➢ Cefiderocol continues to show potent activity against Enterobacterales and non-fermenting clinical isolates from 2019/20.

Update on the comparative *in vitro* activity of cefiderocol and four β-lactam-β-lactamase inhibitor combinations against clinically important Gram-negative pathogens

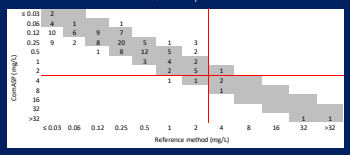
Background

Our previous study showed potent activity of cefiderocol (CID) against clinically relevant Enterobacterales and non-fermenting isolates from 2016/17.[1] The aim of the present study was a follow up investigation of the *in vitro* activity of CID and comparator substances against isolates from 2019/20.

Results

- One third of all isolates was randomly selected for the pretest including *A. baumannii*, n=4; *E. cloacae* complex, n=13; *E. coli*, n=43; *K. pneumoniae*, n=27; *P. aeruginosa*, n=45 and *S. maltophilia*, n=8.
- Overall, the pretest confirmed correlation of both methods (category agreement (CA): 97.9%, essential agreement (EA): 89.5%, Bias: +21.6%) (Figure), with species-related differences.

Figure: Cefiderocol MICs of the pretest of clinical isolates (n=140) using Broth microdilution reference method vs. ComASP plates



- ➢ All species revealed a CA of >95%.
- ➢ EA <90% were observed for *E. cloacae* complex (76.6%; 10/13 isolates) and *A. baumannii* (33.3%; 1/3 isolates).

Table 1: *In vitro* activity of cefiderocol against Gram-negative pathogens study period 2019-20, Germany

Species	n	Numbers of isolates at given MIC (mg/L)												
		≤ 0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	≥ 128
Random sample of isolates (panel I, n=199)														
E. coli	50	1	5	16	16	10	2							
K. pneumoniae	33	2	7	11	10	3								
E. cloacae complex	12			1	4	7								
P. aeruginosa	66	6	8	25	18	6	3							
A. baumannii	6		1	3	2									
S. maltophilia	32		3	18	8	2	1							
Subtotal	199	9	24	74	58	28	6							
Sample of resistant isolates (panel II, n=202) [1]														
E. coli	65			5	23	19	13	2	2	1				
K. pneumoniae	44		3	2	13	13	9	3	1					
E. cloacae complex	19		1	1	3	8	4	2						
P. aeruginosa	66		3	17	26	12	6	1	1					
A. baumannii	8			1	4		1							2
Subtotal	202		7	25	69	52	33	8	4	1				2
Total	**401**	**9**	**31**	**99**	**127**	**80**	**39**	**8**	**4**	**1**				**2**

[1] Panel II comprised ESBL producers, carbapenemase screen-positive isolates and/or colistin-resistant isolates.
The vertical solid line indicates the EUCAST breakpoints for Enterobacterales and *P. aeruginosa* (S ≤ 2 mg/L, R > 2 mg/L).

- CID at ≤2 mg/L inhibited 100% of panel I isolates and 96.5% of panel II isolates (Table 1).
- Susceptibility rates to CID were higher than those to the BL/BLI-combinations in *P. aeruginosa*, but comparable to C/T, CZA and IMR in Enterobacterales (Table 2). In *A. baumannii* and *S. maltophilia* CID revealed lower MIC_{50} and/or MIC_{90} values than the comparators.
- Overall, CID at ≤2 mg/L inhibited 96.3% ESBL-producers, 84.2% carbapenemase-producers, and 95.8% colistin-resistant isolates (Table 3).

Table 2: *In vitro* activity of cefiderocol and four newer BL/BLI-combinations against Gram-negative pathogens stratified by panel of isolates (n=401)

Random sample of isolates (panel I, n=199)					Sample of resistant isolates (panel II, n=202) [1]				
Antibacterial agent	MIC-50 (mg/L)	MIC-90 (mg/L)	Number (%) of isolates S	R	Antibacterial agent	MIC-50 (mg/L)	MIC-90 (mg/L)	Number (%) of isolates S	R
Enterobacterales (n=95) [2]					**Enterobacterales (n=128)** [3]				
CID	0.25	0.5	95 (100.0)	0 (0.0)	CID	0.5	1	124 (96.9)	4 (3.1)
C/T	≤ 0.25	0.5	93 (97.9)	2 (2.1)	C/T	0.5	8	109 (85.2)	19 (14.8)
CZA	≤ 0.25	0.5	95 (100.0)	0 (0.0)	CZA	≤ 0.25	1	127 (99.2)	1 (0.8)
IMR	0.12	0.25	95 (100.0)	0 (0.0)	IMR	0.12	0.25	124 (96.9)	4 (3.1)
MEV	≤ 0.06	≤ 0.06	95 (100.0)	0 (0.0)	MEV	≤ 0.06	≤ 0.06	124 (96.9)	4 (3.1)
***P. aeruginosa* (n=66)**					***P. aeruginosa* (n=66)**				
CID	0.12	0.25	66 (100.0)	0 (0.0)	CID	0.25	1	65 (98.5)	1 (1.5)
C/T	1	4	63 (95.5)	3 (4.5)	C/T	1	≥ 16	53 (80.3)	13 (19.7)
CZA	2	8	64 (97.0)	2 (3.0)	CZA	4	≥ 32	45 (68.2)	21 (31.8)
IMR	0.5	2	64 (97.0)	2 (3.0)	IMR	2	≥ 16	51 (77.3)	15 (22.7)
MEV	0.5	4	63 (95.5)	3 (4.5)	MEV	8	≥ 32	39 (59.1)	27 (40.9)
***A. baumannii* (n=6)**					***A. baumannii* (n=8)**				
CID	0.12	0.25			CID	0.25	≥ 256		
C/T	0.5	≥ 16			C/T	≥ 16	≥ 16		
CZA	4	≥ 32	No EUCAST breakpoints		CZA	≥ 32	≥ 32	No EUCAST breakpoints	
IMR	0.25	≥ 16			IMR	≥ 16	≥ 16		
MEV	0.25	8			MEV	≥ 32	≥ 32		
***S. maltophilia* (n=32)**									
CID	0.12	0.25							
C/T	≥ 16	≥ 16							
CZA	16	≥ 32	No EUCAST breakpoints						
IMR	≥ 16	≥ 16							
MEV	≥ 32	≥ 32							

Abbreviations: S, susceptible; R, resistant; CID, cefiderocol; C/T, ceftolozane-tazobactam; CZA, ceftazidime-avibactam; IMR, imipenem-relebactam; MEV, meropenem-vaborbactam.

[1] See footnote of Table 1 for details.
[2] *Enterobacter cloacae* (n=12), *Escherichia coli* (n=50), *Klebsiella pneumoniae* (n=33)
[3] *Enterobacter cloacae* (n=19), *Escherichia coli* (n=65), *Klebsiella pneumoniae* (n=44)

Table 3: *In vitro* activity of cefiderocol against resistant subgroups of Gram-negative pathogens (panel I plus panel II)

Bacterial group	Numbers of isolates at given MIC (mg/L)												
	≤ 0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	≥ 128
ESBL-producing (n=109) [1]													
CID	2	8	39	32	20	4	3	1					
C/T			**29**	44	16	9	2	4	*5*				
CZA			**89**	11	5	1	1	1		*1*			
IMR	**3**	73	26	3			1	2	*1*				
MEV	**103**	1		1						*4*			
Carbapenemase-producing (n=19) [2]													
CID	2	2	7	4	1		1						2
C/T								2	*17*				
CZA			**1**		3				2	*13*			
IMR				1			1	2	*15*				
MEV	**1**							1		*17*			
Colistin-resistant (n=24) [3]													
CID	1	4	4	7	4	3	1						
C/T			**2**	11	5	1	3	1	*1*				
CZA			**12**	4	1	5			1	*1*			
IMR		7	10	4	1		1		*1*				
MEV	**17**		2	1	1		1		1	*1*			

[1] *E. coli* (CTX-M-1-group, n=45; CTX-M-9-group, n=23; CTX-M-1-group+CTX-M-9-group, n=1; SHV-12, n=1), *K. pneumoniae* (CTX-M-1-group, n=35; CTX-M-9-group, n=4); [2] *A. baumannii* (OXA-23-like, n=7; OXA-23-like(+PER-1), n=2), *K. pneumoniae* (OXA-232, n=3; KPC-2, n=1; NDM-1+OXA-48, n=1), *P. aeruginosa* (IMP-1, n=1; GIM-1, n=1; VIM-2, n=3); [3] *E. cloacae* (n=13), *E. coli* (n=1); *K. pneumoniae* (n=4), *P. aeruginosa* (n=6). Abbreviations: CID, cefiderocol; C/T, ceftolozane-tazobactam; CZA, ceftazidime-avibactam; IMR, imipenem-relebactam; MEV, meropenem-vaborbactam. Numbers in bold include isolates with MIC < value shown; numbers in italic include isolates with MIC > the highest concentration tested.

Methods

Enterobacterales and non-fermenting isolates (n=401) were collected at 22 laboratories in Germany between October 2019 and March 2020. A random sample of respiratory tract and blood isolates (panel I; n=199) and more challenging isolates with certain resistance mechanisms were included (panel II; n=202). MICs were determined by broth microdilution using the ComASP kit from Liofilchem. To confirm reliability of the test kit, a pretest was performed in advance with a subset of isolates (n=140) comparing test device and EUCAST reference method (iron-depleted CAMHB). Resistance genes were confirmed by PCR/Sanger sequencing.[2,3]

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References

1. Wohlfarth E et al., Antibiotics 2023; doi: 10.3390/antibiotics12050864
2. Higgins et al., Antimicrob Agents Chemother 2013, doi: 10.1128/AAC.02413-12
3. Schuster CF et al., J Antimicrob Chemother 2021; https://doi.org/10.1093/jac/dkab407n

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