Compassionate use of cefiderocol as adjunctive treatment of native aortic valve endocarditis due to XDR-Pseudomonas aeruginosa.

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Abstract

Serious infections such as endocarditis due to XDR-Gram-negative bacteria are an increasing challenge. This article presents successful adjunctive use of cefiderocol for a patient with persistently bacteremic healthcare-associated native aortic valve endocarditis due to an ESBL-positive *P. aeruginosa* susceptible in vitro only to colistin, following failure of conventional therapeutic options.

Keywords: Cefiderocol, Endocarditis, Pseudomonas Aeruginosa, Drug Resistance, Microbial

Cefiderocol is a novel parenteral siderophore cephalosporin currently being developed to treat serious infections including those due to carbapenem-resistant Gram-negative strains [1-3]. Cefiderocol has a unique mechanism of cell entry via bacterial iron transport channels, allowing it to enter Gram-negative bacteria efficiently even when accumulation of other agents is reduced due to porin channel loss and increased expression of efflux pumps. Cefiderocol has good stability to all classes of β-lactamases including serine- or metallo- carbapenemases that hydrolyze most or all other β-lactam antibiotics. This combination of properties allows potent antibacterial activity against a wide variety of Enterobacteriaceae and non-fermenting Gram-negative bacteria including *Pseudomonas aeruginosa*, *Acinetobacter baumannii,* and *Stenotrophomonas maltophilia*, even when these have potent combination of β-lactamases. Activity is poor against Gram-positive bacteria and anaerobic bacteria [1, 3].

Cefiderocol has been assessed in early-phase clinical trials for safety, tolerability, and pharmacodynamic behaviour [4, 5]. Cefiderocol was shown to be safe and effective for the treatment of complicated urinary-tract infection in a recently completed phase 2 study (APEKS-cUTI study) involving 452 randomized patients [6], and is now being evaluated in phase 3 studies (CREDIBLE-CR and APEKS-NP). Shionogi, the developers of cefiderocol, will consider unsolicited requests for compassionate use, and were approached to assist with treatment in the following case.

A 78-year-old woman was admitted from an intensive care unit in Kuwait to London Bridge Hospital on October 30th 2017 for specialist urological and respiratory management. She had been in hospital in Kuwait for 3 months following complications of hydronephrosis secondary to a spontaneous ureteric hematoma. She had a past medical history of aortic stenosis, ischaemic heart disease, cerebral infarction, and was in remission from breast cancer.

On arrival in London she was ventilated and received intermittent hemofiltration without hemodynamic support or antimicrobials. Admission blood cultures grew “extremely-drug resistant”(XDR)-*Pseudomonas aeruginosa* susceptible to

gentamicin, amikacin and colistin (MIC <3 mg/L), but resistant to all β-lactams and quinolones. There was no in vitro synergy between antipseudomonal agents and fosfomycin or rifampicin. The isolate lacked carbapenemase genes, and resistance to these agents was inferred to reflect loss of porin (OprD); a bla_{VEB} gene was found by PCR and was considered to account for resistance to penicillins and cephalosporins, including ceftazidime/avibactam and ceftolozane/tazobactam. The patient also had rectal colonisation with OXA-48 *Klebsiella pneumoniae* and OXA-23/OXA-51 *Acinetobacter baumannii*. She was commenced empirically on colistin (9MU loading dose followed by 3MU tds, subsequently changed to 4.5MU bd) together with intermittent gentamicin based on serum levels. A transthoracic echocardiogram showed a thickened aortic valve but no obvious regurgitation or vegetation. Representative clinical and microbiological features from her admission are presented in Figure 1.

She became clinically septic following insertion of percutaneous nephrostomies and started high-flow continuous veno-venous hemofiltration (estimated creatinine clearance 40-50mls/minute). Blood cultures again grew *P. aeruginosa* on days 3, 7 and 10. Gentamicin was stopped after the 3rd dose on Day 5 and replaced with meropenem 2g tds although MICs of the drug for all the *P. aeruginosa* isolates were >32mg/L. Sepsis resolved on Day 14, with a negative blood culture and the CRP falling from 212 to 41; this improvement prompted cessation of antibiotic therapy. Sepsis returned within a few days, however, and the CRP rose to 267 mg/L, with day 22 and 27 blood cultures again growing *P. aeruginosa*, leading to re-commencement of colistin and gentamicin. CRP continued to rise to 327 mg/L and a Day 27 *P. aeruginosa* isolate was reported as intermediately resistant to gentamicin, so gentamicin was again switched to meropenem. A second transthoracic ECHO showed possible vegetation on a tricuspid aortic valve with mild to moderate regurgitation.

Blood cultures were negative on Days 38, 49 and 52 and the patient initially improved clinically whilst undergoing assessment for aortic-valve surgery. However, during that time there was a significant neurological deterioration with a CT scan showing multifocal infarcts consistent with embolization and blood cultures again became positive (Days 56, 62 and 68). A decision was made to source additional active antibiotics to control bacteremia prior to valve surgery.

Accordingly a formal request was made to Shionogi on Day 73 for compassionate use of cefiderocol. The request was agreed and the drug obtained after appropriate governance approvals. Disk diffusion testing performed on Day 3 and Day 68 isolates gave zones of 17.4 and 21.3 mm respectively, against a prospective 18 mm breakpoint for a 30-μg disk. Cefiderocol was administered from Day 83 whilst continuing meropenem and colistin, and aortic valve replacement was performed on Day 85. Intensivists decided on a cefiderocol dose of 2g administered over 3 hours three times a day for the first two days then 2g twice daily, based on a combination of renal function, septic state, complexity of the infection and laboratory susceptibility testing. Blood culture taken before first cefiderocol dose remained positive, but a blood culture taken after the 6th dose, on the day before surgery, was negative after 5 days culture. The valve appeared heavily infected and disrupted at surgery and was positive for *P. aeruginosa* by PCR; nevertheless no Gram-negative bacteria were seen on microscopy and no growth was obtained including on enrichment culture. Meropenem was stopped a week after surgery but the cefiderocol/colistin combination was continued for a further 3 weeks. The neutrophil count fell during the last 4 days of antibiotic treatment to a low of 0.2 10^9/L on the planned last day of antibiotics, then returned to the normal range within a few days after stopping antibiotics. Neutropenia was reported in the Serious Adverse Event report form, with either colistin or cefiderocol being considered the most likely potential causes. Multiple blood cultures after surgery and after stopping antibiotics were negative up to Day 275 whilst the patient receive convalescent care with slow neurological recovery leading up to transfer back to Kuwait.

Discussion

Infective endocarditis due to *P. aeruginosa* is rare, except among intravenous drug users, accounting for <0.5% of all endocarditis cases [7]. A recent literature review of 27 cases over 20 years reported 75% as healthcare associated, of which half required surgery and a third relapsed after apparently adequate treatment [8] *P. aeruginosa* endocarditis is usually treated with combination therapy, such as meropenem or ceftazidime plus an aminoglycoside [7], but these regimens are compromised against XDR strains, as here. Colistin is usually used as backbone therapy for XDR-GNB infections, often with meropenem, but in this case a combination of these agents achieved only temporary blood culture sterility, with no other identified available options. Antibiotic dosing was at the high end of the recommended range and a trough colistin serum level was measured at 6.3mg /ml (target 2-4mg /ml) 2 weeks prior to surgery, so it

was considered that adequate doses were used.

The cause of the endocarditis was not identified but was probably present prior to transfer from Kuwait. *P. aeruginosa* was not grown from any other cultures, including samples from the urinary tract. There were no predisposing factors such as a prosthetic valve or the presence of pacing wires, as reported in other studies [9]. Although *P. aeruginosa* endocarditis can be treated with antibiotics alone, the failure to achieve sterility in this case combined with evolving valvular destruction meant surgery was essential for any prospect of cure; however this was delayed in part due to embolization and was considered unlikely to succeed with persistently positive blood cultures on antibiotic therapy. The addition of cefiderocol led to blood culture sterility within 2 days, allowing potentially curative surgery to proceed. It is not possible to ascribe the relative contribution of surgery versus cefiderocol, but the rapid blood and valve sterility after starting cefiderocol suggest that this cephalosporin made a significant contribution. This report adds to the evidence from ongoing randomized studies that cefiderocol holds promise of being a useful new agent for treating XDR-GNB, including where no other options exist.

From a microbiological perspective, it is striking that for *P. aeruginosa*, where there is easy mutational resistance to carbapenems, an ESBL gave the broadest spectrum of resistance. Also striking, and typical of VEB ESBLs in *P. aeruginosa* is the fact that resistance included ceftolozane/tazobactam and ceftazidime/avibactam [10]. Although VEB enzymes are uncommon in the UK (and US) numbers of producer are increasing, often via imports from the Middle East and Eastern Europe [10], where these enzymes appear to be more prevalent.

Conclusion

The emergence of multi- and extremely-resistant Gram-negative pathogens presents a global health challenge and underscores the urgent need for new antibiotics [11, 12]. Cefiderocol is being developed to address this need, targeting Enterobacteriaceae, *P. aeruginosa*, *Acinetobacter baumannii* and *Stenotrophomonas maltophilia* [1, 2].

This case report documents a patient with XDR-*P. aeruginosa,* who was successfully managed with the addition of cefiderocol to control bacteremia and to allow aortic valve replacement. Compassionate use of cefiderocol was opted for this patient because there were no other available therapeutic options and because conventional agents were failing to control persistent bacteraemia. An episode of transient acute neutropenia occurred during the last few days of treatment with both cefiderocol and colistin, highlighting the importance of continued pharmacovigilance during extended courses of antibiotics.

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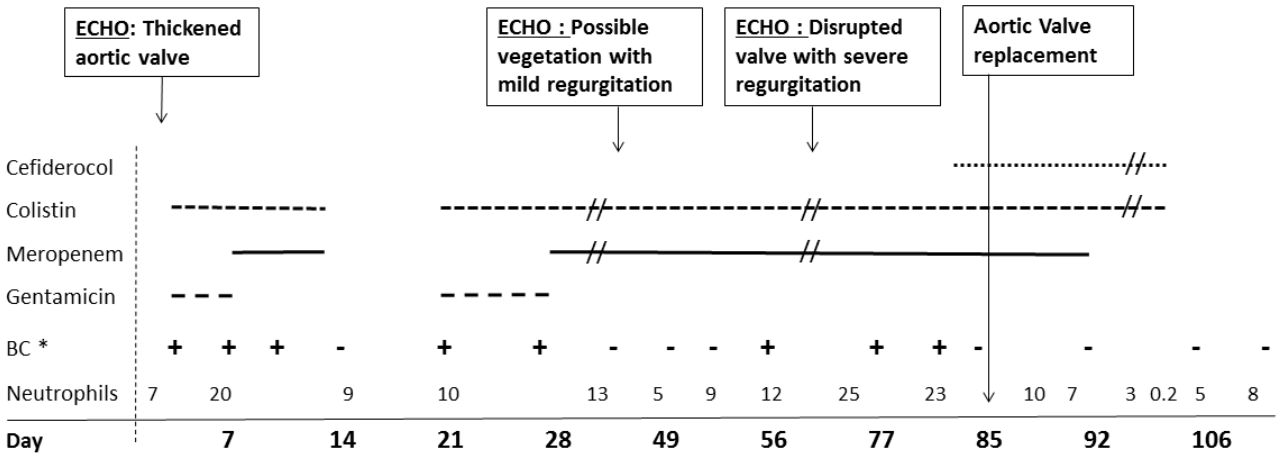
Figure legends

Figure 1 : Clinical, microbiological and antimicrobial treatment course

Figure 1



BC* = Blood culture positive (+) *P. aeruginosa* or negative (-) ECHO = transthoracic echocardiogram