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 into 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 MIC90 of cefiderocol was 0.5 mg/L. For K. pneumoniae, Enterobacter cloacae and Providencia stuartii the MIC90 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 MIC50 (0.06 mg/L) and MIC90 (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.