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Activity of the novel siderophore cephalosporin cefiderocol against multidrug-resistant Gram-negative pathogens

Laurent Poirel, Jan Dobias, Valérie Dénervaud, and Patrice Nordmann

Medical and Molecular Microbiology, Dept of Medicine, INSERM European Laboratory, Faculty of Science, University of Fribourg, Switzerland, National reference Centre for Emerging Antibiotic Resistance, Switzerland

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Introduction

- Due to the increasing threat of multidrug-resistant (MDR) and pandrug-resistant (PDR) bacteria, there is a need for novel antimicrobial molecules
- Cefiderocol is a novel parenteral siderophore cephalosporin, also known as S-649266
- It binds free iron and is then actively transported into bacterial cells across the outer membrane by the way of the iron-transport system. Then, the iron dissociates and the cephalosporin binds to penicillin binding proteins for disrupting the cell wall synthesis
- Cefiderocol exhibits potent *in vitro* and *in vivo* activity against all species of Gram-negative bacteria, including carbapenem-resistant strains of Enterobacteriaceae, *Pseudomonas aeruginosa*, *Acinetobacter baumannii* and even *Stenotrophomonas maltophilia*

Objective of the study

- Our aim was to evaluate the antimicrobial activity of cefiderocol, and other Gram-negative antibiotics, against a panel of 753 MDR clinical isolates with characterized antibiotic resistance mechanisms

Materials

- A total of 753 clinical MDR isolates were studied, representative of the most widespread and broad-spectrum mechanisms of resistance currently observed worldwide. They were from various origin, mostly from urines, broncho-alveolar specimens, blood, pus and stools

Multidrug-resistant isolates tested

- *E. coli* (n=164); OXA-48-like (43), VIM and IMP (22), NDM (45), KPC (11), CTX-M (25), MCR-1 (15), non-MCR-1 colistin-R (3)
- *K. pneumoniae* (n=298) KPC (101), OXA-48-like (94, including 5 ColR strains), NDM (23, including 5 ColR strains), VIM and IMP (20), CTX-M (25), non-MCR-1 colistine-R (35)
- *Enterobacter* spp. (n=159) OXA-48-like (26), NDM (10), VIM and IMP (19), KPC (14), CTX-M (49), VEB (7), SHV (14), AmpC (9), non-MCR-1 colistine-R (11)
- *P. aeruginosa* (n=45) PER (6), SHV and GES (9), IMP and KPC (20), VIM and SPM and GIM (10)
- *A. baumannii* (n=87) OXA-23/40/58/72 (85), NDM and IMP (2)

Methods

- Minimum inhibitory concentrations (MICs) were determined following reference of CLSI broth microdilution guidelines.

- Frozen 96-wells broth microdilution panels with pre-loaded antibiotic-growth medium were supplied by International Health Management Associates, Inc. (IL, USA).

Antibiotic concentration ranges tested

Cefiderocol (S-649266, CFDL) Ceftazidime (CAZ), ceftazidime-avibactam (CZA), ceftolozane-tazobactam (C/T), Meropenem (MEM)	0.03-64 µg/ml
Aztreonam (ATM)	0.5-32 µg/ml
Cefepime (FEP)	0.5-16 µg/ml
Colistin (CST)	0.5-8 µg/ml
Amikacin (AMK)	6-64 µg/ml
Ciprofloxacin (CIP), Tigecycline (TGC)	0.25-4 µg/ml

Results (1)

- The MIC_{90} of cefiderocol (MIC that inhibits 90% of the isolates) reached 2 µg/ml while those of comparative drugs were, in general, higher: >64 µg/ml for C/T, MEM, CAZ, CZA and AMK; >32 µg/ml for ATM; >16 µg/ml for FEP; 8µg/ml for CST. The exception is the tigecycline with the same MIC90 of 2 µg/ml

- MIC_{90} and MIC_{50} of cefiderocol for Enterobacteriaceae producing KPC carbapenemase were ≤2µg/ml and ≤1µg/ml, respectively. The only competitive comparators were CZA (MIC90/50: 4/1), CST (≥8/≤0.5) and TGC (≤1/≤0.5)

Results (2)

- OXA-48-like producing Enterobacteriaceae were susceptible to larger number of antibiotics than the KPC producers were. Again, cefiderocol is one of the antibiotics with the lowest $MIC_{90}/_{50}$ values at 2 and 0.25 μg/ml respectively

- For enterobacterial isolates producing NDM, VIM or IMP carbapenemases, the only antibiotics that have strong activity were cefiderocol (4/1) (MIC90/50 in μg/ml) , colistin (≤1/≤0.5 μg/ml) and tigecycline (≤1/≤0.25 μg/ml)

- Carbapenemase-producing *P. aeruginosa* were susceptible only to CFDL (2/0.5 μg/ml) and CST (1/ ≤0.5 μg/ml). The same resistance trend was observed for carbapenemase-producing *A. baumannii* (CFDC [4/0.12] and CST [1/0.5]), except that they were also susceptible to TGC (2/1)

Results (3)

- Among the 753 isolates tested, only 20 strains had a MIC value for cefiderocol ≥8 µg/ml

- It included a low number of NDM producers in Enterobactericaceae (n=11/79), and to a lesser extent of OXA-23-producing *A. baumannii* (n=4)

Conclusion

- Cefiderocol was more active (MIC_{90} 2-4 µg/ml) than the comparators (MIC_{90} >4->64µg/ml) (cephalosporins, carbapenem, fluoroquinolone and monobactam) against all the tested isolates
- The only antibiotics with equal activity were colistin and tigecycline, with the limitation that TGC was not active against *P. aeruginosa*
- It shall be underlined that cefiderocol displays also much favorable pharmakokinetic parameters than colistin and tigecycline