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Cefiderocol *In Vitro* Activity Against Molecularly Characterized *Acinetobacter baumannii-calcoaceticus* complex and *Pseudomonas aeruginosa* Clinical Isolates Causing Infection in Europe and Adjacent Regions (2020–2021)

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Introduction

- Multidrug-resistant (MDR) *Pseudomonas aeruginosa* and *Acinetobacter baumannii-calcoaceticus* complex (*A. baumannii*) cause serious nosocomial infections, especially in intensive care unit patients.
  - These pathogens may be resistant to many clinically available antimicrobial agents, generating therapeutic challenges.
- Cefiderocol is a siderophore-conjugated cephalosporin with broad activity against aerobic, Gram-negative bacteria, including carbapenem-resistant Enterobacterales (CRE), carbapenem-resistant *P. aeruginosa*, and *A. baumannii.*
  - This cephalosporin utilizes the bacterial iron transport system to gain access to the periplasmic space to reach its targets.
- This study evaluated the activities of cefiderocol and comparator agents against resistant and molecularly characterized *A. baumannii* and *P. aeruginosa* recovered from hospitalised patients as part of the SENTRY Antimicrobial Surveillance Program for Europe and surrounding regions.

Materials and Methods

Bacterial organisms

- This study included a collection of 2,435 *P. aeruginosa* and 931 *Acinetobacter* spp. (855 *A. baumannii-calcoaceticus* and 76 isolates from 13 other species) consecutively collected from 26 centres in Europe, Israel, and Turkey during 2020–2021.
- 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. Cefiderocol used iron-depleted media.

Screening of β-lactamase genes

- *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 *in silico* screening of acquired, known β-lactamase genes.

Results

P. aeruginosa

- A total of 34.7% (845/2,435) *P. aeruginosa* were molecularly screened for β-lactamase genes, and carbapenemase genes were detected in 8.0% (68/845) of these isolates (Table 1).
  - The vast majority of carbapenemase genes were represented by class B genes (73.5%; 50/68), and 1 strain carried both carbapenemases bla_{VIM-2} and bla_{GES-5}.
  - Class A carbapenemases were present in 26.5% (18/68) of isolates, represented by bla_{GES-5} (14) and bla_{GES-6} (4).
- Cefiderocol (98.3–99.9% susceptible) had similar MIC_{50} (0.06–0.12 mg/L) and MIC_{90} (0.25–0.5 mg/L) results against the molecularly characterised and non-characterised *P. aeruginosa* (Table 1).
- Comparator agents had lower activity (35.9–88.8% susceptible) against molecularly characterised *P. aeruginosa* (Table 2).
- Cefiderocol ($MIC_{50/90}$, 0.12–0.25/1–2 mg/L; 94.0–100% susceptible) was the most active agent against subsets of *P. aeruginosa* that carried acquired ESBL, carbapenemase, and/or MBL genes (Table 1).
- Among *P. aeruginosa* without acquired β-lactamase genes, cefiderocol, imipenem-relebactam, ceftazidime-avibactam, and ceftolozane-tazobactam had susceptibilities of 93.2–99.3% (Table 2).
  - Lower percentages of susceptibility were noted for meropenem-vaborbactam (78.6%) and meropenem (39.1%) (Table 2).

***Acinetobacter* spp.**

- A total of 71.8% (614/855) of *A. baumannii* met the molecular screening criteria.
  - Acquired bla_{OXA-23} and bla_{OXA-24} were detected alone in 89.6% (550/614) of these isolates, and each were present in 73.8% (453/614) and 15.8% (97/614) of isolates, respectively (Table 1).
  - Class B carbapenemases (i.e., bla_{NDM-1}) were detected in only 1.1% (7/614) of screened *A. baumannii* (Table 1).
- Cefiderocol had the lowest MIC_{50} and MIC_{90} values against the non-molecularly characterised ($MIC_{50/90}$, 0.06/0.25 mg/L) and molecularly characterised ($MIC_{50/90}$, 0.25/1 mg/L) *A. baumannii* populations (Table 1).
- Ampicillin-sulbactam was only active (99.2% susceptible) against non-molecularly characterised *A. baumannii* (Table 2).
- Cefiderocol was the most active agent against *A. baumannii* carrying bla_{OXA-23} ($MIC_{50/90}$, 0.25/1 mg/L) and bla_{OXA-24} ($MIC_{50/90}$, 0.25/1 mg/L), whereas colistin ($MIC_{50/90}$, 0.5/1 mg/L) had the highest susceptibility against a subset carrying other genes (Table 2).
- Cefiderocol ($MIC_{50/90}$, 0.25/1 mg/L) and imipenem-relebactam ($MIC_{50/90}$, 0.25/0.5 mg/L) had the lowest MIC values against *A. baumannii* without acquired carbapenemases (Table 2).

Table 1. MIC distribution of cefiderocol obtained against *P. aeruginosa*, *A. baumannii*, and resistant subsets from Europe and adjacent regions

Organism/ Group (no. of isolates)	No. and cumulative % of isolates inhibited at MIC (mg/L) of:														MIC$_{50}$	MIC$_{90}$
	≤0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	>16		
P. aeruginosa (2,435)	61 (2.5)	51 (4.6)	89 (8.3)	323 (21.5)	641 (47.8)	719 (77.4)	347 (91.6)	119 (96.5)	54 (98.7)	16 (99.4)	8 (99.7)	3 (99.8)	2 (99.9)	4 (100)	0.12	0.25
MIC screen-negative (1,590) [a]	44 (2.8)	32 (4.8)	66 (8.9)	250 (24.7)	445 (52.6)	464 (81.8)	206 (94.8)	62 (98.7)	20 (99.9)	0 (99.9)	0 (99.9)	1 (100.0)			0.06	0.25
MIC screen-positive (845) [b]	17 (2.0)	19 (4.3)	23 (7.0)	73 (15.6)	196 (38.8)	255 (69.0)	141 (85.7)	57 (92.4)	34 (96.4)	16 (98.3)	8 (99.3)	2 (99.5)	2 (99.8)	2 (100)	0.12	0.5
Class A ESBL/ Carbapenemase (28) [c]					7 (25.0)	13 (71.4)	2 (78.6)	3 (89.3)	3 (100.0)						0.12	1
Class B Carbapenemase (50) [d]	1 (2.0)	0 (2.0)	0 (2.0)	3 (8.0)	4 (16.0)	15 (46.0)	9 (64.0)	5 (74.0)	5 (84.0)	5 (94.0)	2 (98.0)	1 (100.0)			0.25	2
Negative (767) [e]	16 (2.1)	19 (4.6)	23 (7.6)	70 (16.7)	185 (40.8)	227 (70.4)	130 (87.4)	49 (93.7)	26 (97.1)	11 (98.6)	6 (99.3)	1 (99.5)	2 (99.7)	2 (100)	0.12	0.5
Acinetobacter spp. (931) [f]		2 (0.2)	28 (3.2)	95 (13.4)	141 (28.6)	198 (49.8)	175 (68.6)	151 (84.9)	79 (93.3)	30 (96.6)	16 (98.3)	6 (98.9)	5 (99.5)	5 (100)	0.25	1
Non-*A. baumannii-calcoaceticus* complex (76) [g]			5 (6.6)	20 (32.9)	17 (55.3)	19 (80.3)	5 (86.8)	5 (93.4)	2 (96.1)	3 (100)					0.06	0.5
MIC screen-negative (241) [a]		2 (0.8)	22 (10.0)	69 (38.6)	77 (70.5)	37 (85.9)	20 (94.2)	9 (97.9)	3 (99.2)	1 (99.6)	0 (99.6)	1 (100.0)			0.06	0.25
MIC screen-positive (614) [b]			1 (0.2)	6 (1.1)	47 (8.8)	142 (31.9)	150 (56.4)	137 (78.7)	74 (90.7)	26 (95.0)	16 (97.6)	5 (98.4)	5 (99.2)	5 (100)	0.25	1
OXA-23-group (453)				2 (0.4)	36 (8.4)	112 (33.1)	107 (56.7)	103 (79.5)	55 (91.6)	17 (95.4)	11 (97.8)	3 (98.5)	4 (99.3)	3 (100)	0.25	1
OXA-24-group (97)				1 (1.0)	5 (6.2)	18 (24.7)	26 (51.5)	26 (78.4)	13 (91.8)	7 (99.0)	1 (100.0)				0.25	1
Other (39) [h]			1 (2.6)	2 (7.7)	2 (12.8)	5 (25.6)	12 (56.4)	5 (69.2)	2 (74.4)	2 (79.5)	4 (89.7)	2 (94.9)	0 (94.9)	2 (100)	0.25	8
Negative (25) [e]				1 (4.0)	4 (20.0)	7 (48.0)	5 (68.0)	3 (80.0)	4 (96.0)	0 (96.0)	0 (96.0)	0 (96.0)	1 (100.0)		0.25	1

[a] MIC screen negative includes isolates with imipenem and meropenem MIC values ≤2 mg/L and ceftazidime and cefepime MIC values ≤8 mg/L.
[b] MIC screen positive includes isolates with imipenem and/or meropenem MIC values ≥4 mg/L and/or ceftazidime and/or cefepime MIC values ≥16 mg/L.
[c] Includes bla_{GES-1} (3), bla_{GES-5} (14), bla_{GES-6} (4), bla_{PER-1} (1), and bla_{VEB-9} (6).
[d] Includes bla_{FIM-1} (1), bla_{IMP-7} (3), bla_{IMP-13} (3), bla_{NDM-1} (3), bla_{VIM-1} (6), bla_{VIM-2} (27), bla_{VIM-2}/bla_{GES-5} (1), bla_{VIM-4} (4), bla_{VIM-20} (1), and bla_{VIM-43} (1).
[e] Includes isolates in which acquired β-lactamases were not detected.
[f] Includes *A. baumannii-calcoaceticus* complex (855), *A. berezinae* (8), *A. courvalinii* (1), *A. gerneri* (1), *A. gyllenbergii* (1), *A. haemolyticus* (1), *A. johnsonii* (8), *A. junii* (15), *A. lwoffii* (4), *A. proteolyticus* (2), *A. radioresistens* (7), *A. soli* (2), *A. ursingii* (21), *A. vivianii* (2), and unspeciated *Acinetobacter* (3).
[g] Includes non-*A. baumannii-calcoaceticus* complex isolates (76) outlined in footnote (f); no isolates qualified for molecular characterization per the MIC criteria.
[h] Includes bla_{NDM-1} (1), bla_{NDM-1}/bla_{OXA-23} (6), $bla_{OXA-213}$-like (16), bla_{OXA-23}/bla_{OA-58} (9), bla_{OXA-23}/bla_{OXA-72} (4), bla_{OXA-24}/bla_{GES-22} (1), and bla_{PER-7}/bla_{OXA-23} (2).

Table 2. Antimicrobial susceptibility of cefiderocol and main comparator agents against *P. aeruginosa*, *A. baumannii*, and resistant subsets from Europe and adjacent regions

Phenotype/genotype (No. isolates)	MIC$_{50}$/MIC$_{90}$ in mg/L (% susceptible by EUCAST/CLSI criteria)[a]					
	CFDC	IMR	MEV	MER	CZA	CT
P. aeruginosa (2,435)	0.12/0.25 (99.4/99.7)	0.25/1 (94.9)	0.5/8 (90.4)	0.5/8 (77.7)	2/4 (96.1)	0.5/2 (94.7)
MIC screen-negative (1,590) [b]	0.06/0.25 (99.9/99.9)	0.25/0.25 (100)	0.25/1 (100)	0.25/1 (100)	2/2 (100)	0.5/1 (99.9)
MIC screen-positive (845) [c]	0.12/0.5 (98.3/99.3)	1/4 (85.3)	4/>8 (72.3)	4/32 (35.9)	4/16 (88.8)	1/16 (84.9)
Class A ESBL/ Carbapenemase (28) [d]	0.12/1 (100/100)	8/>8 (17.9)	>8/>8 (7.1)	>32/>32 (7.1)	4/32 (71.4)	16/>16 (0.0)
Class B Carbapenemase (50) [e]	0.25/2 (94.0/98.0)	>8/>8 (2.0)	>8/>8 (12.0)	>32/>32 (2.0)	32/>32 (8.0)	>16/>16 (2.0)
Negative (767) [f]	0.12/0.5 (98.6/99.3)	1/2 (93.2)	4/>8 (78.6)	4/16 (39.1)	2/8 (94.8)	1/4 (93.3)
	CFDC	**IMR**	**COL**	**MER**	**CZA**	**A/S**
Acinetobacter spp. (931) [g]	0.25/1 (96.6/98.3)	>8/>8 (37.9)	0.5/>8 (83.4)	>32/>32 (37.9)	32/>32 (33.1)	32/>64 (37.5)
Non-*A. baumannii-calcoaceticus* complex (76) [h]	0.06/0.5 (100/100)	0.06/0.5 (97.4)	0.25/4 (86.8)	0.25/1 (97.4)	4/16 (78.9)	1/4 (94.7)
MIC screen-negative (241) [b]	0.06/0.25 (99.6/99.6)	0.12/0.25 (100)	0.5/1 (98.8)	0.25/1 (100)	4/16 (85.1)	2/4 (99.2)
MIC screen-positive (614) [c]	0.25/1 (95.0/97.6)	>8/>8 (6.2)	0.5/>8 (76.9)	>32/>32 (6.2)	32/>32 (7.0)	64/>64 (6.4)
OXA-23-group (453)	0.25/1 (95.4/97.8)	>8/>8 (0.0)	0.5/>8 (73.7)	>32/>32 (0.0)	32/>32 (3.3)	64/>64 (0.9)
OXA-24-group (97)	0.25/1 (99.0/100)	>8/>8 (1.0)	0.5/>8 (81.4)	>32/>32 (1.0)	16/32 (15.5)	32/>64 (8.2)
Other (39) [i]	0.25/8 (79.5/89.7)	>8/>8 (33.3)	0.5/1 (92.3)	>32/>32 (33.3)	>32/>32 (10.3)	64/>64 (25.6)
Negative (25) [f]	0.25/1 (96.0/96.0)	0.25/0.5 (96.0)	0.25/2 (92.0)	1/2 (96.0)	16/>32 (36.0)	8/32 (68.0)

CFDC, cefiderocol; IMR, imipenem-relebactam; MEV, meropenem-vaborbactam; MER, meropenem; CZA, ceftazidime-avibactam; CT, ceftolozane-tazobactam; COL, colistin; A/S, ampicillin-sulbactam.
[a] Cefiderocol MIC results were interpreted according to EUCAST (PK/PD breakpoints for *A. baumannii-calcoaceticus* complex)/CLSI criteria, whereas comparator agent MIC results were interpreted only with EUCAST criteria, including PK/PD breakpoints for ceftazidime-avibactam for *A. baumannii-calcoaceticus* complex. The one exception was ampicillin/sulbactam, which used CLSI breakpoints.
[b] MIC screen negative includes isolates with imipenem and meropenem MIC values ≤2 mg/L and ceftazidime and cefepime MIC values ≤8 mg/L.
[c] MIC screen positive includes isolates with imipenem and/or meropenem MIC values ≥4 mg/L and/or ceftazidime and/or cefepime MIC values ≥16 mg/L.
[d] Includes bla_{GES-1} (3), bla_{GES-5} (14), bla_{GES-6} (4), bla_{PER-1} (1), and bla_{VEB-9} (6).
[e] Includes bla_{FIM-1} (1), bla_{IMP-7} (3), bla_{IMP-13} (3), bla_{NDM-1} (3), bla_{VIM-1} (6), bla_{VIM-2} (27), bla_{VIM-2}/bla_{GES-5} (1), bla_{VIM-4} (4), bla_{VIM-20} (1), and bla_{VIM-43} (1).
[f] Includes isolates in which acquired β-lactamases were not detected.
[g] Includes *A. baumannii-calcoaceticus* complex (855), *A. berezinae* (8), *A. courvalinii* (1), *A. gerneri* (1), *A. gyllenbergii* (1), *A. haemolyticus* (1), *A. johnsonii* (8), *A. junii* (15), *A. lwoffii* (4), *A. proteolyticus* (2), *A. radioresistens* (7), *A. soli* (2), *A. ursingii* (21), *A. vivianii* (2), and unspeciated *Acinetobacter* (3).
[h] Includes non-*A. baumannii-calcoaceticus* complex isolates (76) outlined in footnote (g); no isolates qualified for molecular characterization per the MIC criteria.
[i] Includes bla_{NDM-1} (1), bla_{NDM-1}/bla_{OXA-23} (6), $bla_{OXA-213}$-like (16), bla_{OXA-23}/bla_{OXA-58} (9), bla_{OXA-23}/bla_{OXA-72} (4), bla_{OXA-24}/bla_{GES-22} (1), and bla_{PER-7}/bla_{OXA-23} (2).

Conclusions

- Acquired carbapenemase genes remained rare among *P. aeruginosa*, despite a great number of resistant strains that met the criteria for molecular characterization (35%).
- Acquired bla_{OXA} carbapenemases were prevalent among *A. baumannii*, whereas class B carbapenemases were rarely detected in these species.
- Cefiderocol showed potent activity against *P. aeruginosa* and *A. baumannii*, including molecularly characterized resistant subsets against which other treatment options showed limited *in vitro* activity.

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