from sputum revealed Influenza A, rhinovirus & *P. aeruginosa* with NDM. However, a concomitant sputum culture did not grow *P. aeruginosa* thus confirming that the etiology of earlier lobar pneumonia was indeed *P. aeruginosa*, which was now culture negative on treatment. TDM-based dose of cefepime/zidebactam was continued for a total period of 11 weeks, including the last 7 weeks of outpatient antibiotic treatment, as cefepime/zidebactam showed a reassuring safety profile during the hospital stay after the dose modification. A significant clinical resolution along with chest-CT findings (Fig. 1d) enabled discontinuation of cefepime/zidebactam treatment. PET- scan done 2 months after stopping cefepime/zidebactam treatment, showed near complete resolution of the right lobar pneumonia(Fig. 1e) and skull base osteomyelitis(Fig. 1f).

Discussion

The presented case highlights a unique challenge faced by clinicians in this part of world. Unlike most other regions, carbapenem-resistance among *P. aeruginosa* in India is primarily driven by carbapenemases, more specifically, NDMs [2]. As a result, β-lactam/β-lactamase inhibitor (BL/BLI) based novel anti-pseudomonal agents, viz. ceftolozane/tazobactam, ceftazidime/avibactam, imipenem/relebactam and meropenem/vaborbactam are of limited use. Novel BL/BLIs launched with the promise of overcoming resistance in some parts of the world remain ineffective in others. As NDM-producing *P. aeruginosa* are mostly resistant to fluoroquinolones and aminoglycosides [3], the treatment choice is essentially restricted to polymyxins and fosfomycin which are associated with inconsistent clinical outcomes and risk of serious adverse events. The combination of aztreonam and ceftazidime/avibactam which is, in effect, aztreonam/avibactam (as ceftazidime is readily hydrolyzed by NDM), has been widely considered for NDM-producing Enterobacterales infections. However, its utility is extremely limited for NDM-producing *P. aeruginosa* because aztreonam is vulnerable to hyper-efflux which is ubiquitously present in this organism [4]. This was corroborated by the lack of in vitro synergy between ceftazidime/avibactam and aztreonam against this isolate. It may be mentioned that The Infectious Disease Society of America (IDSA) guidance

document does not recommend aztreonam plus ceftazidime/avibactam for treatment of infections caused by MBL-producing *P. aeruginosa*.

Cefiderocol has been shown to be active against *P. aeruginosa* including those resistant to carbapenems and merits consideration as a salvage therapy in patient like ours, however data on its clinical efficacy in patients with MBL-pseudomonal-infections is limited and ambiguous [5]. Moreover, reports describing the in vitro activity of cefiderocol against NDM-producing *P. aeruginosa* are limited. Owing to lack of uniform activity against all the carbapenemases, cefiderocol could not be considered as empirical treatment in our patient. Other considerations not favoring the use of cefiderocol in our patient include its poor lung penetration [6], vulnerability to hydrolytic activity of NDM [7] and risk for on-therapy resistance development during prolonged use [8]. With regards to cefepime/taniborbactam, its potential coverage of NDM-producing *P. aeruginosa* is not clear as available data is extremely limited against this resistotype [9].

We chose cefepime/zidebactam as salvage therapy for our patient as large-scale MIC studies demonstrated its potent activity against MBL-producing *P. aeruginosa.* For both, Verona Integron-encoded MBL (VIM) and NDM-producing isolates, the MICs of cefepime/zidebactam hover around 8-16 mg/L [1]. The consistent activity of cefepime/zidebactam against strains expressing diverse carbapenemase as well as non-enzymatic resistance mechanism (hyper-efflux, oprD loss) is due to the β-lactam enhancer activity of zidebactam (a derivative of diazabicyclooctane) arising from its potent affinity for PBP2 in all clinically-important Gram-negative pathogens including *P. aeruginosa* and *Acinetobacter baumannii* [10] (See Table 1).

Unlike classical BL/BLIs, the mechanism of action of cefepime plus zidebactam against MBL-producing Gram-negative bacteria is not dependent on β-lactamase inhibition, but is driven by synergistic inactivation of PBP3 (target of cefepime) and PBP2 (target of zidebactam) thus triggering a rapid bactericidal response [10, 11]. Bactericidal action of human-epithelial-lining fluid (ELF)-simulated regimens of cefepime/zidebactam against MBL-producing *P. aeruginosa* in translational neutropenic murine lung infection models employing isolates with cefepime/zidebactam's MIC up to 32 mg/L has been demonstrated [12]. Further under compassionate use, cefepime/zidebactam was successfully used to treat three cases of serious infections caused by NDM-producing *P. aeruginosa* [13, 14]. All these aspects weighed in favor of cefepime/zidebactam while choosing an appropriate treatment for our patient.

The therapeutic challenges posed in our case were myriad and not restricted to resistance mechanism of the infecting pathogen alone. Additional compounding factors included the sites of infection - lung and bone tissue known for poor antibiotic penetration, inability to perform source control and immunocompromised status. Against this backdrop, the observed clearance of pulmonary and bone-associated infection by cefepime/zidebactam combination is notable, which could be linked with the reported low %*f*T > MIC (low exposure) required to elicit in vivo bactericidal response, a feature uniquely associated with β-lactam enhancer action. Another encouraging aspect was that after the initial dose adjustment, patient tolerated prolonged course (11 weeks) of cefepime/zidebactam treatment well.

Table 1 Summary of observations from whole genome sequencing of infecting pathogen *P. aeruginosa*

MLST	β-lactamases	Antibiotic resistance genes (associated antibiotic class)	Major single nucleotide polymorphisms
ST-357	NDM-1, VEB-9, OXA-846, PDC-374 (impact β-lactam class)	*fosA* (fosfomycin) *aph*(6)-Id, *aph*(3'')-lb (aminoglycosides) *aac*(3)-Id (aminoglycosides) *aac*(6')-II (aminoglycosides) *aph*(3')-IIb (aminoglycosides) *qnr*VC1 (fluoroquinolones) *crpP* (ciprofloxacin) *tet(A)* (tetracycline) *tet(G)* (tetracycline) *arr*-2 (rifampin) *mph(E)* (macrolides) *msr(E)* (macrolides) *floR* & *floR2* (chloramphenicol) *sul1* (sulphonamides) *catB7* (chloramphenicol)	*ftsI* (PBP3): V537L *gyrA*: T83I *parC*: S87L; P752T *parE*: D533E *oprD*:SGS57EGR,V127L,EP185QG,V189T,E202Q,I210A, E230K,S240T,N262T,T276A,A281G,K296Q,Q301E,R310E, A315G,Q424E *AmpC*: P07S; T105A; V205L; G391A *AmpD*: G68D *AmpR*: G109A; S174T; 829-833 deletion; ,283R *MexC*: E218Q,A229E,A244T,H277R,S297A,A345T *MexD*: T87S; S845A *MexE*: S8F,A79G,A231T *MexF*: A843T *MexR*: V126E *MexT*: Deletion of 3 amino acids at position 225; P67I *MexX*: A30T; K329Q; L331V; W358R *nalC*: G53E,S191R *pbpC*:A104P

Concluding remarks

In summary, we report a case of successful treatment of sino-pulmonary infection and skull base osteomyelitis caused by NDM-producing *P. aeruginosa* with an investigational antibiotic, cefepime/zidebactam. Widespread prevalence of NDM among *P. aeruginosa* in India is a serious concern due to limited treatment options. Novel antibiotics like cefepime/zidebactam are promising options for this unmet need.

Author contributions RS – Preparation of manuscript, Supervision. RaS – Preparation of manuscript, Supervision. AS – Critical review of manuscript. NP – Data acquisition and analysis. JM – Data acquisition and analysis. CR – Data analysis. BV – Critical review of manuscript.

Funding The authors declare that no funds were received during the preparation of this manuscript. Cefepime/ Zidebactam was supplied free of charge by Wockhardt.

Data availability Data archieved is not mandated, but data will be made available at reasonable request.

Declarations

Ethical approval It is a case report. Hence Ethics Committee Approval not required as per our institute.

Consent to participate Informed and written consent was taken from the patient.

Consent to publish The authors affirm that the patient provided informed consent for publishing his medical details and images as in Fig. 1a f.

Competing interests The authors have no relevant financial or non-financial interests to disclose.

References

1. Karlowsky JA, Hackel MA, Bouchillon SK, Sahm DF (2020) In Vitro Activity of WCK 5222 (Cefepime-Zidebactam) against Worldwide Collected Gram-negative Bacilli not susceptible to Carbapenems. Antimicrob Agents Chemother 64(12):e01432–e01420
2. Lee YL, Hsueh PR (2023) Poor in vitro activity of ceftazidime/avibactam, ceftolozane/tazobactam, and meropenem/vaborbactam against carbapenem-resistant Pseudomonas aeruginosa in India: results from the Antimicrobial Testing Leadership and Surveillance (ATLAS) program, 2018–2021. J Infect 87(1):e1–e4
3. Shanthi M, Sekar U, Kamalanathan A, Sekar B (2014) Detection of New Delhi metallo beta lactamase-1 (NDM-1) carbapenemase in Pseudomonas aeruginosa in a single centre in southern India. Indian J Med Res 140:546–550
4. Jorth P, McLean K, Ratjen A, Secor PR, Bautista GE, Ravishankar S et al (2017) Evolved Aztreonam Resistance is multifactorial and can produce hypervirulence in Pseudomonas aeruginosa. mBio 8(5):e00517–e00517
5. Timsit JF, Paul M, Shields RK, Echols R, Baba T, Yamano Y et al (2022) Cefiderocol for the Treatment of Infections due to Metallo-B-lactamase-producing pathogens in the CREDIBLE-CR and APEKS-NP phase 3 Randomized studies. Clin Infect Dis 75(6):1081–1084
6. Katsube T, Nicolau DP, Rodvold KA, Wunderink RG, Echols R, Matsunaga Y et al (2021) Intrapulmonary pharmacokinetic profile of cefiderocol in mechanically ventilated patients with pneumonia. J Antimicrob Chemother 76(11):2902–2905
7. Mushtaq S, Sadouki Z, Vickers A, Livermore DM, Woodford N (2020) Vitro Activity of Cefiderocol, a Siderophore Cephalosporin, against Multidrug-Resistant Gram-negative Bacteria. Antimicrob Agents Chemother 64(12):e01582–e01520
8. Simner PJ, Mostafa HH, Bergman Y, Ante M, Tekle T, Adebayo A et al (2022) Progressive Development of Cefiderocol Resistance in Escherichia coli during Therapy is Associated with an increase in blaNDM-5 Copy Number and Gene expression. Clin Infect Dis 75(1):47–54
9. Mushtaq S, Vickers A, Doumith M, Ellington MJ, Woodford N, Livermore DM (2021) Activity of β-lactam/taniborbactam (VNRX-5133) combinations against carbapenem-resistant Gram-negative bacteria. J Antimicrob Chemother 76(1):160–170
10. Moya B, Bhagwat S, Cabot G, Bou G, Patel M, Oliver A (2020) Effective inhibition of PBPs by cefepime and zidebactam in the presence of VIM-1 drives potent bactericidal activity against MBL-expressing Pseudomonas aeruginosa. J Antimicrob Chemother 75(6):1474–1478
11. Hujer AM, Marshall SH, Mack AR, Hujer KM, Bakthavatchalam YD, Umarkar K, Palwe SR, Takalkar S, Joshi PR, Shrivastava R, Periasamy H, Bhagwat SS, Patel MV, Veeraraghavan B, Bonomo RA (2023) Transcending the challenge of evolving resistance mechanisms in Pseudomonas aeruginosa through β-lactam-enhancer-mechanism-based cefepime/zidebactam. mBio 14:e01118–e01123
12. Kidd JM, Abdelraouf K, Nicolau DP (2020) Efficacy of human-simulated bronchopulmonary exposures of cefepime, zidebactam and the combination (WCK 5222) against MDR Pseudomonas aeruginosa in a neutropenic murine pneumonia model. J Antimicrob Chemother 75(1):149–155
13. Tirlangi PK, Wanve BS, Dubbudu RR, Yadav BS, Kumar LS, Gupta A et al (2023) Successful use of Cefepime-Zidebactam (WCK 5222) as a salvage therapy for the treatment of disseminated extensively drug-resistant New Delhi Metallo-β-Lactamase-producing Pseudomonas aeruginosa infection in an adult patient with Acute T-Cell Leukemia. Antimicrob Agents Chemother 67(8):e0050023
14. Dubey D, Roy M, Shah TH, Bano N, Kulshrestha V, Mitra S et al (2023) Compassionate use of a novel β-lactam enhancer-based investigational antibiotic cefepime/zidebactam (WCK 5222) for the treatment of extensively-drug-resistant NDM-expressing Pseudomonas aeruginosa infection in an intra-abdominal infection-induced sepsis patient: a case report. Ann Clin Microbiol Antimicrob 22(1):55