Activity of Cefiderocol and Comparators against Gram-Negative Isolates from US Patients Hospitalized with Pneumonia

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Introduction

- Cefiderocol (CFDC) is a novel siderophore-conjugated cephalosporin with broad activity against Gram-negative (GN) bacteria, *Enterobacterales* including carbapenem-resistant isolates, and nonfermentative organisms including *Pseudomonas aeruginosa*, *Acinetobacter baumannii-calcoaceticus* complex and *Stenotrophomonas maltophilia*.
- CFDC is approved by the FDA for complicated urinary tract infections, hospital-acquired bacterial pneumonia, and ventilator-associated bacterial pneumonia.
- In this study, we analyzed the susceptibility of CFDC and recent β-lactam/β-lactamase inhibitors against aerobic nonfastidious GN isolates collected from US patients hospitalized with pneumonia (PHP) in 2020 as part of the SENTRY Antimicrobial Surveillance Program.

Materials and Methods

- A total of 1,877 Gram-negative isolates were consecutively collected from PHP in 27 US hospitals during 2020.
- Susceptibility testing was performed using the CLSI broth microdilution method.
  - CFDC was tested in iron-depleted cation-adjusted Mueller-Hinton broth.
  - CLSI/FDA (2021) breakpoints were used.
- Both CLSI and FDA (2021) interpretations were used for CFDC:
  - *Enterobacterales,* CLSI/FDA breakpoints (≤4/8/≥16 mg/L);
  - *Pseudomonas aeruginosa*, CLSI (≤4/8/≥16 mg/L) and FDA breakpoints (≤1/2/≥4 mg/L);
  - *Acinetobacter* species, CLSI (≤4/8/≥16 mg/L) and FDA breakpoints (≤1/2/≥4 mg/L);
  - *Stenotrophomonas maltophilia*, CLSI 2021 breakpoints (≤4/8/≥16 mg/L) and CLSI 2022 breakpoints (≤1/—/— mg/L).
- β-lactam/β-lactamase inhibitor (BL/BLI) combinations tested included imipenem-relebactam, meropenem-vaborbactam, ceftazidime-avibactam, and ceftolozane-tazobactam.
- Carbapenem-resistant *Enterobacterales* (CRE, nonsusceptible to imipenem and/or meropenem) and extensively drug resistant (XDR, susceptible to only 1 or 2 drug classes) phenotype isolates also were analyzed (Magiorakos, et al. 2012).

Results

- The most common GN organism isolated from PHP was *Pseudomonas aeruginosa* (PSA, 30%), followed by *Klebsiella pneumoniae* (13%) and *Escherichia coli* (10%; Figure 1).
- The % susceptible and $MIC_{50/90}$ values of CFDC and comparators are shown in Table 1 for all organisms and resistant subsets with both CLSI and FDA breakpoints.
- For *Enterobacterales*, all tested drugs had >99%S against all isolates (Table 1, Figure 2).
- CFDC and ceftazidime-avibactam had the highest susceptibility rate of 94.4% against 18 CRE isolates.
  - Meropenem-vaborbactam had 88.9%S while imipenem-relebactam had 83.3%S.
- CFDC was the most active antimicrobial tested against PSA (99.3/98.4%S, CLSI/FDA) and XDR PSA (94.6/93.2%; Table 1, Figure 3).
  - Imipenem-relebactam was the second most active comparator against PSA (97.2%S) and XDR PSA (81.1%).
- CFDC was very potent against *Acinetobacter baumannii-calcoaceticus* complex (ABC) with 97.0/93.1%S (CLSI/FDA). Against XDR, ABC %S was 94.3/88.6% (Table 1 and Figure 4).
  - The other BL/BLI with ABC breakpoints was imipenem-relebactam, and its %S was 59.4% against ABC and 5.7% against XDR ABC.
- CFDC %S for *Stenotrophomonas maltophilia* (SM) was 100.0/97.1% using CLSI 2021 and 2022 breakpoints, respectively (Table 1).

Conclusions

- CFDC was highly active against US GN isolates from PHP, including ABC, CRE, PSA, SM, and XDR isolates.
- These *in vitro* results suggest that CFDC may be an important option for the treatment of PHP caused by GN organisms, particularly for pathogens that have few treatment options.

Acknowledgements

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References

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Figure 1. Top 10 Gram-negative organisms isolated from pneumonia in hospitalized patients

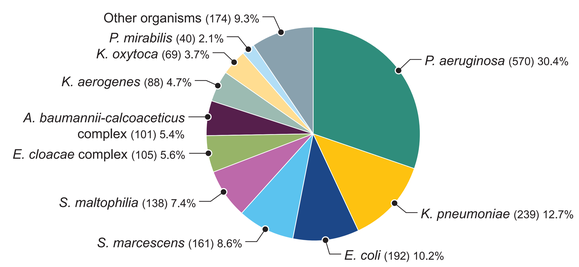
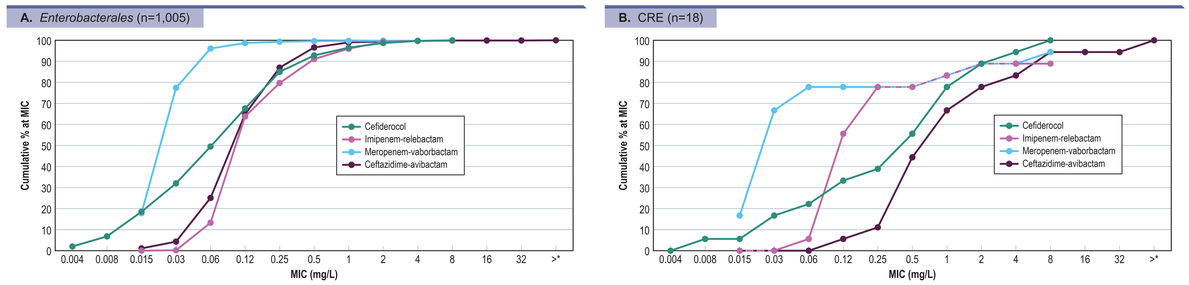
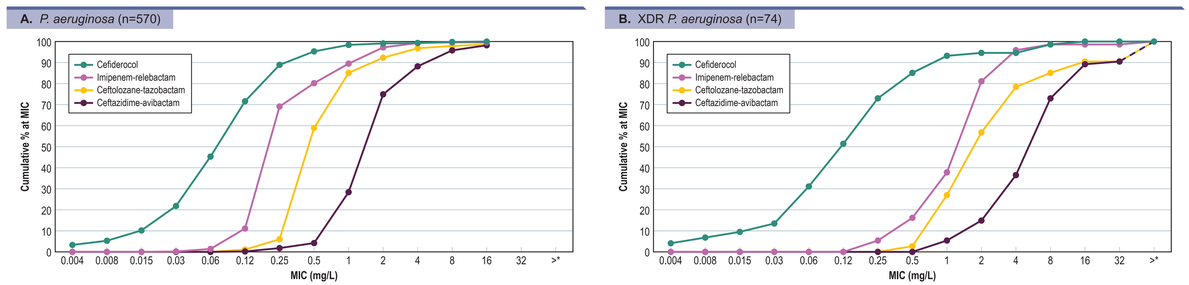


Figure 2. Cumulative MIC distribution of CFDC and comparators against all *Enterobacterales* and CRE



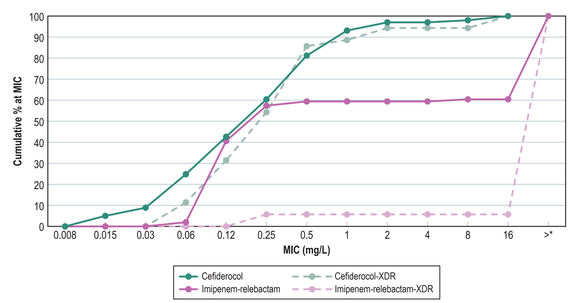
* Greater than highest concentration tested.

Figure 3. Cumulative MIC distribution of CFDC and comparators against *P. aeruginosa* and XDR *P. aeruginosa*



* Greater than highest concentration tested.

Figure 4. Cumulative MIC distribution of CFDC and comparators against all *A. baumannii-calcoaceticus* complex (n=101) and XDR (n=35) isolates



* Greater than highest concentration tested.

Table 1. Susceptibilities of cefiderocol and comparators tested against 1,877 isolates from US patients hospitalized with pneumonia

Organism/Antimicrobial (number of isolates)	mg/L			CLSI/FDA[a]
	MIC_{50}	MIC_{90}	MIC range	%S
Enterobacterales (1,005)				
Cefiderocol	0.12	0.5	≤0.004 to 8	99.7/99.7 [b]
Imipenem-relebactam	0.12	0.5	≤0.03 to >8	99.4 [c]
Meropenem-vaborbactam	0.03	0.06	≤0.015 to >8	99.8
Ceftazidime-avibactam	0.12	0.5	≤0.015 to >32	99.9
CRE (18)				
Cefiderocol	0.5	4	0.008 to 8	94.4/94.4 [b]
Imipenem-relebactam	0.12	>8	0.06 to >8	83.3 [c]
Meropenem-vaborbactam	0.03	8	≤0.015 to >8	88.9
Ceftazidime-avibactam	1	8	0.12 to >32	94.4
P. aeruginosa (570)				
Cefiderocol	0.12	0.5	≤0.004 to 16	99.3/98.4 [b]
Imipenem-relebactam	0.25	2	≤0.03 to >8	97.2
Ceftazidime-avibactam	2	8	0.12 to >32	95.8
Ceftolozane-tazobactam	0.5	2	≤0.12 to >16	96.8
XDR (74)				
Cefiderocol	0.12	1	≤0.004 to 16	94.6/93.2 [b]
Imipenem-relebactam	2	4	0.25 to >8	81.1
Ceftazidime-avibactam	8	32	1 to >32	73
Ceftolozane-tazobactam	2	16	0.5 to >16	78.4
A. baumannii-calcoaceticus complex (101)				
Cefiderocol	0.25	1	0.015 to 16	97.0/93.1 [b]
Imipenem-relebactam	0.25	>8	0.06 to >8	59.4
XDR (35)				
Cefiderocol	0.25	2	0.06 to 16	94.3/88.6 [b]
Imipenem-relebactam	>8	>8	0.25 to >8	5.7
S. maltophilia (138)				
Cefiderocol	0.12	0.5	0.015 to 4	100.0/97.1 [b]
Ceftazidime	>32	>32	2 to >32	10.9
Levofloxacin	1	8	0.12 to 32	79.6
Trimethoprim-sulfamethoxazole	≤0.12	0.5	≤0.12 to >4	99.3

[a] Criteria as published by CLSI and FDA (2021).
[b] CLSI and FDA breakpoints are shown for cefiderocol, see Materials and Methods.
[c] Imipenem-relebactam breakpoints have been applied to all *Enterobacterales* other than *Morganella*, *Proteus*, and *Providencia*