Activity of Cefiderocol and Comparators Against European Isolates of *Pseudomonas aeruginosa*, *Acinetobacter baumannii-calcoaceticus* complex, and *Stenotrophomonas maltophilia* 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.

Cefiderocol was approved by the EMA for the treatment of infections caused by Gram-negative bacteria in adult patients with limited treatment options.

The objective of this study was the analysis of the susceptibilities of cefiderocol, and comparators tested against European isolates of non-glucose-fermenting (NGF) species including *P. aeruginosa*, *A. baumannii-calcoaceticus* complex and *S. maltophilia*, collected in 2020-2021.

Methods

- A total of 2,581 NGF isolates were consecutively collected from 36 hospitals in 18 European countries.
- Isolates from all infection types were included in this study.
- Susceptibility testing was performed using the CLSI broth microdilution method. Cefiderocol was tested in iron-depleted cation-adjusted Mueller-Hinton broth.
- CLSI, FDA, and EUCAST (2022) breakpoints were applied. EUCAST PK/PD (non-species-related) breakpoints were used to assess cefiderocol activity against *A. baumannii-calcoaceticus* complex (ABC) and *S. maltophilia* (SM).
- Extensively-drug-resistant (XDR) isolates were susceptible to 2 or fewer antimicrobial drug classes.
  - Other agents tested included meropenem and imipenem as well as the beta-lactam/beta-lactamase inhibitor (BL/BLI) combinations ceftazidime-avibactam, imipenem-relebactam, and ceftolozane-tazobactam.

Results

Table 1. Susceptibilities of *P. aeruginosa* and Resistant Subgroups

Organism group/ antimicrobial agent	mg/L		CLSI[a]	FDA[a]	EUCAST[a]
	MIC_{50}	MIC_{90}	%S	%S	%S
***P. aeruginosa* (*n* = 1,834)**					
Cefiderocol	0.12	0.25	99.8	99.1	99.6
Meropenem	0.5	8	77.4	77.4	77.4
Imipenem-relebactam	0.25	1	94.9	94.9	94.9
Ceftolozane-tazobactam	0.5	2	94.6	94.6	94.6
Ceftazidime-avibactam	2	4	96.2	96.2	96.2
XDR (*n* = 160)					
Cefiderocol	0.12	0.5	98.8	95.0	98.1
Meropenem	32	>32	1.2	1.2	1.2
Imipenem-relebactam	2	>8	51.2	51.2	51.2
Ceftolozane-tazobactam	2	>16	53.8	53.8	53.8
Ceftazidime-avibactam	4	>32	66.9	66.9	66.9
Ceftazidime-avibactam MIC >8 mg/L (*n* = 69)					
Cefiderocol	0.25	2	97.1	85.5	95.7
Meropenem	>32	>32	7.2	7.2	7.2
Imipenem-relebactam	>8	>8	29.0	29.0	29.0
Ceftolozane-tazobactam	>16	>16	17.4	17.4	17.4

Table 2. Susceptibilities of *A. baumannii-calcoaceticus* complex 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
***A. baumannii-calcoaceticus* (*n* = 447)**					
Cefiderocol	0.25	1	97.8	93.1	95.5
Meropenem	>32	>32	35.8	35.8	35.8
Ampicillin-sulbactam	32	>64	35.6	35.6	
Imipenem-relebactam	>8	>8		35.8	35.8
XDR[b] (*n* = 281)					
Cefiderocol	0.25	1	97.2	90.0	93.6
Meropenem	>32	>32	0.0	0.0	0.0
Ampicilin-sulbactam	64	>64	0.7	0.7	
Imipenem-relebactam	>8	>8		0.0	0.0
Meropenem MIC >4 mg/L (*n* = 289)					
Cefiderocol	0.25	2	96.6	90.0	93.4
Ampicillin-sulbactam	64	>64	1.7	1.7	
Imipenem-relebactam	>8	>8		0.0	0.0
***S. maltophilia* (*n*=221)**					
Cefiderocol	0.12	0.5	99.1		100.0
Trimethoprim-sulfamethoxazole	<=0.12	0.5	95.5		96.8[c]

[a] Breakpoints as published by CLSI, FDA or EUCAST (2022). EUCAST PK/PD breakpoints used for ABC and SM..
[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. All *P. aeruginosa* MIC Distributions

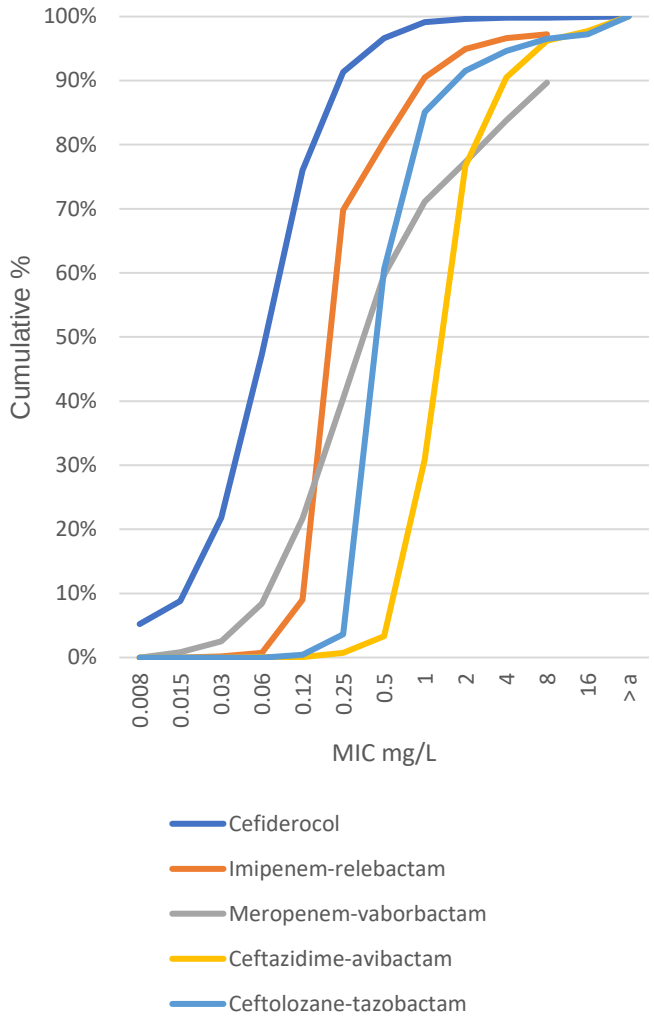


Figure 2. XDR and CZA-R *P. aeruginosa* MIC Distributions

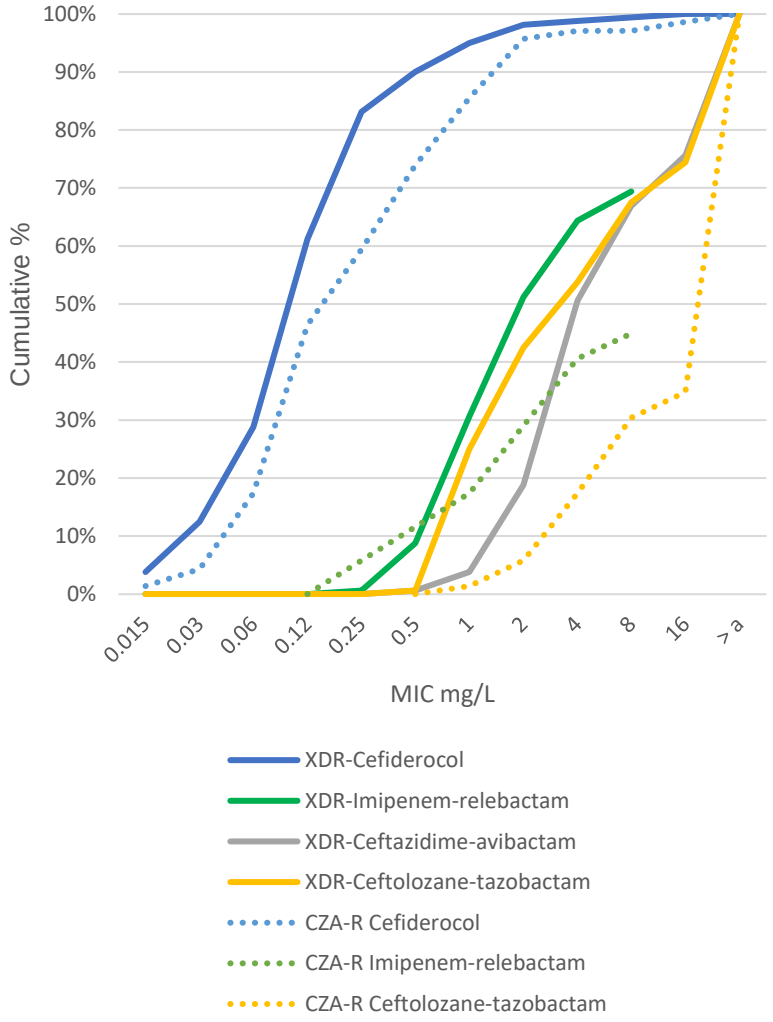
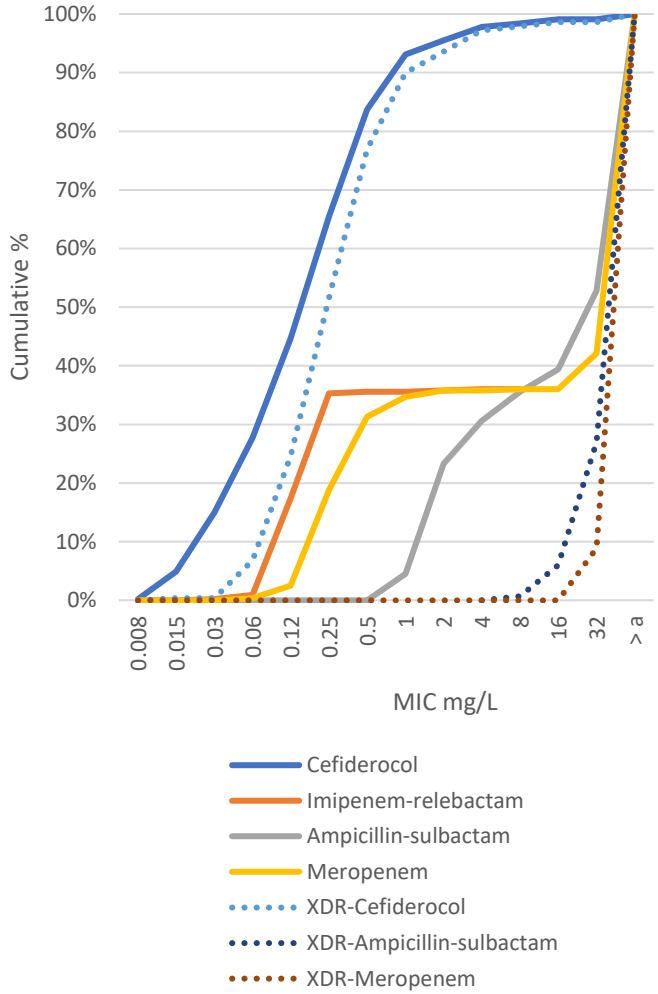


Figure 3. *A. baumannii-calcoaceticus* and XDR MIC Distributions



[a] >, MIC greater than highest dilution tested.

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

Results

- Isolates tested included *Pseudomonas aeruginosa* (PSA, *n* = 1,834), followed by ABC (*n* = 447) and SM (*n* = 221).
  - The most common infection was pneumonia (*n* = 1,259), followed by skin/skin structure infection (*n* = 489).
- For all PSA isolates, cefiderocol and BL/BLI susceptibilities were >94%, susceptibility to meropenem was 77.4% (EUCAST; Table 1, Figure 1).
  - Against XDR PSA, cefiderocol was the most active agent tested with 98.8/95.1/98.1% susceptible (CLSI/FDA/EUCAST, respectively).
  - Susceptibilities of the BL/BLIs ranged from 51.2-66.9% (Table 1, Figure 2).
- Against *A. baumannii-calcoaceticus* complex (ABC), cefiderocol had potent activity (97.8/93.1/95.5% CLSI/FDA/EUCAST; Table 2, Figure 3).
  - XDR ABC isolates had susceptibility of 97.2/90.0/93.6% (CLSI/FDA/EUCAST) to cefiderocol.
- Cefiderocol was very active against SM, with 99.1/100.0% susceptibility (CLSI 2022/EUCAST; Table 2).

Conclusions

- Cefiderocol had broad activity against European isolates of PSA, ABC, and SM.
- The cefiderocol was active against PSA resistant to ceftazidime-avibactam, and meropenem-resistant ABC isolates, which have very limited treatment options.
- Susceptibility of XDR PSA and ABC isolates to cefiderocol was higher than the other agents tested.
- These *in vitro* data suggest that cefiderocol is an important option for the treatment of infections caused by NGF, including meropenem-R, BL-BLI-R and XDR pathogens.

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