



## Case study

## Ceftolozane-tazobactam and Fosfomycin for rescue treatment of otogenous meningitis caused by XDR *Pseudomonas aeruginosa*: Case report and review of the literature

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## ABSTRACT

Extensively drug resistant *Pseudomonas aeruginosa* (XDR-PA) strains with limited or absent residual antimicrobial susceptibility cause a growing burden of difficult-to-treat infections. Treatment options are even more limited for patients with central nervous system (CNS) involvement, as colistin-based regimens are hampered by poor blood brain barrier penetration, being often associated with insufficient clinical and microbiological success. New treatment options are awaited, but evidence from prospective evidence-based evaluations is still lacking. Here we report a case of breakthrough otogenous meningitis caused by XDR-PA in a young patient treated with meropenem and colistin for XDR-PA bloodstream infection and pneumonia after a car-crash polytrauma. The patient was treated with off-label, high-dose ceftolozane-tazobactam and high-dose fosfomycin after characterization of CNS XDR-PA isolates, with rapid clinical and microbiological resolution of meningitis. Our experience, although based on a single case, lends preliminary support to the concept that rescue regimens including ceftolozane-tazobactam and fosfomycin may be considered for XDR-PA CNS infections in patients without alternative therapeutic options.

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## Introduction

In recent years, a remarkable increase in infections caused by *Pseudomonas aeruginosa* strains resistant to widely used antimicrobials, such as antipseudomonal beta-lactams and quinolones, was observed worldwide, especially in South Europe [1]. In patients with Blood Stream Infections and/or pneumonia caused by Extensively Drug Resistant *Pseudomonas aeruginosa* (XDR-PA), use of colistin and/or aminoglycosides consequently increased [2]. Central Nervous System (CNS) infections may be challenging for such alternative regimens, associated with reduced clinical and microbiological success [3–5]. Ceftolozane-tazobactam (C-T), a new combination of antipseudomonal cephalosporin and beta-lactamase inhibitor, exhibiting potent *in vitro* activity against XDR-PA strains and other Gram-negative microorganisms, may

represent an effective alternative for XDR-PA infections with CNS involvement [3,5]. The drug is so far approved for complicated urinary tract infections, including acute pyelonephritis, as well as of complicated intra-abdominal infections, the latter in association with metronidazole [6,7]. Although possibly useful for XDR-PA infections in other clinical settings, including CNS infections, data on clinical efficacy outside the licensed indications are as of yet absent or scanty [8,9]. To the best of our knowledge, C-T has been so far used just once for a CNS infection, in a single patient with meningitis, for whom relapse was reported [8]. Here we report on a young man hospitalized in the ICU due to polytrauma and suffering an otogenous meningitis caused by XDR-PA while on treatment with meropenem and colistin for XDR-PA BSI and pneumonia. High dose Ceftolozane-Tazobactam and Fosfomycin provided a rapid and complete rescue of his CNS infection.

## Case report

A 27-year-old male, with an unremarkable history of chronic otitis media, was transferred to the Emergency Department of

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Pescara General Hospital after a car crash. On admission he was awake, with severe respiratory distress, cyanosis and hemodynamic instability. Point-of-care ultrasound revealed right pneumothorax, and a thoracic drainage was inserted. Upon hemodynamic and respiratory stabilization, a CT scan was performed, revealing bilateral pneumothorax due to rib fractures, multiple pulmonary contusions, sacral wing and right tibial plateau fractures. No traumatic brain injury, however, was found.

Upon ICU admission, he required intubation and mechanical ventilation due to respiratory distress; an additional left chest drainage was inserted. Conscious sedation with dexmetomidine and Remifentanyl was started (RASS-2). Pulmonary contusions were managed with bronchial toilet whenever necessary. Systemic antimicrobial treatment with amikacin and cefazolin was provided until plate osteosynthesis for tibial plateau fractures. Four days after admission, the patient presented a septic episode, without shock. Microbiological sampling included blood cultures and bilateral bronchoalveolar lavage. Empiric antimicrobials were modified to piperacillin-tazobactam and linezolid. Early microbiological results from Gram-staining and Fluorescence *in situ* hybridization (FISH) of blood culture isolates revealed *Pseudomonas spp* and *Staphylococcus spp*. The patient's conditions were unchanged 3 days later, when cultural results yielded XDR *Pseudomonas aeruginosa* (XDR-PA) with residual sensitivity to colistin only [10]. High-dose meropenem and colistin, both with a loading dose, were started. Nebulized colistin was added after evidence of an additional XDR-PA isolate from broncho-alveolar lavage; a pulmonary source for the ensuing sepsis was postulated.

Three days later the patient complained with intense headache and neck rigidity. A lumbar puncture was performed; cerebrospinal fluid (CSF) was cloudy, neutrophils >500/microL, glucose 19 mg/dL, and protein 279 mg/dL. Six hours after CSF sampling, Gram-staining of growing colonies provided preliminary evidence of Gram-negative bacteria compatible with *Pseudomonas spp*. On this basis, it was well plausible that the patient, while on treatment with meropenem and colistin for XDR-PA bacteremia, was suffering an ensuing episode of breakthrough meningitis, likely caused by CNS escape of XDR-PA. Therefore, we immediately started a salvage regimen with high-dose C-T (3 g/q8h), high-dose Fosfomycin (4 g/q6h) and Rifampicin 600 mg/q12 h. Dexamethasone (8 mg/q8h) was added. Head bone high-resolution CT-scans showed right middle-ear and mastoid suppurative infection, without bone fractures. In the next 48 h the meningeal syndrome resolved, and right mastoidectomy with tympanoplasty could be safely postponed after other life-saving surgical interventions. The patient was extubated after ear surgery and transferred to the Infectious Diseases Unit. The final microbiological characterization of CSF XDR-PA isolates revealed the following Minimum Inhibitory Concentrations (MIC): colistin <0,5 mg/L; ceftolozane-tazobactam 3 mg/L (determined with MIC test-strip assay, Liofilchem, Italy). To determine sensitivity/resistance of *P. aeruginosa*, EUCAST breakpoints were used. Isolates were investigated for carbapenemase genes by PCR, and for carbapenemase activity by spectrophotometric assays. MICs for Fosfomycin could not be assayed. Repeated CSF sampling documented sterile CSF with normalized parameters; fosfomycin was discontinued after 7 days, ceftolozane-tazobactam after 14 days. Control head bone CT-scans confirmed complete resolution of otomastoiditis. The patient was discharged without clinically relevant neurological sequelae.

## Discussion

Our report suggests a potentially interesting and highly demanded additional indication for ceftolozane-tazobactam, for

which at present very little information is available: CNS infections caused by XDR-PA [5,8]. Meningitis is the most common intracranial complication of otomastoiditis. The patient had a relevant history of recurring otitis, repeatedly treated with quinolones and cephalosporins without microbiological characterization. Although rare in the young, XDR-PA selection likely occurred in his right mastoid, reached by inadequate antimicrobial concentrations [3,11]. Even in the absence of skull fractures, he suffered severe polytrauma with multiple chest fractures. This may well have triggered his CNS complication, with early dissemination of XDR-PA from skull to bloodstream and bronchi. His bloodstream and pulmonary infections preceded meningitis, and at the onset of his CNS infection our patient was on standard treatment for systemic XDR-PA infection with residual sensitivity to colistin [12]. MICs for colistin of CNS isolates were conserved, suggesting CNS breakthrough infection related to insufficient colistin penetration across the blood brain barrier (BBB), together with inefficient CNS meropenem concentrations on XDR-PA [3,12].

As a consequence, at the time of preliminary characterization of CNS isolates, after phone consultation of the local EC (Ethics Committee) referent, high-dose C-T, in combination with high-dose fosfomycin was prescribed off-label as rescue treatment, in spite of low/absent supporting evidence, to prevent the ominous consequences of XDR-PA CNS infections [8]. Rifampicin was added, considering previous bloodstream staphylococcal isolates, until complete characterization. C-T has a broad spectrum of activity, potentially useful for Gram-negative meningitis. As compared with other beta-lactams, it exhibits superior antibacterial activity against isolates of *Pseudomonas aeruginosa* with an unfavorable sensitivity profile [8,9]. Data on CSF penetration are limited, and that a trial in patients with external ventricular drainage is ongoing [13]. To the best of our knowledge, a single case of XDR-PA meningitis treated with C-T monotherapy was reported, leading to temporary disease remission and relapse by day 30 [8]. Clinical response to rescue treatment was fast in our patient; meningeal syndrome resolving in few hours. A MIC for fosfomycin could not be obtained for XDR-PA isolates, so it is difficult to gauge which role combined high-dose fosfomycin has played. Combination therapy, however, including another potentially efficacious molecule, with a favorable BBB pharmacodynamic profile, was the most adequate option [12,14], in view of recent evidence suggesting in-vitro and in-vivo synergism between C-T and fosfomycin [14]. Surgical management of otomastoiditis, crucial for source control in secondary CNS infections [15], was ancillary in our case; it could be postponed to the other surgical needs.

In conclusion, our experience, based on the successful management of a single case, adds preliminary support to the idea that, pending the ordinary pathway of formal endorsement after adequate evidence collection, rescue regimens including ceftolozane-tazobactam may be considered for XDR-PA CNS infections in patients with limited or absent alternative therapeutic options.

## Ethical approval

The Ethical Committee of our Institution validated our therapeutic choice with an urgent procedure on the next day of off-label prescription.

## Conflict of interest

All authors have no competing interests to declare.

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## Author statement

Antonella Frattari, Giustino Parruti, Donatella Cibelli, Silvia Talamazzi, Donatella Bosco and Augusta Consorte: Conceptualization, Data curation, Writing- Original draft, Preparation, Project Administration; Antonella Frattari, Ennio Polilli, Giustino Parruti: Visualization, Supervision, Resurces; Vincenzo Savini and Paolo Fazio: Supervision and Investigation.

All authors read and approved the manuscript

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