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Activity of cefiderocol (S-649266) against carbapenem-resistant Gram-negative bacteria collected from inpatients in Greek hospitals

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Background: Cefiderocol (S-649266), a siderophore cephalosporin, utilizes a novel mechanism of entry in to the periplasmic space of Gram-negative bacteria and is more stable than other β-lactams to extended-spectrum β-lactamases and carbapenemases.

Material/methods: A collection of carbapenem resistant Gram-negative bacteria isolated (2015-2016) from clinical specimens in 18 Greek hospitals was tested for susceptibility to cefiderocol, meropenem, ceftazidime, cefepime, ceftazidime-avibactam, ceftolozane-tazobactam, aztreonam, amikacin, ciprofloxacin, colistin and tigecycline. Broth microdilution plates were used to determine minimum inhibitory concentration (MIC) values. Cefiderocol was tested in iron-depleted cation-adjusted Mueller Hinton broth, whereas comparators were tested in cation-adjusted Mueller Hinton broth according to current CLSI guidelines for broth microdilution testing and previously published methodology.

Results: 471 carbapenem resistant Gram-negative bacteria were tested; 189 non-fermentative Gram-negative bacteria (107 *Acinetobacter baumannii*, 82 *Pseudomonas aeruginosa*) and 282 Enterobacteriaceae (of which 244 *Klebsiella pneumoniae*, 14 *Enterobacter cloacae*, 11 *Providencia stuartii*). For both *A. baumannii* and *P. aeruginosa* the MIC_{90} of cefiderocol was 0.5 mg/L. For *K. pneumoniae*, *Enterobacter cloacae* and *Providencia stuartii* the MIC_{90} of cefiderocol was 1 mg/L, 1 mg/L, and 0.5 mg/L, respectively. Tigecycline was the second most active antibiotic, followed by colistin. The cumulative percentage of MIC values of *K. pneumoniae*, *A. baumannii*, and *P. aeruginosa* isolates against the tested antibiotics is shown in Figure 1. Resistance to colistin was observed in 154 isolates (91 *K. pneumoniae*, 45 *A. baumannii*, 11 *P. stuartii*, 4 *P. mirabilis*, 1 *P. aeruginosa* and 2 *E. coli*). Cefiderocol MIC_{50} (0.06 mg/L) and MIC_{90} (0.5 mg/L) were not different between colistin resistant

and colistin susceptible *A. baumannii* isolates. Slightly higher MIC_{50} values were observed for colistin resistant *K. pneumoniae* strains (1 versus 0.5 mg/L for all strains); the MIC_{90} was the same (1 mg/L). Six *K. pneumoniae* isolates were resistant or intermediately resistant to colistin, amikacin, and tigecycline. The MIC range of cefiderocol for these isolates was 0.25 to 1 mg/L. Thirteen isolates produced KPC, 12 VIM and 3 strains produced both. Cefiderocol's MIC_{90} for both KPC and VIM producers was 1 mg/L.

Conclusions: Cefiderocol exhibited greater antimicrobial activity *in vitro* against carbapenem resistant Gram-negative bacteria than comparator antibiotics.

Figure 1. Cumulative percentage of *K. pneumoniae*, *A. baumannii*, and *P. aeruginosa* tested isolates against the MIC values of the tested antibiotics.