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

Rodrigo E. Mendes, Timothy B. Doyle, Valerie Kantro, Dee Shortridge, Helio S. Sader, Mariana Castanheira

JMI Laboratories, North Liberty, Iowa, US

Objective

Cefiderocol and comparator activities were analysed against molecularly characterized *A. baumannii-calcoaceticus* complex and *P. aeruginosa* as a part of the SENTRY Antimicrobial Surveillance Program for Europe and surrounding regions.

Methods

- A total of 340 *A. baumannii* and 1,212 *P. aeruginosa* were consecutively collected from 35 medical centres in Europe, Israel, and Turkey during 2020.
- Isolates were tested for susceptibility by broth microdilution method.
  - Cefiderocol was tested with iron-depleted media.
  - MIC interpretation used EUCAST and CLSI breakpoints.
- *A. baumannii* and *P. aeruginosa* with imipenem and/or meropenem MIC ≥4 mg/L or ceftazidime and/or cefepime MIC ≥16 mg/L were subjected to next-generation genome sequencing for screening of acquired extended-spectrum β-lactamase (ESBL) and carbapenemase genes.

Results

Table Activity of cefiderocol and main comparators against *P. aeruginosa* and *A. baumannii* from Europe and adjacent regions, including molecularly characterized clinical isolates

Phenotype/genotype[a] (No. isolates)	MIC_{50}/MIC_{90} in mg/L (% susceptible by EUCAST/CLSI criteria)[b]					
	Cefiderocol	IMR	MEV	MER	CZA	CT
P. aeruginosa						
MIC screen-negative (788)	0.12/0.25 (100/100)	0.25/0.25 (100)	0.25/1 (100)	0.25/1 (100)	2/2 (100)	0.5/1 (99.9)
MIC screen-positive (424)	0.12/0.5 (98.3/99.1)	1/4 (87.5)	4/>8 (71.2)	4/32 (35.4)	4/16 (89.8)	1/16 (85.1)
Carbapenemase[c] (33)	0.12/1 (100/100)	>8/>8 (0.0)	>8/>8 (6.1)	>32/>32 (0.0)	32/>32 (30.3)	>16/>16 (0.0)
A. baumannii						
MIC screen-negative (120)	0.06/0.25 (99.2/99.2)	0.25/0.25 (100)	0.25/1 (100)	0.25/0.5 (100)	4/16 (85.0)	≤0.12/1 (100)
MIC screen-positive (220)	0.5/2 (91.8/96.4)	>8/>8 (3.6)	>8/>8 (4.1)	>32/>32 (3.6)	32/>32 (8.6)	>16/>16 (5.0)
OXA-23-group (164)	0.5/2 (90.2/95.1)	>8/>8 (0.0)	>8/>8 (0.6)	>32/>32 (0.0)	>32/>32 (4.9)	>16/>16 (2.4)
OXA-24-group (45)	0.5/1 (95.6/100)	>8/>8 (0.0)	>8/>8 (0.0)	>32/>32 (0.0)	16/32 (20.0)	16/>16 (4.4)
Other genes[d] (11)	0.25/1 (100/100)	0.25/>8 (72.7)	0.5/>8 (72.7)	1/>32 (72.7)	16/>32 (18.2)	8/>16 (45.5)

[a] MIC screen negative, includes isolates with imipenem and meropenem MIC values ≤2 mg/L, and ceftazidime and cefepime MIC ≤8 mg/L; MIC screen positive, includes isolates with imipenem and/or meropenem MIC values ≥4 mg/L and/or ceftazidime and/or cefepime MIC ≥16 mg/L.

[b] Cefiderocol MIC results were interpreted according to the EUCAST (PK/PD breakpoints for *A. baumannii-calcoaceticus* complex)/CLSI criteria, whereas comparator agent MIC were interpreted based on EUCAST criteria, including PK/PD breakpoints for meropenem-vaborbactam (MEV), ceftazidime-avibactam (CZA) and ceftolozane-tazobactam (CT) for *A. baumannii-calcoaceticus* complex; IMR, imipenem-relebactam.

[c] Includes 16 isolates with bla_{VIM-2}; 8 with bla_{GES-5}; 2 with bla_{IMP-7}; 2 with bla_{VIM-4}; and 1 each of bla_{GES-6}, bla_{VIM-1}, bla_{VIM-20}, bla_{VIM-43} and $bla_{VIM-2/GES-5}$.

[d] Includes other genes detected as follows: 4 isolates with bla_{OXA-51}-like; 5 with $bla_{OXA-213}$-like; and 2 with bla_{OXA-23} and bla_{NDM-1}.

Results

- A total of 35.0% of *P. aeruginosa* met the MIC screening criteria and carbapenemase genes were detected in 7.8% (33/424) of these isolates.
- Cefiderocol (98.3-100% susceptible) had similar MIC_{50} (0.12 mg/L) and MIC_{90} (0.25-0.5 mg/L) values against both susceptible and resistant *P. aeruginosa* populations.
- Other agents had lower activity (35.4-89.8% susceptible) against the resistant population of *P. aeruginosa*.
- Cefiderocol ($MIC_{50/90}$, 0.12/1 mg/L; 100% susceptible) was active against a small subset of *P. aeruginosa* carrying carbapenemase genes. Other agents had limited activity.
- A total of 64.7% (220/340) *A. baumannii* met the MIC screening criteria and acquired bla_{OXA} carbapenemases were detected in 98.2% (216/220) of these isolates.
- Cefiderocol had the lowest MIC_{50} and MIC_{90} values against the susceptible ($MIC_{50/90}$, 0.06/0.25 mg/L) and resistant ($MIC_{50/90}$, 0.5/2 mg/L) populations of *A. baumannii*.
- Imipenem-relebactam, meropenem-vaborbactam, meropenem, and ceftolozane-tazobactam were only active (100% susceptible) against *A. baumannii* that did not meet the MIC criteria for screening of β-lactamase genes.
- Cefiderocol was the only agent active against *A. baumannii* carrying bla_{OXA-23} ($MIC_{50/90}$, 0.5/2 mg/L) and bla_{OXA-24} ($MIC_{50/90}$, 0.5/1 mg/L) as well as against those with other carbapenemases or multiple genes ($MIC_{50/90}$, 0.25/1 mg/L).

Conclusions

- Acquired ESBL and carbapenemase genes remained rare among multidrug-resistant *P. aeruginosa* in Europe and surrounding regions, despite a great number (35%) of strains that met the MIC criteria for screening of β-lactamase genes.
- Acquired *bla*$_{OXA}$ carbapenemase variants were prevalent among *A. baumannii*.
- Cefiderocol showed potent activity against *P. aeruginosa* and *A. baumannii* subsets, where treatment options were limited.
- These data confirm cefiderocol as an important option for the treatment of infections caused by *P. aeruginosa* and *A. baumannii* and the respective resistant subsets.

Acknowledgements

This study was performed at JMI Laboratories and supported by Shionogi & Co. LTD. JMI Laboratories received compensation fees for services in relation to preparing the poster, which was funded by Shionogi & Co. LTD.

Contact

Rodrigo E. Mendes, PhD
rodrigo-mendes@jmilabs.com