In vivo emergence of resistance to cefiderocol in an XDR Pseudomonas aeruginosa and an MDR Citrobacter koseri after prolonged therapy: a case report.

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Case report

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Abstract

The non-fermenters, e.g. Pseudomonas aeruginosa, and the extended spectrum β-lactamases or carbapenemases producing enterobacteriaceae represent a serious threat for patients admitted in Intensive Care Units (ICUs). News antibiotics have been developed to treat multidrug resistant bacteria. However, treatment emerging resistance has been shown for many of these newest antibiotics. Cefiderocol, a siderophore-antibiotic, has been developed to overcome most of the resistance mechanisms and shows great efficacy against most multi-drug resistant and extensively drug resistant Gram-negative bacteria, including the non-fermenters. We report the case of a patient abundantly treated with antibiotics. He received 158 days of antibiotherapy on 230 hospitalization days, including a six-week course of cefiderocol, in 14 different treatment lines. The patient developed a Pseudomonas aeruginosa (MIC: 8 µg/ml, GES type ESBL) and a Citrobacter koseri (MIC: 16 µg/ml, CTX-M group 9 type class A β-lactamase and a class D OXA-1 oxacillinase) resistant to cefiderocol. This antibiotic should be used with caution to preserve its efficacy, within a strict antimicrobial stewardship program.

Introduction

Multidrug resistant (MDR) and extensively drug resistant (XDR) bacteria, the non-fermenters *P. aeruginosa*, *S. maltophilia* and *A. baumanii* as well as Extended Spectrum β-lactamase producing (ESBL) and carbapenemases producing enterobacteriaceae (CPE) are an increasing threat worldwide (1).

Several new antibiotics usually based on the combination of an existing cephalosporin or carbapenem with a new β-lactamase inhibitor have been developed with various efficacy (2). These new antibiotics typically lack efficacy against class B metallo β-lactamase (3).

Cefiderocol is a new siderophore-cephalosporin showing good activity against MDR and XDR bacteria (4). Cefiderocol was shown to rarely stimulate inducible AmpC (5) which along acquisition of ESBLs is a major mechanism of resistance. It is resistant to the hydrolysis produced by ESBL, serine- and metallo-carbapenemases as well as the inducible ampC β-lactamase (6).

Cefiderocol is labelled for short course in urinary tract infection (7). It is evaluated in healthcare associated pneumonia (8). The CREDIBLE study has been designed to enroll patients with carbapenem-resistant Gram-negative infection whatever the site (9).

Cefiderocol has been used for a longer period in some compassionate treatments like osteomyelitis (14 weeks), intra-abdominal (28 days) and endovascular infections (30 days) due to XDR germs. All three patients recovered and no emergence of resistance to cefiderocol was reported (10, 11, 12).

We report the case of a patient receiving cefiderocol as compassionate use for a pancreatic abscess due to XDR *P. aeruginosa*. While the isolate was initially sensitive to cefiderocol, *P. aeruginosa* as well as another Gram-negative enterobacteriaceae became resistant to cefiderocol.

Case Report

A 63-year-old man presented at the ICU for septic shock originating from a diabetic foot related ulcer. His medical history shows obesity, uncontrolled type 2 diabetes, cardiac ischemic disease, disseminated gout arthritis. Stating allergy to penicillin, he received empiric antibiotic therapy with amikacin, aztreonam and clindamycin. With the recognition of *S. aureus* bacteremia, treatment was altered to vancomycin and later oxacillin. Antimicrobial susceptibility testing (AST) included mainly Minimal Inhibitory Concentration (MIC) determination and in rare cases disc diffusion method and AST always follows EUCAST guidelines and breakpoints. An ESBL *Klebsiella pneumoniae,* an oxacillin-sensitive *S. aureus* (MSSA) and a multi-sensitive *Pseudomonas aeruginosa* were recovered from the wound. At day 7, he underwent surgical debridement for a lower limb gangrene and received ceftazidime. On day 10, he developed a central line-associated blood stream infection (CLABSI) due to an ESBL *C. freundii* associated with a MSSA and received meropenem. On day 24, he developed a CLABSI due to an ESBL *K. pneumoniae* (ceftazidime-avibactam susceptible (S), colistin resistant (R), cefiderocol susceptible) and was treated with ceftazidime-avibactam. At day 23, oxacillin was switched to cotrimoxazole to complete a 6-week therapy for lower limb osteomyelitis. On day 26, an XDR *P. aeruginosa* grew from his sputum. This *P. aeruginosa* is a chronic colonizer in our ICUs and expresses a class B VIM metallo β-lactamase, retaining sensitivity only to colistin. Ten days later, he developed a new bacteremia due to an ESBL *K. pneumoniae* (meropenem Intermediate (i), cefiderocol S), recovered from multiple sites including sputum and urines. At the same time, he developed a bacteremia *with B. thetaiotaomicron*, originating from a complicated ischemic pancreatitis, treated by a new cure of meropenem. On day 45, blood cultures grew *K. pneumoniae*, meropenem I, cefiderocol S. High doses meropenem and amikacin were started. Abdominal CT scan revealed a para-duodenal pancreatic collection. On day 51, endoscopic retrograde cholangiopancreatography was performed, and pancreatic pus revealed the XDR *Pseudomonas aeruginosa*, susceptible to colistin and cefiderocol. On day 51, colistin plus meropenem were started and cefiderocol was requested on a compassionate basis. On day 54, treatment was switched to cefiderocol 2 g Q8h (6 weeks) infused over 3 hours plus metronidazole 500 mg TID (2 weeks). Clinical and biological evolution were favorable and cefiderocol was stopped after 6 weeks. Cefiderocol was well tolerated and there was no treatment-related side effect.

Patient was transferred to rehabilitation unit where he developed an ischial eschar. On day 128, from a swab of the eschar grew an XDR *P. aeruginosa* with phenotypic resistance to cefiderocol. In agreement with the patient, his wife and a medical committee, further ICU admission was banned to prevent the spread of this *P. aeruginosa* strain in our wards. Strict prevention control measures were re-enforced.

The strain was sent to the Belgian National Reference Laboratory for Resistant Strains and to the International Health Management Associates Inc in US (IHMA, Reference lab for Shionogi). Cefiderocol resistance was confirmed (MIC: 8 µg/ml) and a GES β-lactamase was identified. Additionally, our patient developed a right ankle arthritis due to an ESBL *Citrobacter koseri*. The *C. koseri* was also confirmed cefiderocol resistant (MIC: 16 µg/ml). A CTX-M group 9 type class A β-lactamase and a class D OXA-1

oxacillinase were identified. *C. koseri* retained susceptibility to ciprofloxacin and the patient was treated with ciprofloxacin for 6 weeks.

On day 224, the patient developed a hospital-associated pneumonia. He received ceftriaxone for two days. XDR *P. aeruginosa* was identified, and the patient was put on colistin plus meropenem. He died after 230 days of hospitalization. The patient spent 158 days on antibiotics (among which 42 days on cefiderocol) during his 230 days hospital stay and received 14 different lines (combination) of antibiotics.

Discussion

We describe the emergence of resistance to cefiderocol in *P. aeruginosa* and C*. koseri*.

Treatment emerging resistance is not limited to Gram-negative non-fermenters, but also concerns many enterobacteriaceae like *K. pneumoniae* (13). It also affects Gram-positive bacteria (14). All class of antibiotics are concerned including the newest antibiotics (ceftazidime-avibactam, ceftolozane-tazobactam, ceftaroline, dalbavancin, etc.) but also colistin and tigecycline (15, 16)

Gram-negative bacteria often express multiple resistance mechanisms including production of various β-lactamases.

aeruginosa, a bug used to survive in hostile environments, is particularly able to limit entry and increase efflux of toxic substances including antibiotics (17).

Impermeability of porins, efflux pumps, antibiotic-inactivating enzymes, modification of antibiotics' targets, survival as a biofilm and formation of persistent cells, individually or in conjunction, are the mechanisms allowing *P. aeruginosa* to acquire antibiotic resistance (18).

Iron is essential for bacterial growth. While also relying on siderophores for iron intake, *P. aeruginosa* developed various ways of absorbing iron (19). Whether this might be an additional resistance pattern to siderophore antibiotics is unknown.

Prevention of treatment emerging resistance may rely on improved PK/PD with optimal antibiotic dosing (20), combination therapy (21), addressing bacteria in biofilms (22), targeting other mechanisms like efflux pumps (23) and modification of *in vivo* conditions like iron availability (24). Prevention and control of these MDR strains is also possible using adequate antimicrobial stewardship program and hospital hygiene guidelines (25). We could not compare the initial strains and those resistant to cefiderocol, which however had an identical antibiotic resistance phenotype. The search of resistance mechanism has been limited to production of β-lactamase while other mechanisms like porin, efflux pump (26), or target protein alterations could not be investigated.

Conclusions

We have described a case of treatment emerging resistance to cefiderocol. It highlights the fact that even the newest drugs can be failed by treatment emerging resistance. Strict antimicrobial stewardship programs and adherence to control and prevention of infections guidelines are the only effective protective barriers to ensure long term availability of antimicrobials against extensively resistant germs. Cefiderocol should be used with caution to preserve its potential. In depth understanding of mechanisms of resistance to siderophore-antibiotics is warranted.

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Declarations

Conflict of Interest

None

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Ethical aspects

The wife of the patient signed a written informed consent to permit the use of anonymized patient’s data to report in the scientific literature.

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