Activity of Cefiderocol and Comparators against US isolates of *Pseudomonas aeruginosa*, *Acinetobacter baumannii-calcoaceticus* species complex, and *Stenotrophomonas maltophilia*, including Carbapenem-Resistant Isolates from the SENTRY Antimicrobial Surveillance Program (2020-2021)

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Objective

Cefiderocol is a siderophore-conjugated cephalosporin with broad activity against Gram-negative bacteria, including non-glucose-fermenting (NGF) species.

Cefiderocol was approved by the FDA for treatment of complicated urinary tract infection, hospital-acquired bacterial pneumonia, and ventilator-associated bacterial pneumonia.

The objective of this study was to analyse the susceptibilities of *P. aeruginosa* (PSA), *A. baumannii-calcoaceticus* (ABC), and *S. maltophilia* (SM) collected in 2020-2021 against cefiderocol and comparators.

Methods

- A total of 2,837 NGF isolates were consecutively collected from 32 US hospitals.
  - Isolates tested: PSA, (*n*=1,859), ABC (*n*=405) and SM (*n*=352).
- Isolates from all infection types were included in the analysis.
  - The most common infection type was pneumonia (*n*=1,503), followed by skin/skin structure infection (*n*=509).
- Susceptibility testing was performed using the CLSI broth microdilution method. Cefiderocol was tested in iron-depleted cation-adjusted Mueller-Hinton broth.
- FDA, CLSI, and EUCAST (2022) breakpoints were applied. EUCAST PK/PD (non-species-related) breakpoints were used for cefiderocol against ABC and SM.
- XDR was defined as nonsusceptibility to at least 1 agent in all but 2 or fewer drug classes using CLSI criteria.
- Other agents tested included meropenem and the beta-lactam/beta-lactamase inhibitor (BL/BLI) combinations ceftazidime-avibactam, ceftolozane-tazobactam, and imipenem-relebactam.

Results

Table 1 Susceptibilities of *P. aeruginosa* (PSA) and Resistant Subgroups

Organism group/ antimicrobial agent	mg/L		CLSI[a]	FDA[a]	EUCAST[a]
	MIC_{50}	MIC_{90}	%S	%S	%S
All PSA (n=1,859)					
Cefiderocol	0.12	0.25	99.7	98.6	99.5
Meropenem	0.5	8	80.2	80.2	80.2
Imipenem-relebactam	0.25	1	97.5	97.5	97.5
Ceftolozane-tazobactam	0.5	2	97.9	97.9	97.9
Ceftazidime-avibactam	2	8	96.6	96.6	96.6
XDR[b] (n=172)					
Cefiderocol	0.12	1	97.1	94.8	96.5
Meropenem	16	32	8.1	8.1	8.1
Imipenem-relebactam	2	4	80.8	80.8	80.8
Ceftolozane-tazobactam	2	8	82.0	82.0	82.0
Ceftazidime-avibactam	8	16	73.8	73.8	73.8
Ceftazidime-avibactam MIC >8 mg/L (n=63)					
Cefiderocol	0.25	1	92.1	90.5	90.5
Meropenem	16	32	12.7	12.7	12.7
Imipenem-relebactam	2	8	66.7	66.7	66.7
Ceftolozane-tazobactam	4	>16	61.9	61.9	61.9

Table 2 Susceptibilities of *A. baumannii-calcoaceticus* species (ABC), and Resistant Subgroups, as well as *S. maltophilia*

Organism group/ antimicrobial agent	mg/L		CLSI[a]	FDA[a]	EUCAST[a]
	MIC_{50}	MIC_{90}	%S	%S	%S
All ABC (n=405)					
Cefiderocol	0.12	1	98.3	92.1	97.3
Meropenem	0.5	>32	66.7	66.7	66.7
Ampicillin-sulbactam	4	64	64.0	64.0	
Imipenem-relebactam	0.25	>8		67.7	67.7
XDR[b] (n=103)					
Cefiderocol	0.25	2	97.1	82.5	94.2
Meropenem	>32	>32	1.9	1.9	1.9
Ampicillin-sulbactam	32	>64	1.9	1.9	
Imipenem-relebactam	>8	>8		2.9	2.9
Meropenem MIC >4 mg/L (n=132)					
Cefiderocol	0.25	2	95.5	82.6	92.4
Ampicillin-sulbactam	32	>64	1.9	1.9	
Imipenem-relebactam	>8	>8		0.8	0.8
S. maltophilia (n=352)					
Cefiderocol	0.06	0.25	98.6		99.7
Trimethoprim-sulfamethoxazole	<=0.12	0.5	98.3		98.6 [c]

[a] Breakpoints as published by CLSI, FDA or EUCAST (2022). EUCAST PK/PD breakpoints used for ABC and *S. maltophilia*.
[b] XDR= extensively drug-resistant: resistant to all but 2 or fewer drug classes using EUCAST breakpoints (2022).
[c] No EUCAST susceptible breakpoint, intermediate, increased exposure is shown.

Results

Figure 1. MIC Distributions of All *P. aeruginosa* Isolates

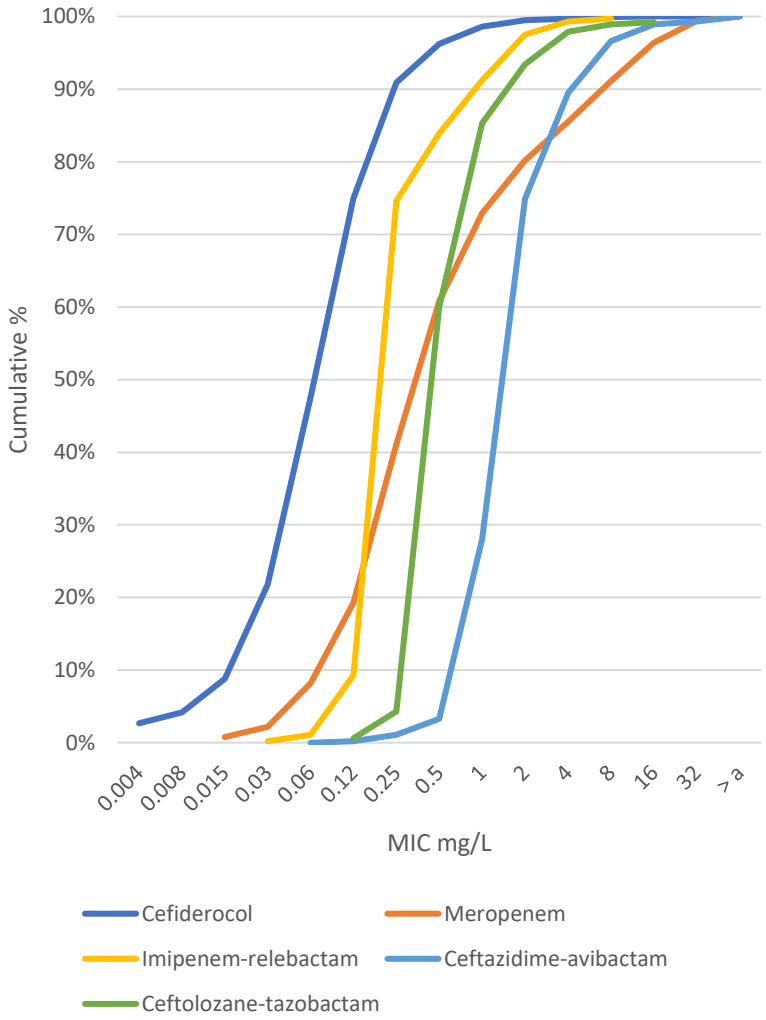


Figure 2. MIC Distributions of XDR and CZA-R *P. aeruginosa Isolates*

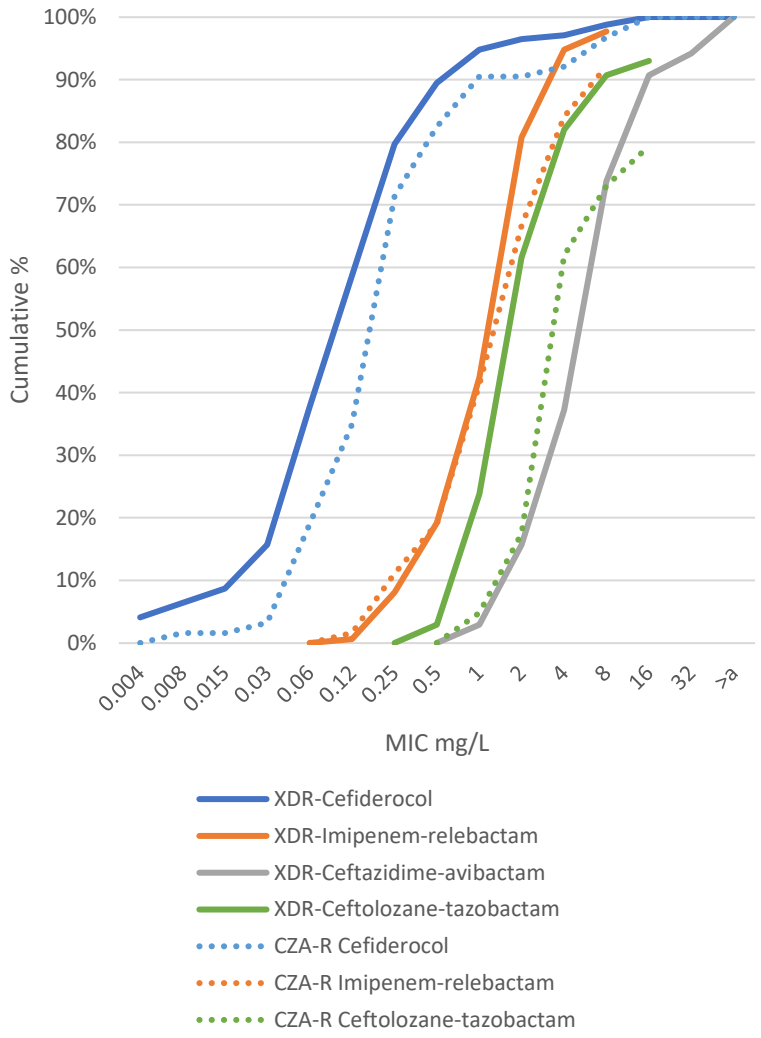
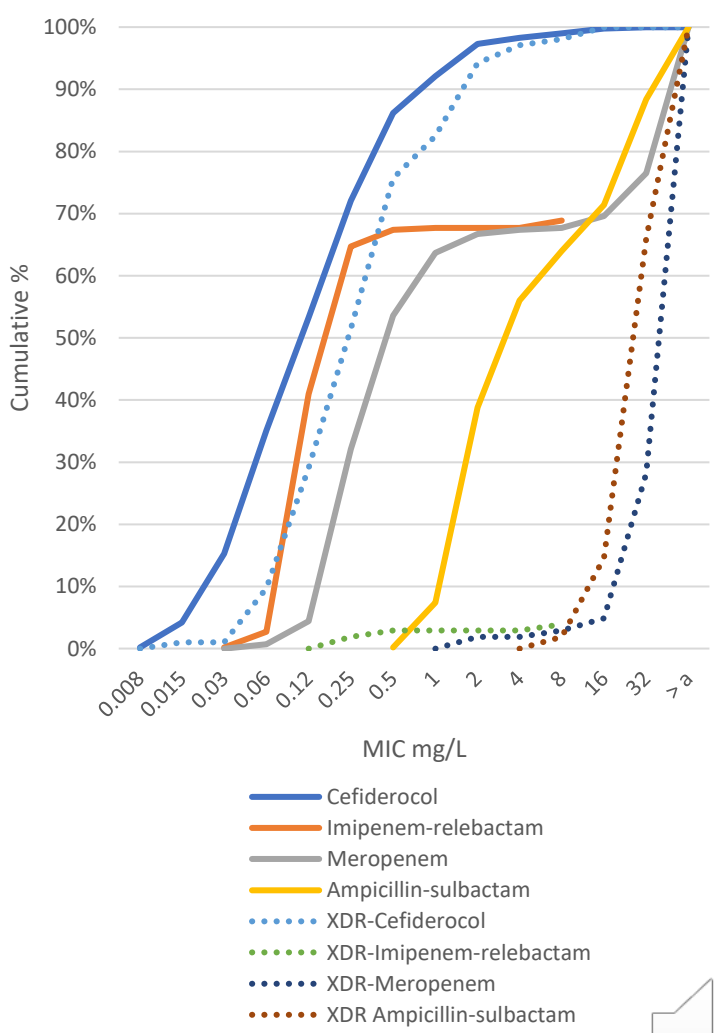


Figure 3. MIC Distributions *of A. baumannii-calcoaceticus* and XDR isolates



[a] > Greater than the highest concentration tested.

XDR, extensively drug resistant; CZA-R ceftazidime-avibactam-resistant

Results

- Cefiderocol and BL/BLI susceptibilities against PSA were >96.0%; susceptibility to meropenem was 80.2% (Table 1, Figure 1).
- Cefiderocol was the most active agent against XDR PSA isolates (susceptibility 97.1/94.8/96.5% CLSI/FDA/EUCAST, respectively); the susceptibilities of BL/BLIs ranged from 39.5-82.0%. (Table 1, Figure 2).
- Cefiderocol was highly active against ABC (98.3/92.1/97.3%, CLSI/FDA/EUCAST; Table 2, Figure 3).
- Cefiderocol susceptibility rates against the XDR and meropenem-resistant ABC subsets were 97.1/82.5/94.2% and 95.5/82.6/92.4%, respectively (CLSI/FDA/EUCAST).
- Cefiderocol was very active against SM, with 98.6/99.7% susceptibility (CLSI/EUCAST).

Conclusions

- Cefiderocol had broad activity against US NGF isolates, including ceftazidime-avibactam-resistant and XDR PSA.
- Cefiderocol was the most active agent tested against ABC including XDR and meropenem-resistant subsets, as well as against SM, where treatment options are limited.
- These *in vitro* data suggest that cefiderocol is an important option for the treatment of infections caused by NGF, including meropenem-resistant, BL/BLI-R and XDR pathogens.

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