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NOVEL ID CASES

Cure of Limb-Threatening XDR *Pseudomonas aeruginosa* Infection: Combining Genome Sequencing, Therapeutic Drug Level Monitoring, and Surgical Debridement

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We describe a case of limb-threatening osteomyelitis and metalware infection with carbapenemase-producing extensively drug-resistant *Pseudomonas aeruginosa* successfully cured with aggressive surgical debridement and combined intravenous fosfomycin and colistin. Real-time therapeutic drug monitoring was used to maximize probability of efficacy and minimize potential for toxicity.

Keywords. XDR gram-negative; fosfomycin; colistin; therapeutic drug monitoring; osteomyelitis.

CASE

A previously fit and active 75-year-old female presented to the Austin Hospital, Melbourne, Australia, with a discharging right ankle wound at the site of a previous internal fixation. Her medical history included osteoporosis and hypertension. The internal fixation was a result of an open right trimalleolar fracture sustained after a mechanical fall while holidaying at Victoria Falls in Zambia 6 months earlier. She was transferred to a tertiary hospital in Johannesburg, South Africa, where she underwent a right ankle open reduction with internal fixation and lateral external fixation. One month later, she was medically evacuated to a private hospital in Melbourne.

On admission to the private hospital, she underwent a rectal screening swab for multidrug-resistant (MDR) organisms, a routine practice for overseas medical repatriations, which identified a carbapenemase-producing *Pseudomonas aeruginosa*. A small wound defect persisted over her right medial ankle, managed with a split graft. Subsequently, a wound swab of the right ankle graft site was also positive for carbapenemase-producing *P. aeruginosa*; however, there was no evidence of clinical infection and she received no antibiotics at this time. She underwent rehabilitation, made an excellent recovery, and was discharged without gait aids.

Six months after her initial injury, she presented to our hospital outpatient clinic with 3 weeks of right ankle pain and a small sinus tract over the right ankle lateral malleolus external fixation site. She had no systemic symptoms. Swabs from the right ankle demonstrated the same carbapenemase-producing extensively drug-resistant (XDR) [1] *P. aeruginosa* identified previously. The strain was resistant to amino-penicillins, third- and fourth-generation cephalosporins, carbapenems, aminoglycosides, and fluoroquinolones; additional drug susceptibility testing was undertaken for ceftolozane-tazobactam, aztreonam, tigecycline, fosfomycin, and colistin (Table 1; [2]). Cefiderocol was not available in Australia at the time.

Whole-genome sequencing (WGS) was performed on the right ankle swab using methods previously described [3]. Briefly, primary specimen cultures were subcultured onto horse blood agar and incubated overnight at 37°C. Genomic DNA was extracted from a single colony using a QIASymphony DSP DNA Mini Kit (Qiagen) according to the manufacturer's instructions, and WGS performed on an Illumina NextSeq platform to generate 150-bp paired-end reads. Raw sequencing reads were trimmed to clip Nextera adapters and low-quality sequence using *Trimmomatic,* version 0.38 [4], and assembled de novo into draft genome sequences using *Shovill,* version 1.0 [5]. The multilocus sequence type and presence of antimicrobial resistance genes were determined in silico using BLAST-based tools [6, 7].

The isolate was ST-111 *P. aeruginosa*, with the genome confirmed to have a $bla_{\text{VIM-2}}$ metallo-beta-lactamase (MBL) gene. In addition, the genome was found to have a *bla*OXA-395 beta-lactamase gene, which is an OXA-50-like gene found in many *P. aeruginosa* isolates and which can result in elevated meropenem minimum inhibitory concentration (MIC) but is regulated by other genes [8]. A chromosomal *fosA* gene was also noted, known to be associated with fosfomycin resistance [9]. On further analysis, the *fosA* gene was truncated with a

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Table 1. MICs of 14 Antibiotics for the Patient's *Pseudomonas aeruginosa* Isolate Using CLSI Breakpoints [2]

Antimicrobial	MIC, µg/mL	Interpretation	Susceptibility Method
Ceftazidime	32	Resistant	Vitek2
Cefepime	32	Resistant	Vitek2
Piperacillin-tazobactam	32	Intermediate	Vitek2
Ticarcillin-clavulanate	≥128	Resistant	Vitek2
Amikacin	≥64	Resistant	Vitek2
Gentamicin	8	Intermediate	Vitek2
Tobramycin	>16	Resistant	Vitek2
Ciprofloxacin	≥4	Resistant	Vitek2
Meropenem	≥64	Resistant	Vitek2 and Etest
Ceftolozane-tazobactam	≥256	Resistant	Etest
Aztreonam	12	Intermediate	Etest
Tigecycline	64	No break point	Etest
Fosfomycin	4	No break point	Agar dilution
Colistin	2	Susceptible	Broth microdilution

Abbreviations: CLSI, Clinical & Laboratory Standards Institute; MIC, minimum inhibitory concentration.

premature stop codon inserted at codon 110, which would have led to a nonfunctional FosA protein.

The patient was admitted for management of the ankle infection, and initial laboratory results demonstrated the following: hemoglobin 127 g/L, white cell count 8.1×10^9/L, erythrocyte sedimentation rate 44 mm/h, C-reactive protein 62.3 mg/L, sodium 141 mmol/L, and potassium 4.3 mmol/L. Treatment commenced with aggressive surgical intervention, including 3 surgical debridements, removal of all metalware, and placement of a vacuum-assisted closure (VAC) device. MBL $bla_{\text{VIM-2}}$ *P. aeruginosa* was isolated from tissue, bone, and metalware specimens from the initial surgery. Empiric antibiotic therapy was initiated after metalware removal; at the time, the patient's serum creatinine was 79 µmol/L (creatinine clearance [CrCl] by Cockcroft-Gault 60 mL/min). An intravenous loading dose (225 mg of colistin base activity, based on ideal body weight) followed by 120 mg every 12 hours [10, 11] was administered, in combination with empiric piperacillin-tazobactam 3-hour extended infusion of 4.5 g every 6 hours and oral rifampicin 600 mg every 12 hours for synergy (described in in vitro studies with colistin and rifampicin) [12, 13]. Aztreonam was considered; however, given that the MIC interpretation was intermediate and therapeutic drug monitoring (TDM) was not possible, there was concern about inadequate tissue penetration at the site of infection.

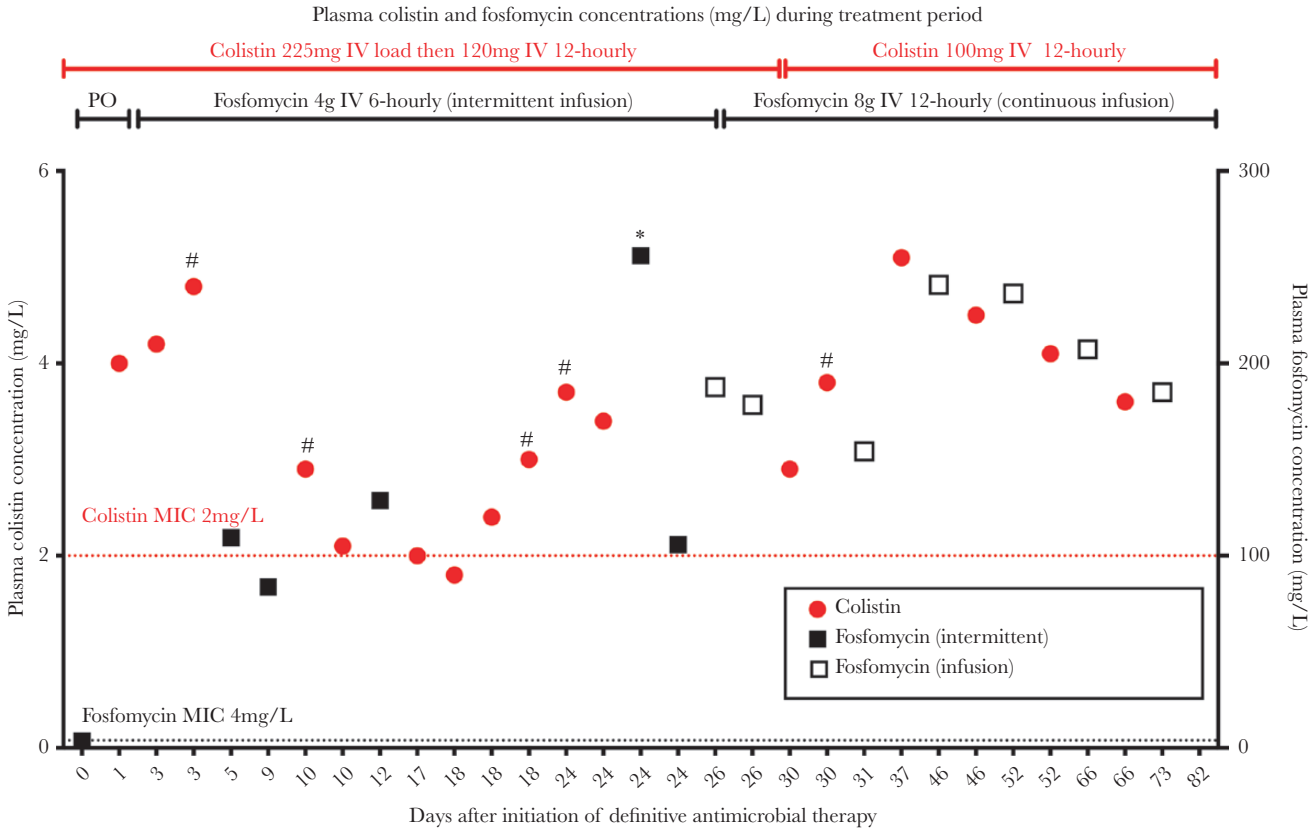
When fosfomycin MIC results were available 4 days later, piperacillin-tazobactam and rifampicin were ceased and fosfomycin was commenced in addition to colistin for definitive treatment. This was initially administered 3 g orally every 24 hours for 4 days, and when intravenous fosfomycin became available, administration was changed to intravenous fosfomycin [9] 4 g infused over 60 minutes every 6 hours (total daily dose 16 g). One month later, fosfomycin dosing was changed to a continuous infusion of 8 g every 12 hours to facilitate outpatient parenteral antibiotic therapy. The total duration of intravenous fosfomycin and colistin treatment was 12 weeks.

The Clinical & Laboratory Standards Institute (CLSI) and European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoint for colistin is ≤2 mg/L [2, 14]. TDM of plasma colistin concentrations was undertaken throughout the treatment course (Figure 1), as recommended and described [10, 11, 15]. Dose reduction of colistin was required due to renal dysfunction, and plasma colistin concentrations remained at or above the recommended target plasma colistin average steady-state concentration of 2 mg/L [10, 11, 16].

There are no CLSI or EUCAST breakpoint criteria to guide fosfomycin use to treat *P. aeruginosa* infections [2, 14]. Given the wide dose range of intravenous fosfomycin both recommended by the manufacturer [17] and in clinical practice [18], TDM of plasma fosfomycin levels was performed. There have been no descriptions of intravenous fosfomycin TDM to date. We used the description of a previous exploratory study of oral fosfomycin TDM at our institution [19] and our institutional experience through development of the fosfomycin assay to determine sampling intervals. During the oral and intravenous intermittent phases of treatment, fosfomycin trough levels (30 minutes predose) were obtained every 3–4 days, and a single peak level was measured to establish the upper levels of plasma concentration (Figure 1). Fosfomycin concentrations remained substantially above the MIC, up to ~60-fold higher, during both intermittent and continuous modes of intravenous dosing, with no adverse effects noted.

During the index admission, the patient also underwent change of the VAC device, a muscle flap repair to close the wound defect, and evacuation of a wound hematoma in addition to the medical therapy described. Progress of hematologic and biochemical parameters in relation to antibiotic therapy and surgical procedures is shown in Figure 2. Two months after antibiotic treatment was ceased, the patient presented with worsening ankle pain. Imaging demonstrated severe degenerative changes of the ankle joint. Bone biopsies taken for culture did not isolate any pathogens. Given the aggressive surgical debridement and serum concentrations of colistin and fosfomycin during treatment, the etiology of the patient's pain and imaging changes were thought mechanical rather than infective, and 5 months later she underwent fusion of the ankle joint with metalware insertion. Intraoperative bone and tissue biopsies were also negative. She now walks unassisted.

Renal impairment was sustained during colistin treatment, with serum creatinine rising to 114 µmol/L (CrCl 41 mL/min) on day 49 of admission (Figure 2); after dose reduction of colistin, her renal function improved, with a serum creatinine of 95 µmol/L (CrCl 49 mL/min) at completion of antibiotic therapy. Seven months after colistin therapy was completed, her serum creatinine essentially returned to baseline (serum



Trough levels indicated unless otherwise specified

* Fosfomycin peak level

Additional colistin 6-hr post level

Note that multiple samples were sometimes collected on the same calendar data

Figure 1. Plasma fosfomycin concentration (mg/L) and colistin concentration (mg/L) during the treatment period. Abbreviations: IV, intravenous; MIC, minimum inhibitory concentration.

creatinine 89 μmol/L, CrCl 52 mL/min). Since treatment completion, the patient has not had clinical or microbiological relapse of infection.

DISCUSSION

This case of limb-threatening osteomyelitis and metalware infection with carbapenemase-producing XDR *P. aeruginosa* was successfully cured with aggressive surgical debridement and combined intravenous fosfomycin and colistin, assisted by knowledge of the pathogen genotype and real-time TDM to maximize probability of efficacy and minimize potential for toxicity.

Fosfomycin has been used to treat MDR and XDR *P. aeruginosa*, largely in pulmonary infections in critically ill patients [20–22]; however, there have been some descriptions of success in treatment of extrapulmonary infections [23]. Fosfomycin was used in this case for 3 reasons. First, it was chosen due to the low MIC and therefore high likelihood of achieving tissue concentrations above the MIC. In spite of the presence of the *fosA* gene, there is known dissociation between the presence of *fosA* and the MIC [24]. Genomic analysis suggested that the *fosA* gene may be truncated, potentially explaining the phenotypically susceptible isolate. To date, no studies have examined the correlation between the presence of *fosA* gene, the resistance phenotype, and clinical outcomes for XDR *P. aeruginosa*. Second, fosfomycin is known to have excellent bone penetration [25, 26], and monotherapy has previously achieved a cure rate of 78% of patients with osteomyelitis [27]. Third, preclinical studies have demonstrated synergy of a combination of fosfomycin and colistin against gram-negative bacteria, including carbapenem-resistant *P. aeruginosa* [9, 28–31]. Published clinical outcomes of combination therapy with colistin and fosfomycin are rare; however, there is evidence that this combination therapy results in cure in MDR and XDR *P. aeruginosa* pneumonia [20, 23]. Clinical failure of monotherapy with fosfomycin against *P. aeruginosa*

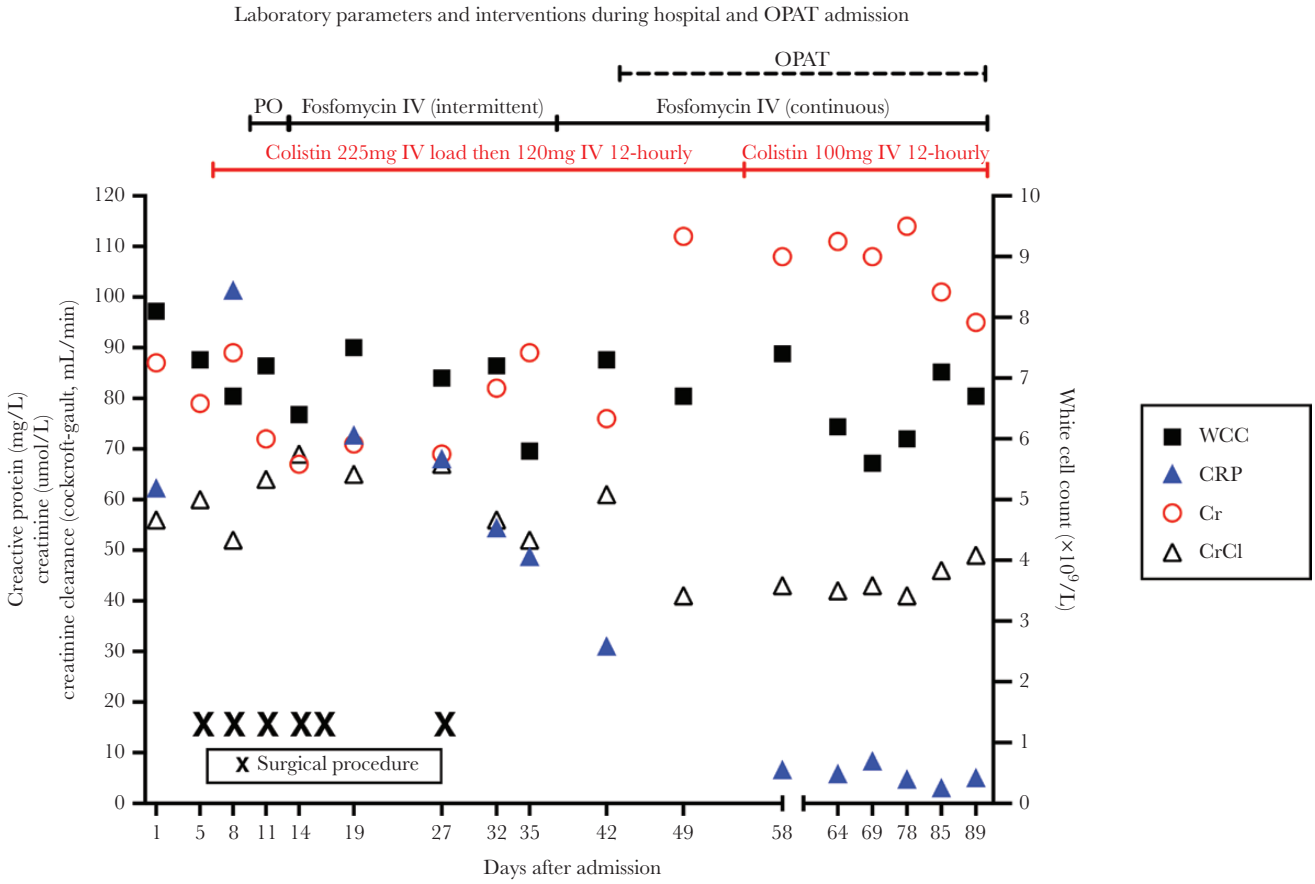


Figure 2. Laboratory parameters and interventions during hospital and outpatient parenteral antibiotic therapy admission. Abbreviations: Cr, creatinine; CrCl, creatinine clearance; CRP, C-reactive protein; IV, intravenous; OPAT, outpatient parenteral antibiotic therapy; PO, per os (oral); WCC, white cell count.

isolates deemed susceptible based on the MIC has been noted, and reservations have been expressed concerning the use of fosfomycin alone [9, 20, 21, 32, 33].

We previously reported on the use of oral fosfomycin in prostatitis treatment, assisted by measurements of plasma fosfomycin concentration [19]. In the current case, intermittent intravenous bolus dosing and continuous infusion of fosfomycin (16 g per day) achieved plasma concentrations of ~80–250 mg/L, which is ~20–60 times the MIC (Figure 1). Based upon the plasma concentrations and previous studies demonstrating a bone-to-plasma concentration ratio of fosfomycin ~0.2 [34], the bone concentration of fosfomycin in the current patient may have been ~16–50 mg/L across the period of intravenous therapy. While these projected bone concentrations are in excess of the MIC of the infecting pathogen, care is needed in use of concentrations of drugs in bone due to the heterogeneous nature of the bone matrix [35].

Against *P. aeruginosa* in static concentration time-kill studies, fosfomycin demonstrated time-dependent killing [32], while in a dynamic in vitro model simulating pharmacokinetic profiles that occur in patients, concentration-dependent killing was observed and the area under the concentration-time curve to MIC ratio (AUC/MIC) was the most predictive pharmacokinetic/pharmacodynamic index [33]. Intermittent short-term infusions and continuous infusion, both of which were used in the present case, are appropriate modes of administration; however, administration by continuous infusion is more convenient in the outpatient setting. In the present patient in whom the drug was administered over almost 3 months, no serious adverse effects attributable to fosfomycin were observed, in keeping with the reported good safety profile of this agent [18, 23]. Previous studies have noted gastrointestinal disorders and hypokalemia to be the most common adverse events associated with fosfomycin [18, 36], the latter thought to be secondary to increased loss of potassium in the distal renal tubules secondary to intravenous fosfomycin. Hypokalemia has been observed to be more common with short intravenous infusions [36], a feature we did not observe in our patient.

There is an emerging role for fosfomycin use in combination therapy for MDR and XDR gram-negative infections due to its excellent plasma drug concentrations, good safety profile, and synergistic nature in combination therapy [37]. This case adds to the evidence supporting its combination use and excellent

tolerability. Further studies are needed to verify the use of fosfomycin in the setting of the *fosA* gene.

For colistin, a target average steady-state plasma concentration of ≥2 mg/L has been recommended [10, 11]. In the current patient, this target informed the choice of the daily dose of intravenous colistin, and the resultant plasma colistin concentrations were ~2–5 mg/L (Figure 1). The risk of colistin-associated nephrotoxicity increases as the concentration exceeds ~2 mg/L [10, 11, 38–40]. A 32% decline in kidney function was indeed observed in the current patient. The decrease in creatinine clearance corresponded to the "risk" category (≥25% decline) of the RIFLE classification scheme for acute renal failure [41]. In an earlier study, a reduction in creatinine clearance of at least 25% was observed in 60% of critically ill patients with baseline creatinine clearance <80 mL/min/1.73 m^2 who had plasma colistin average steady-state concentrations in the range of 1.88–9.79 mg/L, but the majority of those patients experienced reductions in creatinine clearance of ≥50% or ≥75%, corresponding to RIFLE categories of "injury" or "failure" [39].

Several factors have been reported to increase the risk of colistin-associated acute kidney injury, including the magnitude of the daily dose and the resulting plasma colistin concentration, the presence of comorbid conditions, baseline creatinine clearance >80 mL/min/1.73 m^2, and concomitant use of other potentially nephrotoxic drugs [39, 42, 43]. The patient described here had a generally favorable profile in regard to such factors. She had no significant comorbidities, and her baseline Cockcroft-Gault creatinine clearance was 60 mL/min; the only other potentially nephrotoxic agent she received during the treatment period was intravenous contrast medium on day 10, well before the reduction in creatinine clearance observed on day 49 of admission.

Although the reduction in creatinine clearance was relatively small in the current case, it was considered important to modify the dosage regimen because of the low therapeutic index of colistin in relation to nephrotoxicity. Intravenous colistin was continued with the aid of TDM, which informed a reduction in the daily dose of colistin (Figure 1); this approach is in accordance with consensus recommendations to decrease the daily dose to the appropriate renally adjusted dose for a plasma colistin concentration of 2 mg/L [11]. The TDM-guided reduction in daily dose likely contributed to the ability to continue therapy with colistin over a 12-week course.

This case demonstrates the successful treatment of a limb-threatening infection with colistin and fosfomycin combination therapy together with surgical debridement. The case exemplifies the advantages of real-time antibiotic TDM for dose adjustment to maximize the probability of a favorable response and for mitigation of side effects. Although the patient did develop transient worsening in renal function during treatment, we were able to use TDM to guide dose adjustment and avoid possible permanent renal injury. While there are a number of promising new antimicrobials available for treatment of MDR/XDR *Pseudomonas aeruginosa* infection, these remain difficult to access in many countries across the world. Hence furthering our understanding of older drugs for treatment of these infections, such as fosfomycin and colistin, is critical.

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