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In Vitro Antibacterial Activity of Cefiderocol against Difficult-to-treat Resistant (DTR) Gram-negative Pathogens in United States from SENTRY Antimicrobial Surveillance Program in 2020/2021

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INTRODUCTION

- Cefiderocol (CFDC) is a siderophore cephalosporin with activity against a wide variety of Gram-negative bacteria, including carbapenemase-producing isolates. CFDC is highly active as it forms a chelating complex with ferric iron and mimics bacterial siderophores to actively penetrate the outer membrane via siderophore transporters. CFDC also has increased stability to serine- and metallo-type carbapenemases.
- CFDC has been approved in the United States for the treatment of patients with complicated urinary tract infections (cUTI) and hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia (HABP/VABP) caused by Gram-negative bacteria and in Europe for the treatment of infections due to aerobic Gram-negative organisms in adults with limited treatment options in 2019.
- Difficult-to-treat resistant (DTR) isolates are defined as resistance to all first-line high-efficacy, low-toxicity antibiotics (penicillins, cephalosporins, carbapenems and quinolones), leaving physicians with limited treatment options.
- We evaluated the *in vitro* activity of cefiderocol against DTR isolates collected in United States as part of SENTRY surveillance program in 2020 and 2021.

MATERIALS AND METHODS

• ***Bacterial strains***

- As part of SENTRY surveillance studies, a total of 8,326 Enterobacterales, 2,241 *Pseudomonas aeruginosa*, and 586 *Acinetobacter calcoaceticus-baumannii* complex (ACB) clinical isolates from the United States in 2020 to 2021 were evaluated. The sources of the test isolates are shown in Figure 1.
- Among these isolates, 50 Enterobacterales (0.6%), 36 *P. aeruginosa* (1.6%) and 114 ACB (19.5%) isolates showed a DTR phenotype with a definition of DTR as being resistant to cefepime, ceftazidime, ceftriaxone (only for Enterobacterales), imipenem, meropenem, ciprofloxacin and levofloxacin according to 2022 CLSI/FDA breakpoints

• ***MIC determination***

- MICs of CFDC were determined by the broth microdilution methods (BMD) using iron-depleted cation-adjusted Mueller Hinton broth. MICs of comparators were determined by the broth microdilution methods using cation-adjusted Mueller Hinton broth as recommended by CLSI.
- The susceptibility of CFDC and other comparators was interpreted by using the CLSI and FDA breakpoint. The susceptibility breakpoints for CFDC by CLSI and FDA are shown in Table 1.

RESULTS

- The rate of DTR in the US isolates from SENTRY surveillance study is very low (0.6% for Enterobacterales and 1.6% for *P. aeruginosa*), except for for ACB (19.5%). The source of the test isolates are shown in Figure 1.
- The susceptibility rate (%S) of CFDC against DTR Enterobacterales was 98%, which was the highest among the available antibiotics, followed by ceftazidime-avibactam with %S of 86%. Aztreonam-avibactam also showed good activity with the highest MIC of 4 µg/mL although the %S was not calculated due to no available breakpoints. The %S of all other comparators was <75%. (Table 2)
- The %S of CFDC against DTR *P. aeruginosa* was 100% and 97.2% by CLSI and FDA interpretation, respectively. These values were the highest among the available antibiotics. The %S of all other comparators was <75%. (Table 3)
- The susceptibility rate of CFDC against DTR ACB was 92.1% and 75.4% by CLSI and FDA interpretation, respectively. These values were the highest among the available antibiotics. Even for ampicillin/sulbactam and minocycline, the susceptibility was low (2.6% and 56%), respectively (Table 4)
- Cefiderocol showed more potent antibacterial activity against DTR *P. aeruginosa* and ACB than other β-lactam/β-lactamase inhibitor combination drugs (Figures 2 and 3)

Figure 1. The source of the test isolates used in this study

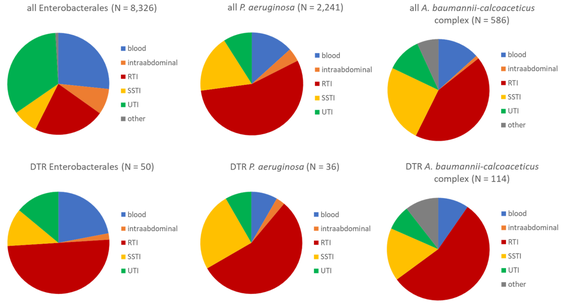


Table 1. Cefiderocol breakpoint interpretation by CLSI and FDA

	Interpretation by CLSI			Interpretation by FDA		
	S	I	R	S	I	R
Enterobacterales	≤ 4	8	≥ 16	≤ 4	8	≥ 16
P. aeruginosa	≤ 4	8	≥ 16	≤ 1	2	≥ 4
A. baumannii-calcoaceticus complex	≤ 4	8	≥ 16	≤ 1	2	≥ 4

Table 2. *In vitro* susceptibility of cefiderocol and comparators to DTR Enterobacterales (N = 50)

	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)	MIC range (µg/mL)	Interpretation by CLSI			Interpretation by FDA		
				%S	%I	%R	%S	%I	%R
Cefiderocol	1	4	0.008 to 8	98.0	2.0	0.0	98.0	2.0	0.0
Imipenem-relebactam	0.12	>8	0.06 to >8	74.0 [a]	2.0	24.0	74.0 [a]	2.0	24.0
Meropenem-vaborbactam	0.25	>8	≤0.015 to >8	74.0	8.0	18.0	74.0	8.0	18.0
Ceftazidime-avibactam	1	>32	≤0.015 to >32	86.0	-[b]	14.0	86.0	-[b]	14.0
Ceftolozane-tazobactam	>16	>16	16 to >16	0.0	0.0	100.0	0.0	0.0	100.0
Aztreonam	>16	>16	≤0.03 to >16	4.0	0.0	96.0	4.0	0.0	96.0
Aztreonam-avibactam	0.25	0.5	≤0.03 to 4	-[b]	-[b]	-[b]	-[b]	-[b]	-[b]
Colistin	0.25	2	0.12 to >8	-[b]	90.0	10.0	-[b]	-[b]	-[b]

a: All Enterobacterales species including imipenem intrinsic resistant species (*Morganella*, *Proteus* and *Providencia* species) are included
b: Breakpoints are not available

Table 3. *In vitro* susceptibility of cefiderocol and comparators to DTR *P. aeruginosa* (N = 36)

	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)	MIC range (µg/mL)	Interpretation by CLSI			Interpretation by FDA		
				%S	%I	%R	%S	%I	%R
Cefiderocol	0.12	1	0.06 to 2	100.0	0.0	0.0	97.2	2.8	0.0
Imipenem-relebactam	4	>8	0.25 to >8	47.2	33.3	19.4	47.2	33.3	19.4
Meropenem-vaborbactam	>8	>8	4 to >8	-[a]	-[a]	-[a]	-[a]	-[a]	-[a]
Ceftazidime-avibactam	16	>32	4 to >32	47.2		52.8	47.2		52.8
Ceftolozane-tazobactam	4	>16	2 to >16	58.3	25.0	16.7	58.3	25.0	16.7
Aztreonam	>16	>16	8 to >16	5.6	0.0	94.4	5.6	0.0	94.4
Aztreonam-avibactam	>16	>16	2 to >16	-[a]	-[a]	-[a]	-[a]	-[a]	-[a]
Piperacillin-tazobactam	>128	>128	16 to >128	8.3	8.3	83.3	8.3	8.3	83.3
Colistin	0.5	1	0.12 to 2	-[a]	100.0	0.0	-[a]	-[a]	-[a]

a: Breakpoints are not available

Table 4. *In vitro* susceptibility of cefiderocol and comparators to DTR *A. baumannii-calcoaceticus* complex (N = 114)

)	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)	MIC range (µg/mL)	Interpretation by CLSI			Interpretation by FDA		
				%S	%I	%R	%S	%I	%R
Cefiderocol	0.5	4	0.015 to >64	92.1	2.6	5.3	75.4	12.3	12.3
Imipenem-relebactam	>8	>8	8 to >8	-[a]	-[a]	-[a]	0.0	0.0	100.0
Meropenem-vaborbactam	>8	>8	>8 to >8	-[a]	-[a]	-[a]	-[a]	-[a]	-[a]
Ceftazidime-avibactam	>32	>32	4 to >32	-[a]	-[a]	-[a]	-[a]	-[a]	-[a]
Ceftolozane-tazobactam	>16	>16	4 to >16	-[a]	-[a]	-[a]	-[a]	-[a]	-[a]
Aztreonam	>16	>16	>16 to >16	-[a]	-[a]	-[a]	-[a]	-[a]	-[a]
Aztreonam-avibactam	>16	>16	4 to >16	-[a]	-[a]	-[a]	-[a]	-[a]	-[a]
Ampicillin-sulbactam	32	>64	8 to >64	2.6	8.8	88.6	2.6	8.8	88.6
Trimethoprim-sulfamethoxazole	>4	>4	≤0.12 to >4	21.9	-[a]	78.1	-[a]	-[a]	-[a]
Minocycline	4	16	0.12 to 32	54.4	13.2	32.5	54.4	13.2	32.5
Colistin	0.5	2	0.12 to >8	-[a]	93.0	7.0	-[a]	-[a]	-[a]

a: Breakpoints are not available
b: N = 113

Figure 2. Cumulative susceptibility curves of cefiderocol and comparator agents against DTR *P. aeruginosa* isolates (N = 34)

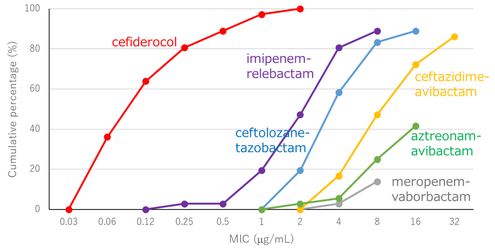
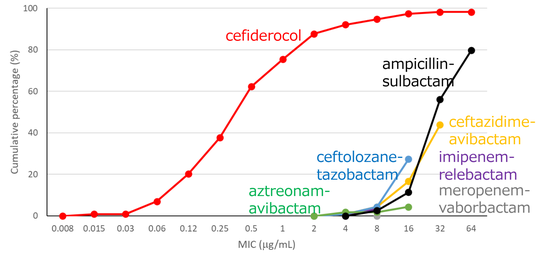


Figure 3. Cumulative susceptibility curves of cefiderocol and comparator agents against DTR *A. baumannii-calcoaceticus* complex isolates (N = 114)



CONCLUSION

Cefiderocol demonstrated potent in vitro activity against DTR isolates of Enterobacterales, *P. aeruginosa* and *A. baumannii-calcoaceticus* complex, indicating cefiderocol has high potential for treating infections caused by these difficult-to-treat strains.

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