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In Vitro Antibacterial Activity of Cefiderocol (S-649266) against Gram-negative Clinical Strains Collected in North America and Europe (SIDERO-WT-2014 study)

M. Hackel[1], M. Tsuji[2], R. Echols[3], D. Sahm[1]

[1]IHMA, Inc. Schaumburg, IL, US, [2]Shionogi & Co., Ltd., Osaka JP, [3]ID3C, LLC, Easton, CT, US

IHMA, Inc.
2122 Palmer Drive
Schaumburg, IL 60173 USA
Phone: +1.847.303.5003
Fax: +1.847.303.5601
www.ihmainc.com

Revised Abstract

Background: Cefiderocol, formerly S-649226, is a novel parenteral siderophore cephalosporin with potent activity against Gram-negative pathogens including carbapenem-resistant isolates and is currently in clinical development by Shionogi & Co., Ltd. This study evaluated the *in vitro* activity of cefiderocol and comparator agents against relevant clinical isolates collected in 2014-2015 in North America (NA) and Europe (EU). **Methods:** 9,205 clinical isolates collected in 2014-2015 in NA (4,239) and EU (4,966) comprising 23 species were tested. MICs were determined for cefiderocol, cefepime (FEP), ceftazidime-avibactam (CZA), ceftolozane-tazobactam (C/T), ciprofloxacin (CIP), colistin (CST), and meropenem (MEM) by CLSI broth microdilution and interpreted following CLSI 2016 guidelines, with the exception that cefiderocol was tested in iron-depleted media. Carbapenem-non-susceptible (CarbNS) isolates were defined as non-susceptible to meropenem using CLSI breakpoints. Quality control testing was performed on each day of testing. In this analysis, we present the results for a total of 8,765 Enterobacteriaceae, *A. baumannii* and *P. aeruginosa*. **Results:** The MIC_{90} values of the test compounds are shown in the table. The cefiderocol MIC_{90} ranged from 0.5 – 1 µg/mL for the species shown below, and 1 – 4 µg/mL for the CarbNS subsets. Greater than 99% of isolates had MIC values ≤4 µg/mL. In particular, the activity of cefiderocol was significantly potent compared to the other the test compounds against the CarbNS subsets.

		MIC_{90}						
Organism	**N**	Cefiderocol	FEP	CZA	C/T	CIP	CST	MEM
A. baumannii	1,148	1	>64	>64	>64	>8	4	>64
A. baumannii, CarbNS	768	1	>64	>64	>64	>8	>8	>64
Enterobacteriaceae	6,087	0.5	8	0.5	2	>8	>8	0.12
Enterobacteriaceae, CarbNS	169	4	>64	>64	>64	>8	>8	>64
P. aeruginosa	1,530	0.5	16	8	2	>8	2	8
P. aeruginosa, CarbNS	353	1	64	32	64	>8	1	64

Conclusions: Cefiderocol demonstrated good *in vitro* potency against *A. baumannii*, Enterobacteriaceae, and *P. aeruginosa*, including CarbNS isolates collected from Europe and North America. Overall, cefiderocol showed promising activity against this collection of recent clinical isolates.

Introduction

Cefiderocol, formerly S-649266, is a novel parenteral siderophore cephalosporin with potent activity against Gram-negative pathogens including carbapenem-resistant isolates and is currently in clinical development by Shionogi & Co., Ltd. This study evaluated the *in vitro* activity of cefiderocol and comparator agents against relevant clinical isolates collected in 2014-2015 in North America (NA) and Europe (EU).

Materials & Methods

9,205 clinical isolates comprising 23 species including 6,087 Enterobacteriaceae, 1,148 *A. baumannii* and 1,530 *P. aeruginosa*, were collected in 2014-2015 in NA (4,239) and EU (4,966) from 99 medical centers in 13 countries in Europe and North America as follows (sites): Canada (9), Czech Republic (3), France (5), Germany (6), Greece (4), Hungary (4), Italy (5), Russia (5), Spain (5), Sweden (2), Turkey (5), the United Kingdom (5), and the United States (41). Each site was requested to collect 100 isolates of a specific species distribution (15 *Escherichia coli*, 15 *Klebsiella pneumoniae*, 5 *Klebsiella* spp. other than pneumoniae, 10 *Enterobacter* spp., 5 *Citrobacter* spp., 10 *Serratia* spp., 15 *Pseudomonas aeruginosa*, 15 *Acinetobacter baumannii*, 5 *Burkholderia cepacia*, and 5 *Stenotrophomonas maltophilia*). All isolates were sent to a central laboratory, International Health Management Associates, Inc. (IHMA) in Schaumburg, Illinois where the isolates were further evaluated and stored. Organism identification was confirmed using MALDI-TOF mass spectroscopy. MICs were determined by broth microdilution and interpreted following CLSI guidelines [1, 2], with the exception that cefiderocol was tested in iron-depleted cation-adjusted Mueller Hinton broth. Percent susceptibility was calculated according to CLSI interpretive criteria where available [2], and the FDA interpretive criteria for ceftazidime-avibactam [3]. In the absence of any CLSI or FDA breakpoints for colistin tested against Enterobacteriaceae, the EUCAST susceptible breakpoint of ≤2 µg/mL was applied [4]. Carbapenem-non-susceptible (CarbNS) isolates were defined as non-susceptible to meropenem using CLSI breakpoints. Quality control testing was performed on each day of testing.

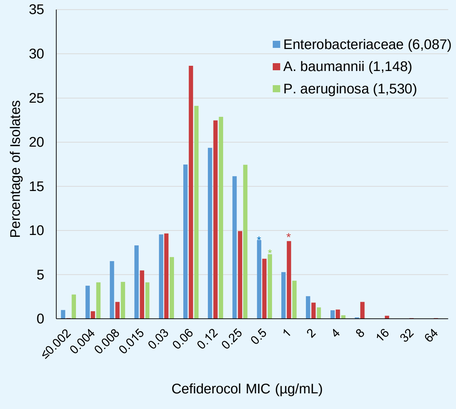
Results

Table 1. *In vitro* Activity of Cefiderocol and Comparators Against 8,765 Gram-negative Clinical Isolates from North America and Europe.

Organism (N)	Compound	%S	%I	%R	MIC_{50}	MIC_{90}	Range
A. baumannii (1,148)	Cefiderocol	na	na	na	0.12	1	≤ 0.002 - 64
	Cefepime	32.6	14.6	52.9	32	> 64	≤ 0.06 - > 64
	Ceftazidime-avibactam	na	na	na	16	> 64	≤ 0.06 - > 64
	Ceftolozane-tazobactam	na	na	na	8	> 64	≤ 0.06 - > 64
	Ciprofloxacin	25.3	0.2	74.6	> 8	> 8	≤ 0.12 - > 8
	Colistin	89.5	0	10.5	1	4	≤ 0.25 - > 8
	Meropenem	33.1	0.9	66.0	32	> 64	≤ 0.06 - > 64
A. baumannii, CarbNS (768)	Cefiderocol	na	na	na	0.12	1	≤ 0.002 - 64
	Cefepime	5.6	17.7	76.7	64	> 64	4 - > 64
	Ceftazidime-avibactam	na	na	na	32	> 64	1 - > 64
	Ceftolozane-tazobactam	na	na	na	16	> 64	0.5 - > 64
	Ciprofloxacin	0.5	0	99.5	> 8	> 8	≤ 0.12 - > 8
	Colistin	84.6	0	15.4	1	> 8	≤ 0.25 - > 8
	Meropenem	0	1.3	98.7	64	> 64	4 - > 64
P. aeruginosa (1,530)	Cefiderocol	na	na	na	0.12	0.5	≤ 0.002 - 8
	Cefepime	83.8	7.8	8.4	4	16	≤ 0.06 - > 64
	Ceftazidime-avibactam	94.8	0	5.2	2	8	≤ 0.06 - > 64
	Ceftolozane-tazobactam	94.3	1.6	4.1	0.5	2	≤ 0.06 - > 64
	Ciprofloxacin	76.0	5.8	18.3	0.25	> 8	≤ 0.12 - > 8
	Colistin	99.1	0.5	0.4	1	2	≤ 0.25 - > 8
	Meropenem	76.9	5.6	17.5	0.5	8	≤ 0.06 - > 64
P. aeruginosa, CarbNS (353)	Cefiderocol	na	na	na	0.12	1	≤ 0.002 - 4
	Cefepime	50.1	19.8	30.0	8	64	1 - > 64
	Ceftazidime-avibactam	77.9	0	22.1	4	32	0.5 - > 64
	Ceftolozane-tazobactam	77.1	5.4	17.6	1	64	0.25 - > 64
	Ciprofloxacin	38.5	8.2	53.3	4	> 8	≤ 0.12 - > 8
	Colistin	99.2	0.9	0	1	1	≤ 0.25 - 4
	Meropenem	0	24.4	75.6	8	64	4 - > 64
Enterobacteriaceae (6,087)	Cefiderocol	na	na	na	0.12	0.5	≤ 0.002 - 8
	Cefepime	87.6	2.6	9.8	≤ 0.06	8	≤ 0.06 - > 64
	Ceftazidime-avibactam	99.2	0	0.8	0.12	0.5	≤ 0.06 - > 64
	Ceftolozane-tazobactam	90.6	2.1	7.3	0.25	2	≤ 0.06 - > 64
	Ciprofloxacin	83.3	1.6	15.1	≤ 0.12	> 8	≤ 0.12 - > 8
	Colistin	82.2	0	17.8	0.5	> 8	≤ 0.25 - > 8
	Meropenem	97.2	0.3	2.5	≤ 0.06	0.12	≤ 0.06 - > 64
Enterobacteriaceae, CarbNS (169)	Cefiderocol	na	na	na	1	4	0.008 - 8
	Cefepime	7.1	5.3	87.6	> 64	> 64	≤ 0.06 - > 64
	Ceftazidime-avibactam	76.3	0	23.7	1	> 64	≤ 0.06 - > 64
	Ceftolozane-tazobactam	6.5	3.0	90.5	> 64	> 64	0.5 - > 64
	Ciprofloxacin	12.4	4.1	83.4	> 8	> 8	≤ 0.12 - > 8
	Colistin	71.6	0	28.4	0.5	> 8	≤ 0.25 - > 8
	Meropenem	0	10.7	89.4	16	> 64	2 - > 64

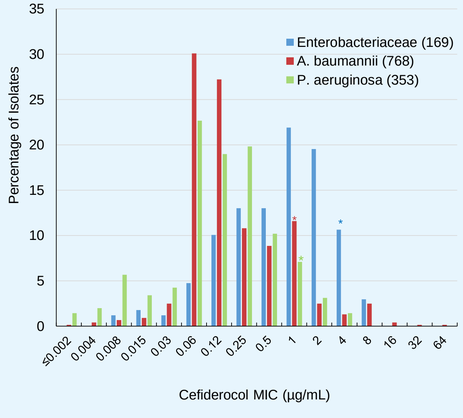
CarbNS, carbapenem (meropenem) non-susceptible based on CLSI breakpoints [2]; MIC_{50}, MIC_{90}, and Range in µg/mL; na, no available breakpoints

Figure 1. Cefiderocol MIC Distribution of 8,765 Gram-negative Clinical Isolates from Europe and North America.



*MIC_{90} Enterobacteriaceae; *MIC_{90} *A. baumannii*; *MIC_{90} *P. aeruginosa*

Figure 2. Cefiderocol MIC Distribution of 1,290 Meropenem Non-susceptible Gram-negative Clinical Isolates from Europe and North America.



*MIC_{90} Enterobacteriaceae; *MIC_{90} *A. baumannii*; *MIC_{90} *P. aeruginosa*

Figure 3. Cumulative Percent Cefiderocol MIC Distribution of 768 Meropenem Non-susceptible *A. baumannii* from Europe and North America.

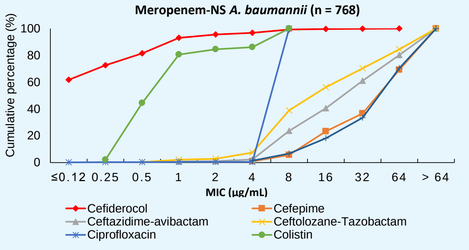


Figure 4. Cumulative Percent Cefiderocol MIC Distribution of 353 Meropenem Non-susceptible *P. aeruginosa* from Europe and North America.

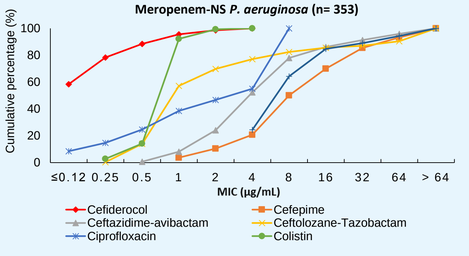
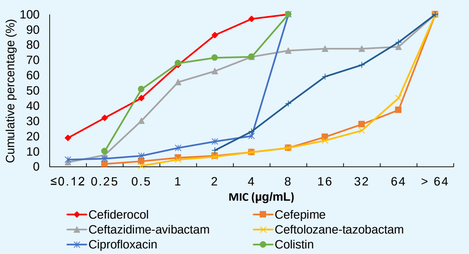


Figure 5. Cumulative Percent Cefiderocol MIC Distribution of 169 Meropenem Non-susceptible Enterobacteriaceae from Europe and North America.



Results Summary

- **Cefiderocol MIC_{50} and MIC_{90} values were the lowest of all compounds tested (Table 1, Figure 3, Figure 4, Figure 5).**
- **The cefiderocol MIC_{90} value was 1 µg/mL and the mode was 0.06 µg/mL for all *A. baumannii* isolates and for meropenem non-susceptible *A. baumannii* isolates (Table 1, Figure 1, Figure 2). A total of 1,120 isolates (97.6%) exhibited cefiderocol MIC values of ≤4 µg/mL (Figure 1).**
- **The cefiderocol MIC_{90} value was 0.5 µg/mL for all *P. aeruginosa* isolates and 1 µg/mL for meropenem non-susceptible isolates (Table 1). The mode for all *P. aeruginosa* and for meropenem non-susceptible strains was 0.06 µg/mL (Figure 1, Figure 2). A total of 1,529 *P. aeruginosa* isolates (99.9%) exhibited cefiderocol MIC values of ≤4 µg/mL (Figure 1).**
- **Cefiderocol MIC_{90} values were 1 µg/mL for all Enterobacteriaceae and 4 µg/mL for meropenem non-susceptible isolates (Table 1). The mode was 0.12 µg/mL for all isolates and 1 µg/mL for meropenem non-susceptible strains (Figure 1, Figure 2). A total of 6,078 Enterobacteriaceae isolates (99.9%) exhibited cefiderocol MIC values of ≤4 µg/mL (Figure 1).**

Conclusions

Cefiderocol showed potent *in vitro* activity against the majority of gram-negative isolates tested in this analysis, with 99.6% of MICs ≤4 µg/mL. The activity of cefiderocol observed in this study suggests that further in vitro and clinical work is warranted to explore the utility of this investigational agent.

References

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