CASE REPORT

Treatment of a complex orthopaedic infection due to extensively drug-resistant *Pseudomonas aeruginosa*Sidra Hassan,¹ Mani D Kahn,² Nidhi Saraiya,³ Priya Nori⁴¹Department of Medicine, Jacobi Medical Center, Albert Einstein College of Medicine, Bronx, New York, USA²Department of Orthopedic Surgery, Montefiore Medical Center, Bronx, New York, USA³Department of Pharmacy, Montefiore Wakefield Campus, Bronx, New York, USA⁴Department of Medicine, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, New York, USA**Correspondence to**Dr Sidra Hassan,
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SUMMARY

According to the Centers for Disease Control and Prevention (CDC), approximately 51 000 healthcare-associated infections caused by *Pseudomonas aeruginosa* occur annually in the USA, more than 6000 of which (13%) are caused by multidrug resistant (MDR) strains. Ceftolozane/tazobactam (TOL/TAZ) (Zerbaxa) was approved by the US Food and Drug Administration (FDA) in December 2014 for the treatment of complicated intra-abdominal and urinary tract infections. At this time, clinical data on the role of TOL/TAZ treatment outside of FDA-approved indications is limited. Herein, we present a case of extensively drug-resistant (XDR) *P. aeruginosa* osteomyelitis of the upper extremity, which was successfully treated with TOL/TAZ for 8 weeks with optimal clinical and laboratory responses. Monotherapy with TOL/TAZ appears effective for treatment of complicated bone and joint infections with XDR *P. aeruginosa* in combination with comprehensive surgical management, particularly when few antibiotic options exist.

BACKGROUND

Multidrug-resistant (MDR) bacteria are non-susceptible to at least one agent in at least three antibiotic categories, whereas extensively drug-resistant (XDR) bacteria are non-susceptible to at least one agent in all but two or fewer antibiotic categories.¹ In 2013, the Centers for Disease Control and Prevention (CDC) estimated that two million people per year suffer from infections due to MDR bacteria resulting in over 23 000 deaths annually.² Due to increased public health emphasis on the emerging threat of MDR infections and improved molecular detection methods since 2013, the prevalence of MDR infections is likely more than initially described.³ A well described pathogen in both community-acquired and hospital onset infections, multidrug resistant *Pseudomonas aeruginosa* remains clinically challenging to treat and eradicate, owing to limited available antibiotic options.⁴

MDR mechanisms in *P. aeruginosa* can be mediated by: (1) imported resistance mechanisms on mobile genetic elements or plasmids (eg, production of inactivating beta (β)-lactamases or enzymatic inactivation of the drug molecule through chemical modification such as phosphorylation, acetylation or methylation); (2) a combination of imported and chromosomally encoded resistance mechanisms; (3) accumulation of multiple chromosomal changes over time (4) or a single mutational

event leading to the overexpression of an MDR mechanism (eg, AmpC cephalosporinase, the OprD outer membrane porin and the multidrug efflux pumps).^{5 6}

Ceftolozane/tazobactam (TOL/TAZ) is a combination of a novel antipseudomonal cephalosporin and a well-known β -lactamase inhibitor.⁷ It has activity against several *Pseudomonas* species and Enterobacteriaceae except carbapenemase producing strains. Among Gram positives, it is active against *Streptococcus* species but has limited activity against *Staphylococcus* species and minimal activity against *Enterococcus* species. However, given several available therapeutic options for Gram-positive infections, the feature role of TOL/TAZ lies in its activity against resistant Gram-negative bacteria. It has limited activity against Gram-negative anaerobes.⁸ Ceftolozane's increased efficacy profile against resistant Gram-negative bacteria is mainly attributed to its increased stability against AmpC β -lactamases and enhanced binding to penicillin-binding proteins, rendering it less subject to changes in porin permeability and efflux pumps.^{9 10} A fixed ratio of 2:1 for TOL/TAZ was FDA approved in December 2014 for the treatment of complicated intra-abdominal (in combination with metronidazole for anaerobic activity) and urinary tract infections^{11–13}; however, there is less clinical data on its use beyond the FDA-approved indications. Notable reports in the literature include several cases of MDR or XDR *Pseudomonas* bacteraemia, skin and soft tissue infections or osteomyelitis successfully treated with TOL/TAZ monotherapy.^{14–19}

Herein we report a case of XDR *P. aeruginosa* osteomyelitis associated with infected orthopaedic hardware of the upper extremity, which was successfully treated with an extended course of TOL/TAZ monotherapy after comprehensive surgical management.

CASE PRESENTATION

A 62-year-old man presented to the emergency department (ED) with purulent drainage from surgical wounds on his left forearm in December 2016. He was struck by a motor vehicle as a pedestrian in Jamaica in November 2016 and sustained a right humeral shaft fracture and open radius and ulnar comminuted fractures requiring open reduction and internal fixation (ORIF). He remained hospitalised in Jamaica for nearly a month and received intravenous antibiotics but could not recall which agents. His postoperative course was

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Table 1 Susceptibility results of *Pseudomonas aeruginosa* isolates

Antibiotic	Isolate no. 1 19 December 2016 (MIC)	Isolate no. 2 19 December 2016	Isolate no. 3 17 June 2017
Aztreonam	R (KB)	Not checked	Not checked
Cefepime	R, 16 µg/mL	S, 2 µg/mL	R, 16 µg/mL
Ciprofloxacin	R, >2 µg/mL	S, <=0.5 µg/mL	R, >2 µg/mL
Gentamicin	S, 4 µg/mL	S, <=2 µg/mL	S, 4 µg/mL
Meropenem	R, >8 µg/mL	Not checked	R, >8 µg/mL
Piperacillin-Tazobactam	R, >64/4	S, 8/4	R, >64/4
Tobramycin	S, <=2 µg/mL	S, <=2 µg/mL	S, <=2 µg/mL
Ceftolozane-Tazobactam	Not checked	Not checked	S (KB)
Ceftazidime-Avibactam	Not checked	Not checked	S, 6.0 µg/mL
Polymyxin B	Not checked	Not checked	S, 1.0 µg/mL

KB, Kirby Bauer; R, resistant; S, sensitive. MIC: Minimum inhibitory concentration

complicated by radial nerve palsy and wrist drop, which impeded his work as a dental assistant.

On returning home to the Bronx, New York, he noted purulent drainage from his wounds along with significant swelling, tenderness and limited functioning of his right arm. He presented to our ED at the Montefiore Medical Center and was admitted to orthopaedic service. He underwent debridement 4 days later, at which time purulent fluid in the ulnar incision was noted superficially without appearance of obvious bony infection. A mid-incision pyogenic granuloma was excised. An unhealed ulnar fracture was also noted along with superficial suture abscesses of the radial incision, which were excised. Operating room (OR) cultures revealed two separate isolates of *P. aeruginosa*, both an XDR isolate and a ciprofloxacin susceptible isolate (table 1). Infectious diseases (ID) consultative service recommended high-dose cefepime 2 g every 8 hours with oral ciprofloxacin 750 mg every 12 hours for at least an 8-week course, despite coexistence of an XDR isolate. This regimen was recommended with the caveat that maximal chance of cure was limited by retention of orthopaedic hardware.

INVESTIGATIONS

On hospital discharge, the patient was closely followed in the outpatient parenteral antibiotic therapy (OPAT) clinic and was noted to be improving. Surgical wounds had healed without abnormal drainage. Erythrocyte sedimentation rate (ESR) declined from 44 mm/hour to 17 mm/hour, and C reactive protein (CRP) declined from 3.7 to 0.7 mg/dL at the completion of the 8-week antibiotic course in February 2017. He continued to report ongoing swelling of forearm but range of motion had improved with occupational therapy. However, follow-up X-ray of the right arm could not rule out ongoing osteomyelitis based on a lucency at the fracture site. A broken distal screw was still noted and hardware loosening at right radial plate could not be excluded. After a few weeks off antibiotics, inflammatory markers again rose (ESR 35, CRP 7.2) and pain and swelling persisted but surgical wounds remained healed. On follow-up with orthopaedics, repeat X-ray confirmed loosening of ulnar plate and screw device with loss of alignment. By May 2017, patient reported increased arm pain with a new lump at the ulnar aspect of his forearm.

TREATMENT

Patient was ultimately taken back to the OR in June 2017 for forearm and humerus irrigation and debridement, hardware removal, forearm non-union takedown, placement of vancomycin/tobramycin beads, wound vacuum and external fixation of the forearm, followed by repeat irrigation and debridement, bead exchange and wound closure several days later. Purulent drainage and bony destruction of radius, ulna and humerus were noted with non-union of radius and ulna. Operating room cultures again revealed XDR *P. aeruginosa*. Microbiology testing on request confirmed susceptibility to both ceftazidime-avibactam (CAZ/AVI) and TOL/TAZ. ID was again consulted and recommended an 8-week course of TOL/TAZ 1.5 g every 8 hours via peripherally inserted central catheter and close follow-up in OPAT clinic.

OUTCOME AND FOLLOW-UP

The patient tolerated TOL/TAZ well without adverse reactions or abnormalities on weekly laboratory monitoring. At the completion of antibiotics in August 2017, the patient reported improved pain and swelling, healed surgical wounds and some improvement in range of motion and sensation. On repeat follow-up in September 2017, he remained symptomatically improved and inflammatory markers normalised (ESR 2, CRP 0.1). In November 2017, he underwent successful removal of the external fixator, ORIF of the right radius and ulna, fibular autograft and split-thickness skin graft placement to right ulnar defect. No signs of infection were noted in the OR and on outpatient follow-up. Chronic oral antibiotic suppression with ciprofloxacin is not an option due to his XDR *P. aeruginosa* isolate.

DISCUSSION

According to CDC, approximately 51 000 healthcare-associated infections caused by *P. aeruginosa* occur annually in the USA, and more than 6000 of these infections (13%) are caused by MDR strains.^{20 21} The rapid emergence of MDR strains is likely due to overuse of existing antibiotics, lack of standardised antimicrobial stewardship and infection prevention practices, particularly in low/middle-income nations and dearth of development of new antimicrobial agents with novel mechanisms of action.²² Several newer antimicrobial agents in the cephalosporin class effective against MDR Gram-negative organisms are now available for clinical use including CAZ/AVI and TOL/TAZ.²² TOL/TAZ differs from other cephalosporins due to its increased activity against AmpC β-lactamases and some carbapenem-resistant strains of MDR *P. aeruginosa* that do not produce carbapenemases. The addition of tazobactam renders activity against some extended spectrum β-lactamase-producing Enterobacteriaceae (ESBL) and anaerobes (certain *Bacteroides* spp and *Prevotella* spp).^{7 23 24} Similarly, CAZ/AVI has also demonstrated potent in vitro activity against resistant Enterobacteriaceae isolates, including AmpC and ESBL producers; however, it is only moderately active against *Acinetobacter* spp, anaerobes (excluding *Bacteroides fragilis*, *Clostridium perfringens*, *Prevotella* spp and *Porphyromonas* spp) and Gram-positive cocci.²⁵

Two cases of MDR pseudomonal skin and soft tissue infections, two cases of pseudomonal osteomyelitis (1 MDR, 1 XDR) and two cases of pseudomonal bacteraemia successfully treated with TOL/TAZ monotherapy have been reported.^{14–19} A multicentre study comparing the in vitro inhibitory activity of CAZ/AVI and TOL/TAZ against meropenem non-susceptible *P. aeruginosa* from 34 US hospitals revealed significantly higher inhibitory activity of TOL/TAZ as compared with CAZ/

AVI.²⁶ In another study comparing the susceptibilities of TOL/TAZ and other antibiotics against drug-resistant *P. aeruginosa* (15.8% were MDR and 9.4% were XDR), TOL/TAZ (97%) was second only to colistin (99.2%) in percentage of susceptible isolates.²⁷ Similarly, another study of *P. aeruginosa* isolates from Australia and New Zealand showed TOL/TAZ and was the most potent β -lactam tested (MIC_{50/90} 0.5/2 μ g/mL), inhibiting 95.7% at an MIC of ≤ 4 μ g/mL. It also had reliable activity against non-Carbapenem Resistant Enterobacteriaceae (CRE) strains of ESBL Enterobacteriaceae (MIC_{50/90} 0.5/2 μ g/mL), but lacked activity (MIC, > 32 μ g/mL) against the single isolate with a CRE phenotype.²⁷

Despite infection with two *P. aeruginosa* strains with different susceptibility profiles, the patient initially responded clinically to 8 weeks of high-dose cefepime and oral ciprofloxacin. Unfortunately, within a few months, he developed a relapse of infection due to the XDR *P. aeruginosa*. After explant of orthopaedic hardware and extensive debridement, he received targeted antibiotic therapy with 8 weeks of TOL/TAZ monotherapy. The patient tolerated the regimen well and achieved short-term cure. After completion of his course, significant improvement in pain, swelling, neuropathy, functionality and inflammatory markers was noted. He eventually received successful ORIF and autograft placement without signs of residual infection. Although some complex orthopaedic infections may require extended oral antibiotic suppression after initial intravenous treatment, this strategy is not an option in our patient.²⁸ Close postantibiotic, postsurgical follow-up is planned to ensure long-term patient cure.

Learning points

- Extensively drug-resistant (XDR) infections acquired in low/middle-income countries requiring infectious diseases and orthopaedic expertise in USA or Europe represent an increasingly prevalent clinical scenario.
- Clinicians should be aware of the risk factors for multidrug resistance, particularly recent hospitalisation in low/middle-income nations with variable infection prevention and antibiotic stewardship policies and practices and significant antibiotic exposure.
- Management of these challenging infections requires a comprehensive surgical and antibiotic strategy with close follow-up to ensure maximal chance of cure.
- There is mounting literature on the successful use of extended courses of ceftolozane–tazobactam monotherapy for treatment of orthopaedic infections with XDR *Pseudomonas aeruginosa*.

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