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Cefiderocol Activity Against Multidrug-resistant and Molecularly Characterized *Pseudomonas aeruginosa* and *Acinetobacter baumannii-calcoaceticus* complex Clinical Isolates Causing Infection in United States Hospitals (2020–2022)

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SENTRY ANTIMICROBIAL SURVEILLANCE

Introduction

- *Pseudomonas aeruginosa* and *Acinetobacter baumannii-calcoaceticus* complex, particularly multidrug-resistant (MDR) organisms, can cause serious nosocomial infections, especially in intensive care unit patients.
  - These pathogens may be resistant to many clinically available antimicrobial agents and bring therapeutic challenges.
- Cefiderocol is a siderophore-conjugated cephalosporin with broad activity against aerobic, Gram-negative bacteria. This new cephalosporin utilizes the bacterial iron transport systems to gain access to the periplasmic space and reach its targets, the penicillin-binding proteins.
- This siderophore cephalosporin possesses broad activity against Gram-negative bacteria, including multidrug-resistant (MDR) organisms like carbapenem-resistant Enterobacterales, carbapenem-resistant *P. aeruginosa*, and *A. baumannii*.
- This study evaluated the activities of cefiderocol and comparator agents against resistant and molecularly characterized *A. baumannii-calcoaceticus* complex and *P. aeruginosa* recovered from hospitalized patients in US centers as part of the SENTRY Antimicrobial Surveillance Program.

Materials and Methods

Bacterial organisms

- This study comprised a collection of 3,384 *P. aeruginosa* and 1,186 *Acinetobacter* spp. (980 *A. baumannii-calcoaceticus* complex) consecutively collected from 64 US sites in all 9 Census Divisions during 2020–2022.
- 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 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.
- MIC interpretations were performed using CLSI and FDA breakpoints for cefiderocol and CLSI criteria for comparators, with the exception that EUCAST breakpoints for meropenem-vaborbactam were used for *P. aeruginosa* and EUCAST breakpoints for imipenem-relebactam were used for *Acinetobacter* spp.
- *P. aeruginosa* and *A. baumannii* isolates with imipenem and/or meropenem MICs ≥4 mg/L or ceftazidime and/or cefepime MICs ≥16 mg/L were subjected to next-generation genome sequencing for the screening of acquired β-lactamase genes, including carbapenemases. Isolates were classified as MDR when a resistance phenotype was observed to ≥3 classes of agents.

Screening of β-lactamase genes

- Selected isolates had total genomic DNA extracted by the 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™ library construction protocol (Illumina, San Diego, CA, USA) following the manufacturer's instructions and were sequenced on Illumina 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 31.3% (1,058/3,384) of *P. aeruginosa* met the MIC criteria for screening of β-lactamase genes, of which 37.2% (394/1,058) were resistant to cephalosporins (ceftazidime and/or cefepime) and carbapenems (meropenem and/or imipenem). In addition, 14.7% (497/3,384) showed an MDR phenotype (Table 1).
  - A small proportion of *P. aeruginosa* (0.9%; 10/1,058) carried acquired carbapenemase genes, which were comprised by class A serine (2) and class B metallo (8) carbapenemases (Table 1).
- Cefiderocol had similar activities against *P. aeruginosa* that did not meet ($MIC_{50/90}$, 0.06/0.25 mg/L) and did meet ($MIC_{50/90}$, 0.12/0.5 mg/L) the MIC screening criteria, as well as against the MDR subset or those isolates resistant to both cephalosporins (ceftazidime and/or cefepime) and carbapenems (meropenem or imipenem) ($MIC_{50/90}$, 0.12/1 mg/L).
- Cefiderocol (99.4% susceptible), imipenem-relebactam (91.7% susceptible), ceftazidime-avibactam (89.0% susceptible) and ceftolozane-tazobactam (91.9% susceptible) were the most active agents tested against *P. aeruginosa* that met the MIC screening criteria (Table 1).
  - Cefiderocol (98.8% susceptible) had the greatest activity against the MDR and cephalosporin-carbapenem-resistant subsets of *P. aeruginosa*, whereas other agents tested showed susceptibility results <85% (Table 1).
- Among *Acinetobacter* spp., 39.0% (463/1,186) of isolates met the MIC screening criteria, of which 61.3% (284/463) were cephalosporin-carbapenem-resistant. In addition, 30.6% (363/1,186) had an MDR phenotype (Table 1) .
  - 60.3% (279/463) of isolates carried acquired carbapenemase genes (all *A. baumannii-calcoaceticus* complex).
- MIC_{90} values of 1-2 mg/L were obtained for cefiderocol against *Acinetobacter* spp. in general and its subsets (Table 1).
- Only cefiderocol ($MIC_{50/90}$, 0.25–0.5/1-2 mg/L) was active against *Acinetobacter* spp. that met the MIC screening criteria, including all subsets (Table 1).

Table 1. The activity of cefiderocol and comparator agents against *P. aeruginosa* and *Acinetobacter* spp., including resistant subsets, from the USA

Organism	MIC_{50}/MIC_{90} in µg/mL (% susceptible by FDA/CLSI)[b]					
Phenotype/genotype[a] (No. tested)	**Cefiderocol**	**Imipenem-relebactam**	**Meropenem-vaborbactam**	**Meropenem**	**Ceftazidime-avibactam**	**Ceftolozane-tazobactam**
P. aeruginosa (3,384)	0.12/0.25 (98.5/99.8)	0.25/1 (97.4)	0.5/8 (91.1)	0.5/8 (80.2)	2/8 (96.5)	0.5/2 (97.5)
MIC screen-positive[a] (1,058)	0.12/0.5 (96.4/99.4)	0.5/2 (91.7)	4/>8 (71.7)	4/32 (36.8)	4/16 (89.0)	1/1 (91.9)
Cephalosporin-carbapenem-R[a] (394)	0.12/1 (93.7/98.5)	1/4 (80.7)	>8/>8 (45.9)	16/32 (3.3)	8/32 (73.4)	2/16 (80.5)
Carbapenemase-positive[c] (10)	0.12/2 (80.0/100)	>8/>8 (30.0)	>8/>8 (20.0)	32/>32 (0.0)	16/>32 (30.0)	>16/>16 (10.0)
MDR (497)	0.12/1 (94.8/98.8)	1/4 (84.1)	8/>8 (52.7)	8/32 (16.7)	8/16 (77.3)	2/8 (83.9)
	Cefiderocol	**Imipenem-relabactam**	**Colistin**	**Meropenem**	**Ceftazidime**	**Ampicillin-sulbactam**
Acinetobacter spp. (1,186)	0.12/1 (94.0/98.7)	0.25/>8 (76.1)	0.5/1 (-)	0.5/>32 (75.1)	8/>32 (69.4)	4/32 (72.8)
MIC screen-positive[a] (463)	0.25/2 (86.4/96.8)	>8/>8 (38.7)	0.5/1 (-)	32/>32 (36.3)	>32/>32 (21.6)	32/64 (35.0)
Cephalosporin-carbapenem-R[a] (284)	0.5/2 (84.2/96.1)	>8/>8 (3.2)	>8/>8 (-)	>32/>32 (0.4)	>32/>32 (16.9)	32/>64 (12.3)
Carbapenemase[d] (279)	0.25/2 (87.5/97.5)	>8/>8 (9.0)	0.5/1 (-)	>32/>32 (8.2)	>32/>32 (23.7)	32/>64 (12.5)
OXA-23 (149)	0.25/2 (84.6/97.3)	>8/>8 (1.3)	0.5/2 (-)	>32/>32 (1.3)	>32/>32 (16.8)	32/>64 (2.7)
OXA-24 (93)	0.25/1 (93.5/98.9)	>8/>8 (0.0)	0.5/1 (-)	>32/>32 (0.0)	>32/>32 (25.8)	32/>64 (11.8)
Other[e] (37)	0.25/2 (83.8/94.6)	0.25/>8 (62.2)	0.5/1 (-)	1/>32 (56.8)	16/>32 (45.9)	8/>64 (54.1)
Non-carbapenemase[f] (184)	0.25/2 (84.9/95.7)	0.25/8 (83.8)	0.5/2 (-)	0.5/16 (78.9)	32/>32 (18.4)	8/32 (69.2)
MDR (363)	0.25/2 (84.8/96.1)	>8/>8 (22.0)	0.5/1 (-)	>32/>32 (19.6)	>32/>32 (18.7)	32/>64 (18.5)

Abbreviations: MDR, multidrug resistant isolate (resistant to ≥3 classes); "—", susceptible breakpoint not available.
[a] MIC screen-positive includes isolates with imipenem and/or meropenem MIC values ≥4 µg/mL and/or ceftazidime and/or cefepime MIC values ≥16 µg/mL. Cephalosporin-carbapenem-R represents those isolates that showed a resistance phenotype to both imipenem and/or meropenem (MIC, ≥4 µg/mL) and ceftazidime and/or cefepime MIC values ≥16 µg/mL.
[b] MIC interpretations were performed using CLSI breakpoints for cefiderocol and comparators, with the exception that EUCAST breakpoints for meropenem-vaborbactam were used for *P. aeruginosa* and EUCAST breakpoints for imipenem-relebactam were used for *Acinetobacter* spp.
[c] Includes the following acquired-carbapenemase genes: bla_{VIM-2} (4), bla_{IMP-1} (2), bla_{NDM-1} (2), bla_{GES-5} (1), bla_{GES-1} (1), bla_{IMP-13} (1), and bla_{KPC-2} (1).
[d] All *A. baumannii*-calcoaceticus complex where acquired carbapenemase genes were detected.
[e] Includes $bla_{OXA-217}$-like (21 isolates), bla_{OXA-23} and bla_{OXA-24} (6), $bla_{OXA-136}$ (4), bla_{OXA-23} and bla_{NDM-1} (1), bla_{OXA-58} and bla_{NDM-1} (1), $bla_{OXA-217}$-like and bla_{OXA-72} (1), $bla_{OXA-229}$-like (1), bla_{OXA-23} and bla_{OXA-72} (1), and bla_{OXA-23} and bla_{PER-1} (1).
[f] Isolates where acquired carbapenemase genes were not detected.

Conclusions

- Many *P. aeruginosa* (31.3%) met the MIC screening criteria but few had acquired carbapenemase genes (0.9%).
- Many *Acinetobacter* spp. (39.0%) met the MIC screening criteria, as well as showed a multidrug resistance phenotype (30.6%).
  - In contrast to the *P. aeruginosa* isolates, the presence of carbapenemase genes was high among *Acinetobacter* spp.
- Cefiderocol showed potent *in vitro* activity against *P. aeruginosa* and *Acinetobacter* spp. causing infections in US hospitals, including across resistant and molecularly characterized subsets, for which treatment options are limited.

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