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Cefiderocol Activity against *Pseudomonas aeruginosa*, Including Resistant Subsets and Isolates Carrying Carbapenemase β-lactamase Genes, from United States Hospitals (2020–2023)

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Introduction

- *Pseudomonas aeruginosa* possess various intrinsic treatment-limiting resistance mechanisms, leading to decreased antibiotic permeability.
  - Isolates may acquire β-lactamase genes, such as those encoding class A carbapenemases and especially class B metallo-β-lactamases further decreasing susceptibility to numerous β-lactams.
- Cefiderocol is approved by the US Food and Drug Administration (FDA) for the treatment of complicated urinary tract infections, including pyelonephritis, as well as hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia.
- Cefiderocol is a siderophore cephalosporin with broad activity against Gram-negative bacteria, including multidrug-resistant (MDR) organisms like carbapenem-resistant Enterobacterales (CRE), carbapenem-resistant *Pseudomonas aeruginosa*, and *Acinetobacter baumannii*.
- In this study, the activities of cefiderocol and comparator agents were evaluated against *P. aeruginosa* causing infections in US hospitals, including resistant subsets, as part of the SENTRY Antimicrobial Surveillance Program during 2020–2023.

Materials and Methods

Bacterial organisms

- This study comprised a collection of 4,400 *P. aeruginosa* cultured from various clinical specimens in patients hospitalized in 38 medical centers in all 9 US Census Divisions during 2020–2023. Only consecutive isolates (1 per patient infection episode) responsible for documented infections according to local criteria were included.
- Bacterial identification was confirmed by standard algorithms supported by matrix-assisted laser desorption ionization-time of flight mass spectrometry (Bruker Daltonics, Bremen, Germany).

Susceptibility testing

- Isolates were tested for susceptibility by broth microdilution following the Clinical and Laboratory Standards Institute (CLSI) M07 (2018) guidelines.
- Frozen-form broth microdilution panels were manufactured by Element Iowa City (JMI Laboratories) (North Liberty, IA, USA) and contained cation-adjusted Mueller-Hinton broth for comparator agents.
- Susceptibility testing for cefiderocol used broth microdilution panels containing iron-depleted media per CLSI guidelines.
- Quality assurance was performed by sterility checks, colony counts, and testing CLSI-recommended quality control reference strains.
- Cefiderocol MIC results were interpreted according to the CLSI and FDA criteria, whereas comparator agent MIC values were interpreted based on CLSI breakpoints.
- Carbapenem-nonsusceptible isolates were those nonsusceptible to imipenem and/or meropenem based on CLSI criteria (MIC, ≥4 mg/L). MDR was classified as nonsusceptible to ≥3 drug classes using CLSI breakpoints; extensively drug-resistant (XDR) was defined as nonsusceptible to all but 2 or fewer drug classes using CLSI breakpoints.

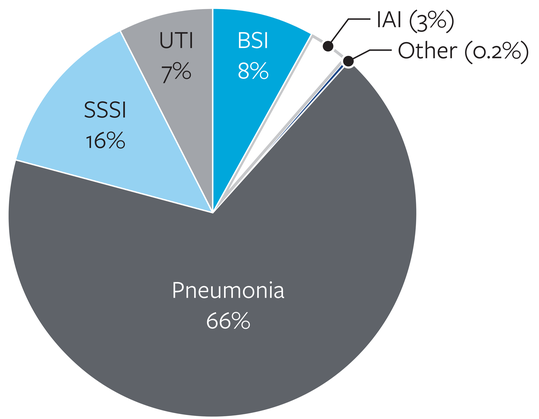
Screening of β-lactamase genes

- Selected isolates had total genomic DNA extracted by the fully automated Thermo Scientific™ KingFisher™ Flex Magnetic Particle Processor (Cleveland, OH, USA), which was used as input material for library construction.
- DNA libraries were prepared using the Nextera™ or Illumina DNA Prep™ library construction protocol (Illumina, San Diego, CA, USA) following the manufacturer's instructions and were sequenced on MiSeq or NextSeq Sequencer platforms at JMI Laboratories.
- FASTQ format sequencing files for each sample set were assembled independently using *de novo* assembler SPAdes 3.15.3. An in-house software was applied to align the assembled sequences against a comprehensive in-house database containing known β-lactamase genes.

Results

- A total of 14.6% (643/4,400) and 4.7% (206/4,400) *P. aeruginosa* isolates were categorized as MDR and XDR, respectively (Table 1).
  - In addition, 22.3% (980/4,400) *P. aeruginosa* were carbapenem-nonsusceptible, and 99.1% (971/980) were carbapenemase-negative.
  - Most carbapenem-nonsusceptible *P. aeruginosa* originated from pneumonia patients, whereas smaller percentages were from skin and skin-structure infections (16%), bloodstream infections (8%), and urinary tract infections (7%) (Figure 1).
- Cefiderocol and β-lactam/β-lactamase inhibitor (BL/BLI) combinations showed susceptibilities of >96% against all *P. aeruginosa*, except for piperacillin-tazobactam (79.9% susceptible) (Table 1).
- Cefiderocol (90.8–99.4% susceptible) showed MIC_{50} of 0.12 mg/L and MIC_{90} of 0.5–1 mg/L against MDR, XDR, and carbapenem-nonsusceptible isolates (Table 1).
  - BL/BLI combinations showed various lower degrees of susceptibilities (2.9–84.1% susceptible) against the MDR and XDR subsets.
  - Imipenem-relebactam, ceftazidime-avibactam, and ceftolozane-tazobactam showed susceptibilities of 86.9–90.2% against carbapenem-nonsusceptible *P. aeruginosa*.
  - Piperacillin-tazobactam inhibited 49.7% of carbapenem-nonsusceptible isolates at the CLSI breakpoint for susceptibility.
- Cefiderocol (100% susceptible) inhibited all *P. aeruginosa* carrying carbapenemases at ≤2 mg/L (Table 1).
  - Other comparators showed susceptibilities of <34% against *P. aeruginosa* carrying carbapenemases.
- Cefiderocol ($MIC_{50/90}$, 0.12/0.5 mg/L; 96.8–99.4% susceptible), imipenem-relebactam ($MIC_{50/90}$, 1/2 mg/L; 90.0% susceptible), and ceftolozane-tazobactam ($MIC_{50/90}$, 1/4 mg/L; 90.9% susceptible) were the most active agents against carbapenem-nonsusceptible *P. aeruginosa* without carbapenemase genes (Table 1).
  - Ceftazidime-avibactam (87.4% susceptible) showed a marginal and lower activity against this subset.

Figure 1. Distribution of infection types[a] caused by carbapenem-nonsusceptible *P. aeruginosa*



[a] BSI, bloodstream infections; SSSI, skin and skin structure infections; and UTI, urinary tract infections.

Table 1. Activity of cefiderocol and β-lactam-β-lactamase inhibitor combinations against *P. aeruginosa* and resistant subsets from the USA

Phenotype/genotype[a] (No. tested)	MIC_{50}/MIC_{90} in mg/L (% susceptible by CLSI/FDA criteria)[b]					
	FDC	IMR	CZA	C/T	P/T	MER
All (4,400)	0.12/0.25 (99.9/98.5)	0.25/1 (97.6)	2/4 (96.7)	0.5/2 (97.4)	4/128 (79.9)	0.5/8 (81.1)
MDR (643)	0.12/0.5 (99.1/95.0)	1/4 (84.1)	8/16 (78.1)	2/16 (83.8)	128/>128 (11.4)	8/32 (17.9)
XDR (206)	0.12/1 (98.5/90.8)	2/8 (56.3)	8/>32 (62.1)	4/>16 (69.9)	128/>128 (2.9)	16/32 (1.9)
Carbapenem-nonS (980)	0.12/0.5 (99.4/96.6)	1/4 (89.5)	4/16 (86.9)	1/4 (90.2)	32/>128 (49.7)	8/32 (15.7)
Carbapenemase-positive[c] (9)	0.12/— (100/77.8)	>8/— (33.3)	16/— (33.3)	>16/— (11.1)	128/— (22.2)	>32/— (0.0)
Carbapenemase-negative (971)	0.12/0.5 (99.4/96.8)	1/2 (90.0)	4/16 (87.4)	1/4 (90.9)	16/>128 (50.0)	8/32 (15.9)

Abbreviations: FDC, cefiderocol; IMR, imipenem-relebactam; CZA, ceftazidime-avibactam; C/T, ceftolozane-tazobactam; P/T, piperacillin-tazobactam; MER, meropenem.
[a] Carbapenem-nonS, isolates nonsusceptible to imipenem and/or meropenem based on CLSI criteria (MIC values ≥4 mg/L); MDR, multidrug-resistant isolates classified as nonsusceptible to ≥3 drug classes using CLSI breakpoints; XDR, extensively drug-resistant, defined as nonsusceptible to all but 2 or fewer drug classes using CLSI breakpoints.
[b] Cefiderocol MIC results were interpreted according to the CLSI/FDA criteria, whereas comparator agent MIC values were interpreted based on CLSI criteria.
[c] Includes bla_{KPC-2} (1), bla_{NDM-1} (1), bla_{NDM-12} (1), bla_{NDM-7} (1), bla_{OXA-1} (2), and bla_{VIM-2} (3).

Conclusions

- Cefiderocol showed potent activity against *P. aeruginosa* clinical isolates from US hospitals, including resistant subsets, and carbapenem-nonsusceptible isolates with or without carbapenemase genes.
- These data demonstrated cefiderocol *in vitro* activity against *P. aeruginosa* resistant subsets, for which antibiotic treatment options are limited.

Acknowledgements

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