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Activity of Cefiderocol and Comparator Agents against US Isolates of *Pseudomonas aeruginosa*, *Acinetobacter baumannii-calcoaceticus* species complex, and *Stenotrophomonas maltophilia*, Including Carbapenem-Resistant Isolates from the SENTRY Antimicrobial Surveillance Program (2020–2022)

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Introduction

- Cefiderocol is a siderophore-conjugated cephalosporin with broad activity against Gram-negative bacteria, including multidrug-resistant organisms.
- Cefiderocol was approved by the EMA for the treatment of infections caused by Gram-negative bacteria in adult patients with limited treatment options and the US FDA for complicated urinary tract infection, hospital-acquired bacterial pneumonia, and ventilator-associated bacterial pneumonia.
- Non–glucose-fermenting species including *Pseudomonas aeruginosa*, *Acinetobacter baumannii-calcoaceticus* complex, and *Stenotrophomonas maltophilia* are often extensively drug-resistant (XDR), presenting serious treatment challenges.
- The susceptibility of cefiderocol and comparator agents was investigated against non–glucose-fermenting US isolates collected in 2020–2022 as part of the SENTRY Antimicrobial Surveillance Program.

Materials and Methods

- A total of 2,982 *P. aeruginosa*, 799 *A. baumannii-calcoaceticus* species complex, and 585 *S. maltophilia* were isolated from hospitalised patients in 63 US medical centres.
- Susceptibility testing was performed using the broth microdilution method with cation-adjusted Mueller-Hinton broth (CAMHB) for comparator agents and iron-depleted CAMHB for cefiderocol.
- CLSI, FDA, and EUCAST breakpoints were applied.
- For the EUCAST assessment of cefiderocol activity against *A. baumannii-calcoaceticus* species complex and *S. maltophilia*, PK/PD (non–species-related) breakpoints were used.
- XDR was defined as non-susceptible to at least 1 agent in all but 2 or fewer drug classes using CLSI criteria.
- Other agents tested included meropenem, levofloxacin, trimethoprim-sulfamethoxazole, and the β-lactam/β-lactamase inhibitor (BL/BLI) combinations ampicillin-sulbactam, ceftazidime-avibactam, ceftolozane-tazobactam, imipenem-relebactam, and meropenem-vaborbactam.

Results

- The most common infection type from which isolates were collected was pneumonia (*n*=2,340), followed by skin and skin structure (*n*=827), bloodstream infection (*n*=543), urinary tract infection (*n*=391), intra-abdominal infection (*n*=142), and other sites (*n*=123).
- *P. aeruginosa* susceptibilities to cefiderocol and BL/BLI combinations were >96.0%, except for meropenem-vaborbactam (90.8%; Table 1).
- Cefiderocol was the most active agent against XDR *P. aeruginosa* isolates (susceptibility 98.2/97.1/93.0% CLSI/EUCAST/FDA, respectively). The susceptibilities of the BL/BLI combinations against these XDR isolates ranged from 42.1% to 78.8%.
- Cefiderocol had higher susceptibilities than comparator agents against BL/BLI-resistant *P. aeruginosa* isolates (Table 1, Figure 1).
- *A. baumannii-calcoaceticus* complex susceptibility to cefiderocol was 98.5/97.2/93.6% (CLSI/EUCAST/FDA; Table 2, Figure 1).
- Cefiderocol retained good activity against XDR, meropenem-resistant, or imipenem-relebactam–resistant *A. baumannii-calcoaceticus* complex isolates, with ≥85.0% susceptibility.
- Cefiderocol was active against *S. maltophilia* (98.5/99.3% susceptible, CLSI/EUCAST; Table 2, Figure 1).

Conclusions

- Cefiderocol was the most active β-lactam with broad activity against contemporary US isolates of drug-resistant subsets of *P. aeruginosa* and *A. baumannii-calcoaceticus* complex as well as *S. maltophilia*, where treatment options are limited.
- These *in vitro* data suggest that cefiderocol is an important treatment option for infections caused by non–glucose-fermenting pathogens, including meropenem-, BL/BLI-resistant, and XDR isolates.

Acknowledgments

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Table 1. Susceptibilities of *Pseudomonas aeruginosa* isolates and resistant subgroups, collected in the SENTRY (2020–2022) study, for cefiderocol and comparator agents

Organism/organism group Antimicrobial agent	MIC_{50} (mg/L)	MIC_{90} (mg/L)	%S CLSI[a]	%S EUCAST[a]	%S US FDA[a]
All (*n*=2,982)					
Cefiderocol	0.12	0.25	99.8	99.6	98.5
Meropenem	0.5	8	80.4	80.4	80.4
Meropenem-vaborbactam	0.5	8		90.8	
Imipenem-relebactam	0.25	1	97.3	97.3	97.3
Ceftolozane-tazobactam	0.5	2	97.4	97.4	97.4
Ceftazidime-avibactam	2	8	96.4	96.4	96.4
XDR[b] (*n*=273)					
Cefiderocol	0.12	1	98.2	97.1	93.0
Meropenem	16	32	7.3	7.3	7.3
Meropenem-vaborbactam	>8	>8		42.1	
Imipenem-relebactam	2	4	77.7	77.7	77.7
Ceftolozane-tazobactam	2	16	78.8	78.8	78.8
Ceftazidime-avibactam	8	32	69.6	69.6	69.6
Meropenem MIC >4 mg/L (*n*=418)					
Cefiderocol	0.12	0.5	99.3	98.6	95.7
Meropenem	16	32	0.0	0.0	0.0
Meropenem-vaborbactam	>8	>8		35.2	
Imipenem-relebactam	2	4	81.1	81.1	81.1
Ceftolozane-tazobactam	2	8	85.6	85.6	85.6
Ceftazidime-avibactam	4	16	79.9	79.9	79.9
Meropenem-vaborbactam MIC >8 mg/L (*n*=273)					
Cefiderocol	0.12	0.5	98.9	98.2	94.5
Meropenem	16	32	0.0	0.0	0.0
Meropenem-vaborbactam	>8	>8		0.0	
Imipenem-relebactam	2	8	74.0	74.0	74.0
Ceftolozane-tazobactam	2	16	82.1	82.1	82.1
Ceftazidime-avibactam	8	32	72.2	72.2	72.2
Imipenem-relebactam MIC >4 mg/L (*n*=30)					
Cefiderocol	0.25	1	100.0	100.0	90.0
Meropenem	32	>32	0.0	0.0	0.0
Meropenem-vaborbactam	>8	>8		3.3	
Imipenem-relebactam	8	>8	0.0	0.0	0.0
Ceftolozane-tazobactam	8	>16	46.7	46.7	46.7
Ceftazidime-avibactam	16	>32	33.3	33.3	33.3
Ceftolozane-tazobactam MIC >8 mg/L (*n*=43)					
Cefiderocol	0.5	8	88.4	83.7	69.8
Meropenem	16	>32	7.0	7.0	7.0
Meropenem-vaborbactam	>8	>8		30.2	
Imipenem-relebactam	2	>8	55.8	55.8	55.8
Ceftolozane-tazobactam	>16	>16	0.0	0.0	0.0
Ceftazidime-avibactam	>32	>32	16.3	16.3	16.3
Ceftazidime-avibactam MIC >8 mg/L (*n*=106)					
Cefiderocol	0.25	2	95.3	92.5	87.7
Meropenem	16	>32	10.4	10.4	10.1
Meropenem-vaborbactam	>8	>8		28.3	
Imipenem-relebactam	2	8	66.0	66.0	66.0
Ceftolozane-tazobactam	4	>16	54.7	54.7	54.7
Ceftazidime-avibactam	16	>32	0.0	0.0	0.0

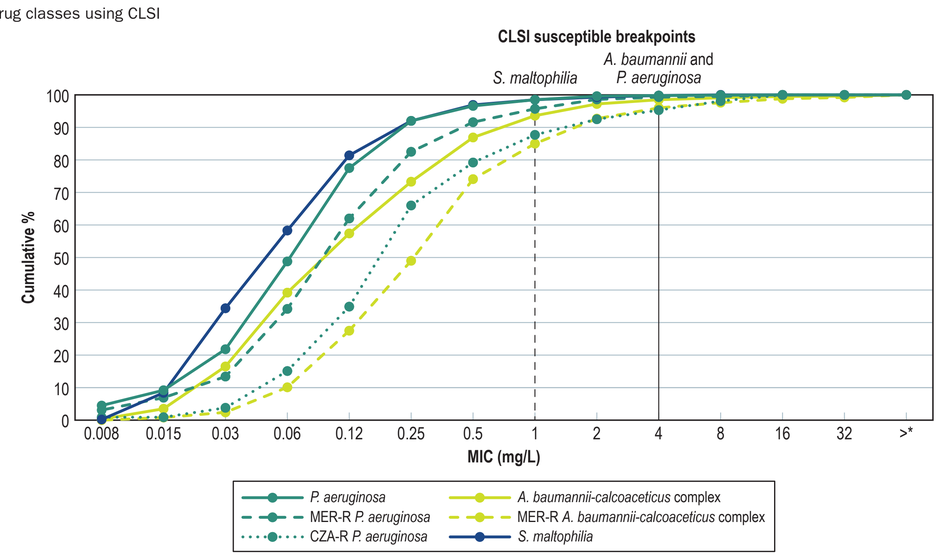
[a] Breakpoints as published by CLSI, EUCAST, and US FDA (2022).
[b] XDR, extensively drug-resistant, defined as non-susceptible to all but 2 or fewer drug classes using CLSI breakpoints (2022).

Table 2. Susceptibilities of *Acinetobacter baumannii-calcoaceticus* species isolates, including resistant subgroups, and *Stenotrophomonas maltophilia* collected in the SENTRY (2020–2022) study for cefiderocol and comparator agents

Organism/organism group Antimicrobial agent	MIC_{50} (mg/L)	MIC_{90} (mg/L)	%S CLSI[a]	%S EUCAST[a]	%S US FDA[a]
All *A. baumannii-calcoaceticus* complex (*n*=799)					
Cefiderocol	0.12	1	98.5	97.2	93.6
Meropenem	0.5	>32	68.3	68.3	68.3
Imipenem-relebactam	0.25	>8		69.6	69.6
Ampicillin-sulbactam	4	64	67.1		67.1
Minocycline	0.12	8	84.9		84.9
Colistin	0.5	1		96.0	
XDR[b] (*n*=192)					
Cefiderocol	0.5	2	96.4	92.7	85.4
Meropenem	>32	>32	3.1	3.1	3.1
Imipenem-relebactam	>8	>8		4.7	4.7
Ampicillin-sulbactam	32	>64	4.2		4.2
Minocycline	8	16	42.7		42.7
Colistin	0.5	2		92.7	
Meropenem MIC >4 mg/L (*n*=247)					
Cefiderocol	0.5	2	96.0	92.7	85.0
Meropenem	>32	>32	0.0	0.0	0.0
Imipenem-relebactam	>8	>8		1.6	1.6
Ampicillin-sulbactam	32	>64	10.1		10.1
Minocycline	4	16	57.9		57.9
Colistin	0.5	1		94.3	
Imipenem-relebactam MIC >2 mg/L (*n*=243)					
Cefiderocol	0.5	2	95.9	93.0	85.2
Meropenem	>32	>32	0.0	0.0	0.0
Imipenem-relebactam	>8	>8		0.0	0.0
Ampicillin-sulbactam	32	>64	9.5		9.5
Minocycline	4	16	58.4		58.4
Colistin	0.5	1		94.2	
S. maltophilia (*n*=585)					
Cefiderocol	0.06	0.25	98.5	99.3	
Levofloxacin	1	8	82.4		
Trimethoprim-sulfamethoxazole	≤0.12	0.5	97.8	98.5[c]	
Minocycline	0.5	1	99.8		

[a] Breakpoints as published by CLSI, EUCAST, and US FDA (2022).
[b] XDR, extensively drug-resistant, defined as non-susceptible to all but 2 or fewer drug classes using CLSI breakpoints (2022).
[c] Susceptible-increased exposure shown (EUCAST, 2022).

Figure 1. Cefiderocol MIC distributions of *P. aeruginosa*, all isolates and those resistant to meropenem or ceftazidime-avibactam; *A. baumannii-calcoaceticus* complex, all isolates and those resistant to meropenem; *S. maltophilia*, all isolates



*Greater than the highest concentration tested.
Abbreviations: MER-R, meropenem-resistant; CZA-R, ceftazidime-avibactam–resistant.

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