

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

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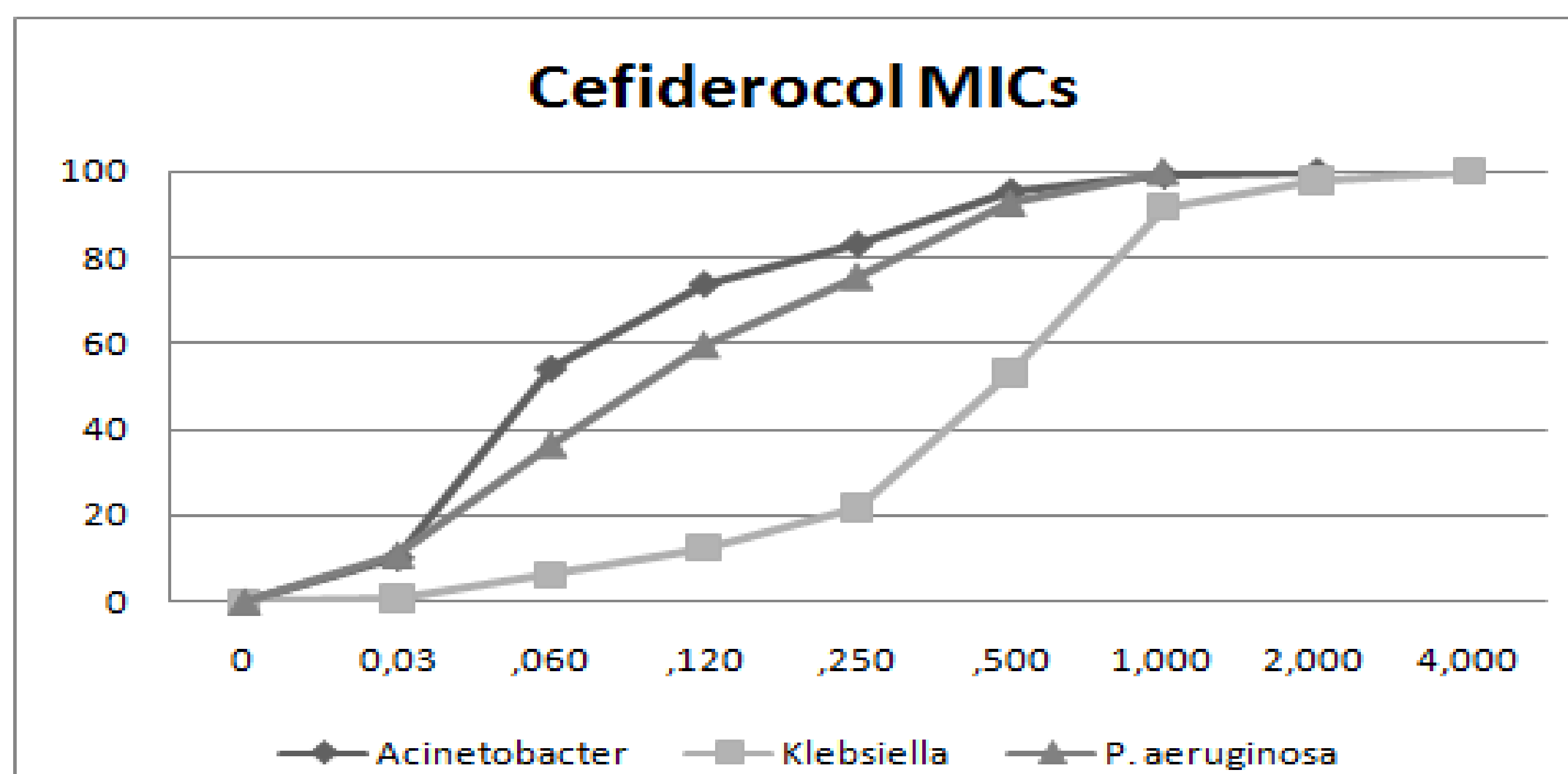
**Background:** Cefiderocol (S-649266), a siderophore cephalosporin, utilizes a novel mechanism of entry in to the periplasmic space of Gram-negative bacteria (GNB) and is broadly stable to ESBLs and carbapenemases [1].

**Material/methods:** A collection (2015-2016) of non-duplicate carbapenem resistant (CR) GNB isolated from clinical specimens in 18 Greek hospitals was tested for susceptibility to cefiderocol. Frozen broth microdilution plates were used to determine minimum inhibitory concentration (MIC) values for cefiderocol and comparators (meropenem, ceftazidime, cefepime, ceftazidime-avibactam, ceftolozane-tazobactam, aztreonam, amikacin, ciprofloxacin, colistin and tigecycline).

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 [2]. The breakpoints for all species were defined according to the CLSI guidelines.

**Results:** 471 CR GNB were tested; 189 non-fermentative GNB (107 *Acinetobacter baumannii*, 82 *Pseudomonas aeruginosa*) and 282 Enterobacteriaceae (of which 244 *Klebsiella pneumoniae*, 14 *Enterobacter cloacae*, 11 *Providencia stuartii*). For all 471 isolates tested regardless of species, cefiderocol had the lowest MIC values among the eleven antibiotics.

**Figure 1. Cumulative percentage of cefiderocol's MICs (mg/L) for *K. pneumoniae*, *A. baumannii*, and *P. aeruginosa*.**



For both *A. baumannii* and *P. aeruginosa* the MIC<sub>90</sub> of cefiderocol was 0.5 mg/L. For *K. pneumoniae*, *Enterobacter cloacae* and *Providencia stuartii* the MIC<sub>90</sub> of cefiderocol was 1 mg/L, 1 mg/L, and 0.5 mg/L, respectively. The cumulative percentage of MICs for *A. baumannii*, *P. aeruginosa* and *K. pneumoniae* is shown in Figure 1. The cumulative percentage of MICs for all studied antibiotics is shown in Figure 2.

The highest MIC value for cefiderocol was 4 mg/L, seen in 6 isolates (5 *K. pneumoniae* and 1 *E. cloacae*). These 6 isolates were all resistant to meropenem, ceftazidime, aztreonam, and cefepime, 5 were resistant to amikacin and ciprofloxacin (the susceptible strain was *E. cloacae*), 1 was resistant to colistin (*K. pneumoniae*) and all were susceptible to tigecycline. The MIC range of ceftolozane/tazobactam and ceftazidime/avibactam for these 6 isolates was 32 to >64 mg/L and 1 to >64 mg/L, respectively.

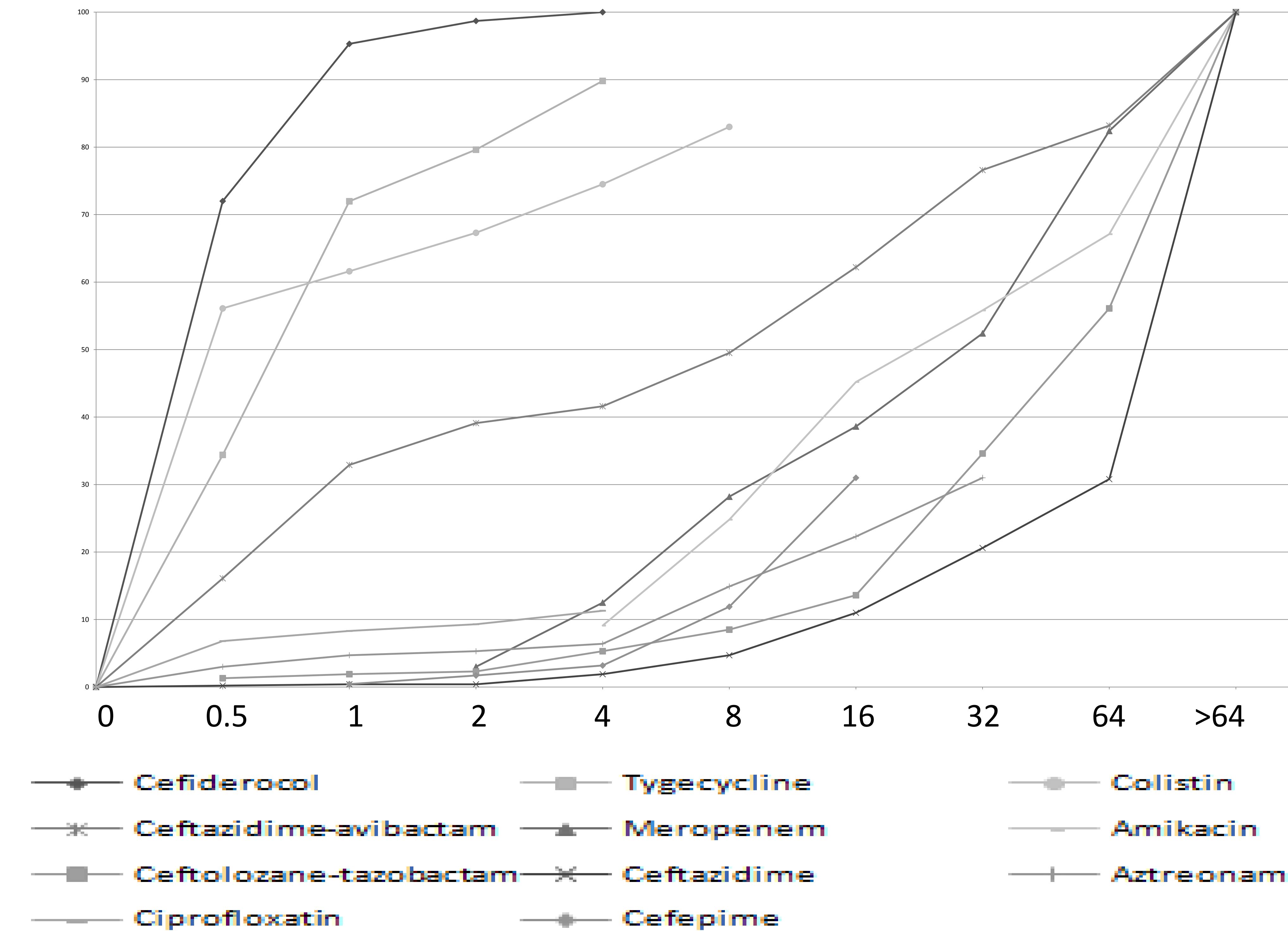
The MIC<sub>50</sub> and MIC<sub>90</sub> of isolates resistant or susceptible to colistin, tigecycline and amikacin, and for KPC and VIM producing isolates is shown in the Table. Six *K. pneumoniae* isolates were resistant or intermediately resistant to all colistin, amikacin, and tigecycline. The MIC range of cefiderocol for these isolates was 0.25 to 1 mg/L.

**Table. Comparison of S-649266 MIC (mg/L) values between antibiotic resistant and susceptible isolates.**

Species	MIC <sub>50</sub>	MIC <sub>90</sub>	MIC <sub>50</sub>	MIC <sub>90</sub>
	<b>Colistin resistant</b>		<b>Colistin susceptible</b>	
<i>A. baumannii</i>	0.06 (n=45)	0.5 (n=45)	0.06 (n=62)	0.5 (n=62)
<i>K. pneumoniae</i>	1 (n=91)	1 (n=91)	0.5 (n=153)	1 (n=153)
	<b>Tigecycline resistant/intermediate (n=24)</b>		<b>Tigecycline susceptible (n=217)</b>	
<i>K. pneumoniae</i>	0.5	1	0.5	1
	<b>Amikacin resistant/intermediate</b>		<b>Amikacin susceptible</b>	
<i>A. baumannii</i>	0.06 (n=100)	0.5 (n=100)	0.06 (n=7)	0.25 (n=7)
<i>K. pneumoniae</i>	1 (n=94)	2 (n=94)	0.5 (n=150)	1 (n=150)
<i>P. aeruginosa</i>	0.12 (n=49)	0.5 (n=49)	0.06 (n=33)	0.25 (n=33)
	<b>VIM producers (n=12)</b>		<b>KPC producers (n=13)</b>	
<i>K. pneumoniae</i>	1	1	0.5	1

Abbreviations: MIC minimum inhibitory concentration, KPC *Klebsiella pneumoniae* carbapenemase, VIM Verona integron metallo-β-lactamase

**Figure 2. Cumulative percentage of MICs for the studied antibiotics for all CR GNB.**



## Discussion:

Cefiderocol had the lowest MICs among the eleven antibiotics in the study against CR GNB and showed potent antimicrobial activity with MIC<sub>90</sub> values ≤1 mg/L for all groups of organisms. The MIC<sub>90</sub> values of cefiderocol were lower for non-fermenting Gram-negative bacteria than Enterobacteriaceae.

Cefiderocol could be considered as a promising candidate for the treatment of patients with infections due to CR GNB.

## References:

- Falagas ME, Mavroudis AD, Vardakas KZ. The antibiotic pipeline for multi-drug resistant gram negative bacteria: what can we expect? *Expert Rev Anti Infect Ther* 2016; **14**: 747-63.
- Clinical Laboratory Standards Institute. CLSI document M07-A10. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standards -- Tenth Edition. Tenth Edition ed. CLSI, Wayne, PA: CLSI, 2015.