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Comparative *in-vitro* activity of cefiderocol and four newer beta-lactam/beta-lactamase inhibitor combinations against two panels of clinically important Gram-negative pathogens from Germany

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Disclosures

- The authors declare the following real or perceived conflicts of interest during the last 3 years in relation to this presentation: MK is a partner and CEO of Antiinfectives Intelligence GmbH (AI), a research organisation providing services to pharmaceutical companies; EW is an employee of AI.
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Background & Methods

- Cefiderocol (CFDC), a siderophore cephalosporin, possesses potent activity against Gram-negative bacteria, including all WHO critical pathogens. However, there are few data on the comparative *in-vitro* activity of CFDC and the newer beta-lactam/beta-lactamase inhibitor (BL/BLI) combinations ceftolozane-tazobactam (C/T), ceftazidime-avibactam (CZA), imipenem-relebactam (IMR), and meropenem-vaborbactam (MEV).
- The present study aimed to compare the *in-vitro* activity of cefiderocol and the four BL/BLI combinations against two panels of Gram-negative pathogens collected during the multicentre surveillance study conducted by the Paul Ehrlich Society.
- Isolates (n=312) of *Acinetobacter baumannii* [ABA], *Enterobacter cloacae* complex [ECC], *Escherichia coli* [ECO], *Klebsiella pneumoniae* [KPN], *Pseudomonas aeruginosa* [PAE], and *Stenotrophomonas maltophilia* [SMA]) were collected at 22 laboratories between October 2016 and March 2017. Panel I (n=195) comprised a random sample of respiratory tract and blood isolates, while panel II (n=117) included ESBL producers, carbapenemase (CP) producers and/or colistin-resistant isolates.
- MICs were determined by microdilution and interpreted by EUCAST criteria (v.12.0). Iron-depleted Mueller-Hinton broth was used for cefiderocol. ECO and KPN isolates with an ESBL phenotype, and CP screen-positive isolates of ABA, PAE, ECC, ECO, and KPN were examined for the presence of beta-lactamase genes by PCR.

Results I

Table 1: *In-vitro* activity of cefiderocol against Gram-negative pathogens

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=195)														
E. coli	52	14	12	10	5	9	2							
K. pneumoniae	34	10	7	6	3	7		1						
E. cloacae	25	1	1	3	2	13	3		1				1	
P. aeruginosa	58	4	25	17	1	6	3	1	1					
A. baumannii	9		5	1		3								
S. maltophilia	17	2	9	3		2		1						
Subtotal	195	31	59	40	11	40	8	3	2				1	
Sample of resistant isolates (panel II, n=117) [1]														
E. coli	22	2	3	2		11	4							
K. pneumoniae	15	1	1	4	2	4	3							
E. cloacae	16			2	1	9	1		3					
P. aeruginosa [2]	50	3	12	6	5	13	9	1		1				
A. baumannii	14		6	1	1	4		1				1		
Subtotal	117	6	22	15	9	41	17	2	3	1		1		
Total	**312**	**37**	**81**	**55**	**20**	**81**	**25**	**5**	**5**	**1**		**1**	**1**	

[1] Panel II comprised ESBL producers, carbapenemase screen-positive isolates and/or colistin-resistant isolates. [2] Thirty-two isolates were colistin-resistant wild-type organisms with an MIC of 4 mg/L. The vertical solid line indicates the EUCAST breakpoint.

Among panel I isolates, 15 produced a CTX-M-type ESBL, and 4 produced a CP (ABA, n=2, OXA-23 each; KPN, VIM-1; PAE, NDM-1-like). Of the panel II isolates, 30 produced a CTX-M-type ESBL and 26 a CP (ABA, n=13, OXA-23 [n=11], OXA-58, NDM-1; ECC, OXA-48; KPN, VIM-1; PAE, n=11, GIM [n=2], IMP [n=3], VIM [n=6]). Sixty-four isolates were colistin-resistant, 32 of which were PAE wild-types (MIC 4 mg/L). CFDC at ≤2 mg/L inhibited >98% of panel I isolates and >95% of panel II isolates.

Table 2: *In-vitro* activity of cefiderocol and four newer BL/BLI combinations against Gram-negative pathogens stratified by panel of isolates (n=312)

Random sample of isolates (panel I, n=195)					**Sample of resistant isolates (panel II, n=117) [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=111) [2]					**Enterobacterales (n=53) [3]**				
CFDC	0.12	0.5	109 (98.2)	2 (1.8)	CFDC	0.5	1	50 (94.3)	3 (5.7)
C/T	≤ 0.25	1	103 (92.8)	8 (7.2)	C/T	0.5	≥ 16	41 (77.4)	12 (22.6)
CZA	≤ 0.12	0.5	110 (99.1)	1 (0.9)	CZA	0.25	1	52 (98.1)	1 (1.9)
IMR	0.12	0.5	110 (99.1)	1 (0.9)	IMR	0.12	0,5	52 (98.1)	1 (1.9)
MEV	≤ 0.06	≤ 0.06	110 (99.1)	1 (0.9)	MEV	≤ 0.06	0.12	53 (100)	0 (0)
***P. aeruginosa* (n=58)**					***P. aeruginosa* (n=50) [4]**				
CFDC	0.06	0.5	57 (98.3)	1 (1.7)	CFDC	0.25	1	49 (98.0)	1 (2.0)
C/T	1	4	53 (91.4)	5 (8.6)	C/T	1	≥ 16	35 (70.0)	15 (30.0)
CZA	2	8	55 (94.8)	3 (5.2)	CZA	8	≥ 16	31 (62.0)	19 (38.0)
IMR	0.5	2	56 (96.6)	2 (3.4)	IMR	2	≥ 16	29 (58.0)	21 (42.0)
MEV	1	≥ 16	52 (89.7)	6 (10.3)	MEV	8	≥ 16	25 (50.0)	25 (50.0)
***A. baumannii* (n=9)**					***A. baumannii* (n=14)**				
CFDC	0.06	0.5			CFDC	0.12	2		
C/T	2	≥ 16	No EUCAST breakpoints		C/T	≥ 16	≥ 16	No EUCAST breakpoints	
CZA	≥ 16	≥ 16			CZA	≥ 16	≥ 16		
IMR	0.5	≥ 16	7 (77.8)	2 (22.2)	IMR	≥ 16	≥ 16	1 (7.1)	13 (92.9)
MEV	0.5	≥ 16	No EUCAST breakpoints		MEV	≥ 16	≥ 16	No EUCAST breakpoints	
***S. maltophilia* (n=17)**									
CFDC	0.06	0.5							
C/T	≥ 16	≥ 16							
CZA	≥ 16	≥ 16	No EUCAST breakpoints						
IMR	≥ 16	≥ 16							
MEV	≥ 16	≥ 16							

[1] See footnote of Table 1 for details.
[2] *Enterobacter cloacae* (n=16), *Escherichia coli* (n=22), *Klebsiella pneumoniae* (n=15)
[3] *Enterobacter cloacae* (n=25), *Escherichia coli* (n=52), *Klebsiella pneumoniae* (n=34)
[4] Including 32 wild-type organisms with an MIC of 4 mg/L

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

Susceptibility rates of Enterobacterales to CFDC were comparable to CZA, IMR and MEV, while the susceptibility rates of PAE to CFDC were higher than those to the BL/BLI combinations. CFDC was more active than any BL/BLI combination against ABA and SMA.

Results II & Conclusions

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=45) [1]													
CFDC	3	4	6	4	21	7							
C/T				**2**	25	9	4		2	*3*			
CZA			**14**	20	8	2	1						
IMR			30	11	2	1	1						
MEV		**40**	3				1	1					
Carbapenemase-producing (n=30) [2]													
CFDC	1	6	1	2	12	4	2	1			1		
C/T								2	1	*27*			
CZA						1			1	*28*			
IMR						1			2	*27*			
MEV							1	1	1	*27*			
Colistin-resistant (n=64) [3]													
CFDC	**3**	16	12	5	21	5	1	1					
C/T				**13**	17	20	4	2	1	*7*			
CZA			**8**	8	4	5	22	6	4	*7*			
IMR			9	14	23	5	7		2	*4*			
MEV		**22**	1	6	6	9	5	2	4	*9*			

[1] *E. coli* (n=29), *K. pneumoniae* (n=16); [2] *A. baumannii* (n=15), *E. cloacae* (n=1), *K. pneumoniae* (n=2), *P. aeruginosa* (n=12);
[3] *A. baumannii* (n=2), *E. cloacae* (n=13), *E. coli* (n=4); *K. pneumoniae* (n=4), *P. aeruginosa* (n=41, including 32 wild-type organisms with an MIC of 4 mg/L). Abbreviations: CFDC, 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.

CFDC at ≤2 mg/L inhibited 100% ESBL-producers, 93.3% CP-producers, and 98.4% colistin-resistant isolates.

Conclusions:

- Cefiderocol and the approved BL/BLI combinations provide different levels of *in-vitro* coverage.
- Cefiderocol presented the broadest spectrum and best *in-vitro* activity against carbapenemase-producing pathogens.