



Ref. No.: WOCK/SEC/SE/2023-24/073

11th March, 2024

BSE Limited Corporate Relations Department P J Towers, Dalal Street Mumbai - 400 001 <u>Scrip Code: 532300</u>	National Stock Exchange of India Limited Listing Department Exchange Plaza Bandra Kurla Complex, Bandra (E), Mumbai - 400 051 <u>NSE Symbol – WOCKPHARMA</u>
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Dear Sir/ Madam,

Sub: Press Release

Please find enclosed herewith the Press Release titled “**A leading European Journal reports a challenging Clinical Case of Successful use of under-trial drug Zidebactam/Cefepime (WCK 5222, Zaynich™) to Treat Skull Bone Infection & Pneumonia caused by Extreme-drug Resistant Pseudomonas in Renal Transplant Patient**” along with relevant extract of European Journal of Clinical Microbiology & Infectious Diseases, which is self-explanatory.

Kindly take the above information on record.

Thanking you,

For **Wockhardt Limited**

Rashmi Mamtura
Company Secretary

Encl: As above



Mumbai, 11th March 2024

A leading European Journal reports Renal Transplant Patient's unique Clinical Case of Successful use of Zidebactam/Cefepime (WCK 5222, Zaynich™) to Treat Skull Bone Infection & Pneumonia caused by Extreme-drug Resistant Pseudomonas

A recent publication highlights the multidimensional nature of antimicrobial resistance challenges in India and the need for novel versatile antibiotics to tackle growing number of multi-drug resistant infections. A publication, which recently appeared in a peer reviewed journal, European Journal of Clinical Microbiology & Infectious Diseases (EJCMID) describes an exceptionally complex case of sino-pulmonary infection and skull base osteomyelitis in a renal transplant patient caused by an extreme-drug-resistant Gram-negative bacterial pathogen, Pseudomonas. As all the available antibiotics failed to treat the infection, the patient was successfully treated with Zidebactam/Cefepime (WCK 5222, Zaynich™) under compassionate grounds following due approval from Drugs Controller General of India.

Dr. Rajeev Soman, leading infectious diseases specialist and lead author of the publication said "Recalcitrant skull-base bone infections involving extreme-drug-resistant bugs is difficult-to-treat as the antibiotic needs to reach the site of infection in adequate concentration and the antibiotic should be active against such pathogens. The present case was even more complicated as controlling the source of infection through surgical intervention was not possible and the patient was severely immunocompromised. With no options left, we treated the patient with last resort combinations of Polymyxins and Fosfomycin, however the patient clinically worsened. To save this patient, we requested for Zidebactam/Cefepime under compassionate use since this antibiotic is currently in Phase 3 trials. With just few days of treatment, the patient started responding well and finally complete clinical resolution of infection was attained, as verified 2 months after the end of Zidebactam/Cefepime treatment". The scientific publication also highlighted safety of prolonged use of Zidebactam/Cefepime.

Dr V Balaji, a co-author of the case study and leading clinical microbiologist said "the pathogen from this patient was Pseudomonas aeruginosa which produced NDM enzyme capable of inactivating last-line safe antibiotic meropenem and a number of other resistance mechanisms. As a result, this pathogen was resistant to range of newer antibiotics such Ceftazidime/Avibactam (often combined with Aztreonam), Meropenem/vaborbactam, Ceftolozane/Tazobactam, and Imipenem/Relebactam and as well as non-β-lactam class mainstay antibiotics such as Amikacin and Ciprofloxacin/Levofloxacin".

PRESS RELEASE



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“India has become a global hotspot of antibiotic resistance and moreover, the antibiotic resistant mechanisms prevalent in India are much tougher. Transplant and cancer patients are highly vulnerable to antibiotic resistance infections due to need for sustained immunosuppression and frequent exposure to hospitals. In this context, novel antibiotics like Zidebactam/Cefepime are promising life-saving options for such nearly untreatable infections in our country inflicting huge mortality and morbidity,” said Dr. Rajeev Soman.

About Wockhardt

Wockhardt is a research based Global Pharmaceutical and Biotech company. Wockhardt’s New Drug Discovery programme has focussed on unmet need of Anti-bacterial drugs that are effective against the menace of untreatable superbugs. Wockhardt is the only company in the world where USFDA has given QIDP Status (Qualified Infectious Disease Product) for 6 of our Anti-bacterial discovery programmes - 3 of them are Gram Negative and 3 Gram Positive effective against untreatable “Superbugs”. It has a comprehensive Drug Discovery team and clinical organisation.

Wockhardt is employing around ~2600 people and 27 nationalities with presence in USA, UK, Ireland, Switzerland, France, Mexico, Russia and many other countries. It has manufacturing and research facilities in India, USA & UK and a manufacturing facility in Ireland. Wockhardt has a significant presence in USA, Europe and India, with 78% of its global revenues coming from international businesses.



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)

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Received: 8 December 2023 / Accepted: 21 February 2024

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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 cavitory 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

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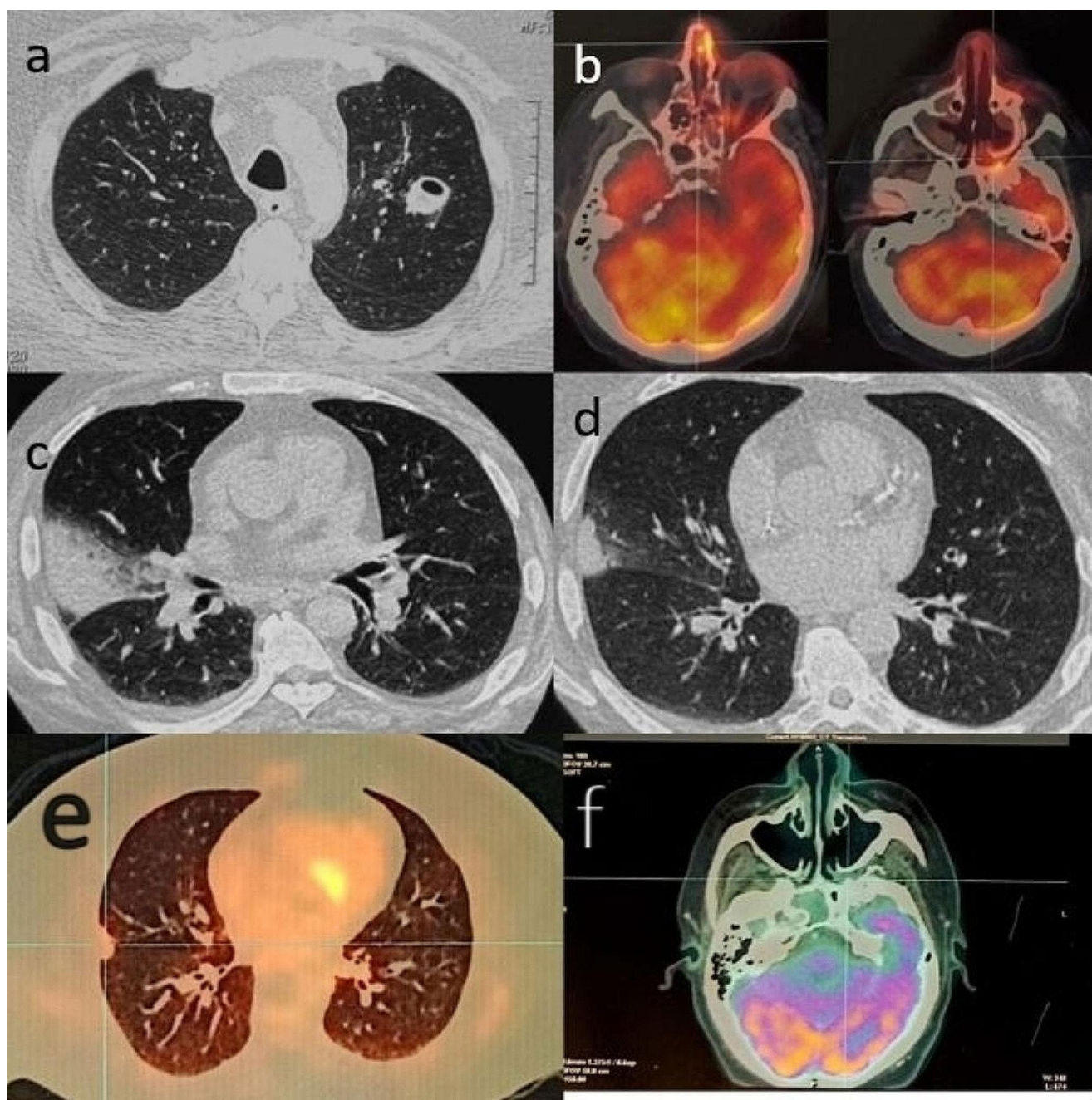


Fig. 1 Images before (a-c) and after (d-f) treatment with cefepime/zidebactam. (a) CT image of lung showing cavitary nodule in left lung. (b) PET-scan image of facial region showing FDG uptake in the nasal & sphenopalatine region indicating rhino-sinusitis & skull base osteomyelitis. (c) Right sided 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 30 mL/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 Enterobacteriales 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 ceftazidime/taniborbactam, its potential coverage of NDM-producing *P. aeruginosa* is not clear as available data is extremely limited against this resistotype [9].

We chose ceftazidime/taniborbactam 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 ceftazidime/taniborbactam hover around 8-16 mg/L [1]. The consistent activity of ceftazidime/taniborbactam 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 taniborbactam (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 ceftazidime plus taniborbactam against MBL-producing Gram-negative bacteria is not dependent on β -lactamase inhibition, but is driven by synergistic inactivation of PBP3 (target of ceftazidime) and PBP2 (target of taniborbactam) thus triggering a rapid bactericidal response [10, 11]. Bactericidal action of ceftazidime/taniborbactam against MBL-producing *P. aeruginosa* in translational neutropenic murine lung infection models employing isolates with ceftazidime/taniborbactam's MIC up to 32 mg/L has been demonstrated [12]. Further under compassionate use, ceftazidime/taniborbactam 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 ceftazidime/taniborbactam 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 ceftazidime/taniborbactam combination is notable, which could be linked with the reported low %fT > 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 ceftazidime/taniborbactam 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)	<i>fosA</i> (fosfomycin) <i>aph(6)-Id</i> , <i>aph(3'')</i> -Ib (aminoglycosides) <i>aac(3)-Id</i> (aminoglycosides) <i>aac(6')</i> -II (aminoglycosides) <i>aph(3')</i> -IIb (aminoglycosides) <i>qnrVC1</i> (fluoroquinolones) <i>crpP</i> (ciprofloxacin) <i>tet(A)</i> (tetracycline) <i>tet(G)</i> (tetracycline) <i>arr-2</i> (rifampin) <i>mph(E)</i> (macrolides) <i>msr(E)</i> (macrolides) <i>floR</i> & <i>floR2</i> (chloramphenicol) <i>sulI</i> (sulphonamides) <i>catB7</i> (chloramphenicol)	<i>ftsI</i> (PBP3): V537L <i>gyrA</i> : T83I <i>parC</i> : S87L; P752T <i>parE</i> : D533E <i>oprD</i> :SGS57EGR,V127L,EP185QG,V189T,E202Q,I210A,E230K,S240T,N262T,T276A,A281G,K296Q,Q301E,R310E,A315G,Q424E <i>AmpC</i> : P07S; T105A; V205L; G391A <i>AmpD</i> : G68D <i>AmpR</i> : G109A; S174T; 829-833 deletion; ,283R <i>MexC</i> : E218Q,A229E,A244T,H277R,S297A,A345T <i>MexD</i> : T87S; S845A <i>MexE</i> : S8F,A79G,A231T <i>MexF</i> : A843T <i>MexR</i> : V126E <i>MexT</i> : Deletion of 3 amino acids at position 225; P67I <i>MexX</i> : A30T; K329Q; L331V; W358R <i>nalC</i> : G53E,S191R <i>pbpC</i> :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 archived 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.

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