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Activity of the novel siderophore cephalosporin cefiderocol (S-649266) against Gram-negative pathogens

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Background: The novel siderophore cephalosporin cefiderocol (S-649266) with potent activity against Gram-negative pathogens was recently developed (Shionogi & Co., Ltd). The purpose of this study was to evaluate the activity of this new molecule and comparators against a collection of previously characterized bacterial isolates using broth microdilution (BMD) panels.

Material/methods: A total of 753 clinical MDR or XDR Gram-negative isolates collected from 20 hospitals worldwide were tested against cefiderocol and antibiotic comparators for their susceptibility. Cefiderocol was tested in iron-depleted cation-adjusted Mueller Hinton broth (ID-CAMHB), whereas comparators (ceftolozane-tazobactam [C/T], meropenem [MEM], ceftazidime [CAZ], ceftazidime-avibactam [CZA], colistin [CST], aztreonam [ATM], amikacin [AMK], ciprofloxacin [CIP], cefepime [FEP] and tigecycline [TGC]) were tested in cation-adjusted Mueller Hinton broth (CAMHB) according to current CLSI guidelines for BMD testing.

The clinical isolate collection included *Escherichia coli* (n=164), *Klebsiella pneumoniae* (n=298), *Enterobacter* sp. (n=159), *Pseudomonas aeruginosa* (n=45)

and *Acinetobacter baumannii* (n=87). Resistance mechanisms included carbapenemases of the OXA-48 type (n=162), VIM (n=36), IMP (n=44), NDM (n=79), KPC (n=132), SPM (n=5) and GIM (n=2), but also expanded-spectrum ß-lactamases (ESBL) of the CTX-M (n=99), VEB (n=7), AmpC (n=9), PER (n=6), GES (n=3), and narrow-spectrum ß-lactamases of the SHV type (n=20). In addition, a series of colistin-resistant enterobacterial isolates were tested, including MCR-1 producers (n=16) and non-producers (n=59).

Results: The MIC90 of cefiderocol was 2 µg/ml, while those of comparative drugs were >64 for C/T, MEM, CAZ, CZA, and AMK, >32 for ATM, >16 for FEP, 8 for CST, and 2 for TGC. MIC50 of cefiderocol was at 0.5 µg/ml, while those of other drugs were >64 for ATM, 64 for C/T, >32 for ATM, >16 for FEP, 8 for MEM and AMK, >4 for CIP, 1 for CZA, 0.5 for TGC, and <0.5 for CST. Among the 753 isolates tested, only 20 exhibited an MIC of cefiderocol ≥8 µg/ml, among which a high proportion of NDM producers was found (n=11), and to a lesser extend of OXA-23-producing *A. baumannii* (n=4). Compared to other drugs, the activity of cefiderocol was greater, with the exceptions of colistin and tigecycline.

Conclusions: Cefiderocol displayed a potent activity against the selected resistant clinical Gram-negative isolates collection, including carbapenemases and ESBLs producers, and colistin-resistant isolates. Noteworthy, the MIC90 of cefiderocol was higher than that of the recently launched ceftazidime/avibactam combo, while MIC50s were in the same range. The activity of cefiderocol was greater compared to other drugs, except for colistin and tigecycline. However, the increasing rate of colistin resistance currently observed significantly compromises the use of this drug as last resort, and cefiderocol may potentially represent an interesting alternative.