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Cefepime-Zidebactam (WCK 5222) Activity against Clinical Isolates of Non-Fermentative Gram-Negative Bacilli Collected Worldwide in 2018

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Introduction

- Zidebactam is a non-β-lactam agent with a dual mechanism of action: selective and high-affinity gram-negative penicillin-binding-protein (PBP) 2 binding and β-lactamase inhibition
- Zidebactam demonstrates antibacterial activity against various *Enterobacterales* isolates and non-fermentative gram-negative bacilli (NF-GNB) due to PBP2 binding
- Cefepime is a parenteral fourth-generation oxyimino-cephalosporin with broad-spectrum activity against aerobic gram-positive and gram-negative bacteria, including *Pseudomonas aeruginosa*, that was initially approved by the United States Food and Drug Administration (US FDA) in 1997
- Clinical indications currently approved by the US FDA for treatment with cefepime include moderate to severe pneumonia, complicated and uncomplicated urinary tract infections, complicated intra-abdominal infections, and uncomplicated skin and skin structure infections, as well as empiric therapy for febrile neutropenic patients
- Cefepime-zidebactam is in clinical development at 2g/1g q8 hours as a 60-minute infusion dosage
- We evaluated the *in vitro* activity of cefepime-zidebactam against contemporary clinical isolates from NF-GNB collected from medical centers worldwide during 2018

Materials and Methods

- A total of 3,711 NF-GNB isolates were collected by the 2018 SENTRY Antimicrobial Surveillance Program, including:
  - *Pseudomonas aeruginosa*: 2,719 isolates
  - *Acinetobacter* spp.: 624 isolates
  - *Stenotrophomonas maltophilia*: 326 isolates
  - *Burkholderia cepacia*: 42 isolates
- Susceptibility testing was performed in a central laboratory by a reference broth microdilution method against cefepime-zidebactam (1:1 ratio) and comparators
- The cefepime susceptible breakpoint of ≤8 mg/L (CLSI, high dose) was applied for cefepime-zidebactam for comparison purposes only, and a cefepime-zidebactam susceptible breakpoint of ≤64 mg/L has been proposed based on pharmacokinetic/pharmacodynamic target attainment and was applied for NF-GNB
- CLSI breakpoints were applied for comparators, when available
- Multidrug-resistant (MDR) and extensively drug-resistant (XDR) *P. aeruginosa* strains were classified according to recommended guidelines (Magiorakos et al., 2012) as follows
  - MDR: 3 or more drug classes have a nonsusceptible drug
  - XDR: all but 2 or fewer classes have a nonsusceptible drug

Results

- Cefepime-zidebactam exhibited potent activity against *P. aeruginosa* ($MIC_{50/90}$, 1/4 mg/L) with 99.0% (Asia-Pacific region [APAC]) to 100.0% (Latin America [LATAM]) of isolates inhibited at ≤8 mg/L and 100.0% of all global isolates inhibited at ≤32 mg/L (Table 1 and Figure 1)
- *P. aeruginosa* susceptibility rates for ceftazidime-avibactam, ceftolozane-tazobactam, piperacillin-tazobactam, and meropenem were 95.0%, 94.9%, 76.3%, and 76.5%, respectively (Table 1 and Figure 2)
- Cefepime-zidebactam retained potent activity against MDR ($MIC_{50/90}$, 4/8 mg/L; 96.5%/100.0% inhibited at ≤8/≤64 mg/L) and XDR ($MIC_{50/90}$, 4/8 mg/L; 95.1%/100.0% inhibited at ≤8/≤64 mg/L; Table 1)
- Cefepime-zidebactam inhibited 92.8% of ceftolozone-nonsusceptible (n=142) and 86.7% of ceftazidime-avibactam-nonsusceptible (n=135) isolates at ≤8 mg/L (highest MIC, 32 mg/L)

Table 1 Activity of cefepime-zidebactam and comparator antimicrobial agents when tested against 2,719 *Pseudomonas aeruginosa* isolates collected worldwide during 2018

Antimicrobial agent	MIC_{50}	MIC_{90}	% susceptible[a] (no. of isolates)				
			USA	EUR	APAC	LATAM	All
All *P. aeruginosa*			(1,315)	(926)	(311)	(167)	(2,719)
Cefepime-zidebactam	1	4	[99.1][b]	[99.4][b]	[99.0][b]	[100.0][b]	[99.2][b]
Ceftazidime-avibactam	2	8	96.0	93.1	97.1	94.0	95.0
Ceftolozane-tazobactam	1	2	96.1	92.6	95.9	94.2	94.9
Piperacillin-tazobactam	4	128	78.1	71.9	82.6	75.4	76.3
Meropenem	0.5	16	77.9	71.8	83.0	79.0	76.5
Cefepime	2	16	82.2	79.3	90.4	80.2	82.0
Ceftazidime	2	32	81.8	75.2	86.2	80.2	80.0
Amikacin	4	16	94.1	89.0	95.8	83.8	91.9
Gentamicin	2	>16	84.0	78.1	90.4	74.3	82.1
Tobramycin	0.5	8	92.7	82.7	94.5	81.4	88.8
Levofloxacin	0.5	32	74.4	68.9	85.5	74.1	73.8
Ciprofloxacin	0.25	16	78.9	73.3	86.8	78.3	77.9
Colistin	0.5	1	99.7	99.7	99.0	100.0	99.6
MDR *P. aeruginosa*			(271)	(254)	(43)	(41)	(609)
Cefepime-zidebactam	**4**	**8**	**[95.6][b]**	**[97.6][b]**	**[93.0][b]**	**[100.0][b]**	**[96.5][b]**
Ceftazidime-avibactam	**4**	**32**	**81.5**	**75.2**	**79.1**	**75.6**	**78.3**
Ceftolozane-tazobactam	**2**	**>16**	**82.2**	**73.4**	**71.4**	**75.0**	**77.6**
Piperacillin-tazobactam	64	>128	20.3	12.2	9.3	19.5	16.1
Meropenem	**8**	**>32**	**23.2**	**18.5**	**20.9**	**26.8**	**21.3**
Tobramycin	2	>16	70.1	41.3	65.1	39.0	55.7
Colistin	0.5	1	98.9	99.6	93.0	100.0	98.8
XDR *P. aeruginosa*			(173)	(180)	(27)	(25)	(405)
Cefepime-zidebactam	**4**	**8**	**[93.1][b]**	**[97.2][b]**	**[88.9][b]**	**[100.0][b]**	**[95.1][b]**
Ceftazidime-avibactam	**8**	**32**	**75.1**	**67.8**	**70.4**	**68.0**	**71.1**
Ceftolozane-tazobactam	**2**	**>16**	**74.8**	**64.2**	**57.7**	**72.0**	**67.8**
Piperacillin-tazobactam	128	>128	5.8	2.2	3.7	0.0	3.7
Meropenem	**16**	**>32**	**10.4**	**8.9**	**3.7**	**8.0**	**9.1**
Tobramycin	8	>16	64.2	29.4	51.9	28.0	45.7
Colistin	0.5	1	98.8	99.4	88.9	100.0	98.5

[a] Criteria as published by CLSI (2018).
[b] Percentage inhibited at ≤8 mg/L for comparison purposes; highest MIC was 32 mg/L.
Abbreviations: USA, United States of America; EUR, Europe; APAC, Asia-Pacific region; LATAM, Latin America; MDR, multidrug-resistant; XDR, extensively drug-resistant.

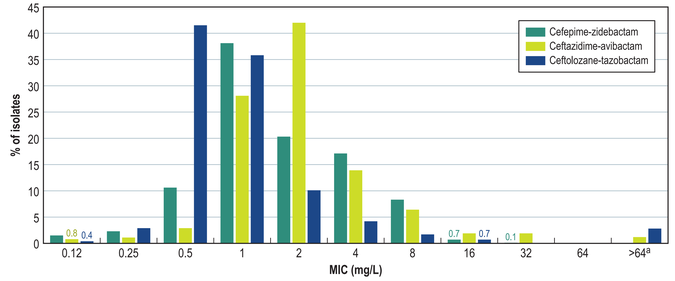
- Against *Acinetobacter* spp., percentages inhibited at ≤8/≤64 mg/L of cefepime-zidebactam were 73.4/99.4% in the USA, 44.9/99.2% in Europe (EUR), 59.1/100.0% in APAC and 29.8/100.0% in LATAM, and meropenem susceptibility rates were 69.8%, 24.2%, 43.5% and 8.3% in the USA, EUR, APAC, and LATAM, respectively (Table 2)
- Cefepime-zidebactam inhibited 76.7% (EUR) to 100.0% (LATAM) of *S. maltophilia* isolates at ≤8 mg/L and 99.4% (USA) to 100.0% (EUR, APAC, and LATAM) at ≤64 mg/L (Table 3)
- Against *B. cepacia* overall, 88.1% were inhibited at ≤8 mg/L cefepime-zidebactam and 100.0% were inhibited at ≤64 mg/L (Table 3); cefepime-zidebactam MIC >16 mg/L was observed only in the APAC region

Table 2 Activity of cefepime-zidebactam and comparator antimicrobial agents when tested against 624 *Acinetobacter baumannii-calcoaceticus* species complex collected worldwide during 2018

Antimicrobial agent	MIC_{50}	MIC_{90}	% susceptible[a] (no. of isolates)				
			USA (169)	EUR (256)	APAC (115)	LATAM (84)	All (624)
Cefepime-zidebactam	8	32	[73.4/99.4][b]	[44.9/99.2][b]	[59.1/100.0][b]	[29.8/100.0][b]	[53.2/99.5][b]
Ceftazidime-avibactam	16	>32	[61.5][c]	[25.4][c]	[50.4][c]	[10.7][c]	[37.8][c]
Ceftolozane-tazobactam	8	>16	[67.6][c]	[27.8][c]	[50.9][c]	[9.0][c]	[44.2][c]
Piperacillin-tazobactam	>128	>128	59.0	17.3	39.3	6.0	31.0
Ampicillin-sulbactam	32	>64	66.3	22.7	42.6	10.7	36.5
Cefepime	32	256	62.7	19.1	40.9	9.5	33.7
Ceftazidime	>32	>32	70.4	19.1	41.7	10.7	36.1
Meropenem	>32	>32	69.8	24.2	43.5	8.3	38.0
Amikacin	32	>32	85.8	30.9	50.4	13.1	47.0
Gentamicin	16	>16	78.7	28.9	46.1	13.1	43.4
Tobramycin	4	>16	82.8	41.0	47.8	26.2	51.6
Levofloxacin	16	>32	68.0	19.5	43.5	8.3	35.6
Ciprofloxacin	>16	>16	64.3	18.8	41.7	7.1	33.7
Colistin	0.25	1	91.1	88.6	94.8	100.0	92.0

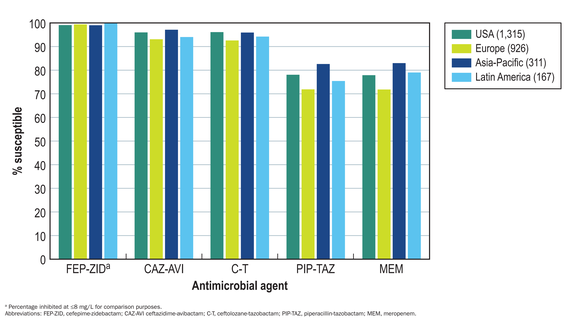
[a] Criteria as published by CLSI (2018) and EUCAST (2018).
[b] Percentage inhibited at ≤8/≤64 mg/L for comparison purposes.
[c] Percentage inhibited at CLSI susceptible breakpoint established for *P. aeruginosa* (≤8 mg/L) for comparison purposes.
[d] Percentage inhibited at CLSI susceptible breakpoint established for *P. aeruginosa* (≤4 mg/L) for comparison purposes.
Abbreviations: USA, United States of America; EUR, Europe; APAC, Asia-Pacific region; LATAM, Latin America.

Figure 1 Antimicrobial activity of cefepime-zidebactam, ceftazidime-avibactam, and ceftolozane-tazobactam against *P. aeruginosa*



[a] Greater than the highest dilution tested, which is >32 mg/L for ceftazidime-avibactam and >16 mg/L for ceftolozane tazobactam.

Figure 2 Antimicrobial susceptibility of *P. aeruginosa* isolates collected worldwide and stratified by geographic region



[a] Percentage inhibited at ≤8 mg/L for comparison purposes.
Abbreviations: FEP-ZID, cefepime-zidebactam; CAZ-AVI ceftazidime-avibactam; C-T, ceftolozane-tazobactam; PIP-TAZ, piperacillin-tazobactam; MEM, meropenem.

Table 3 Activity of cefepime-zidebactam and comparator antimicrobial agents when tested against *Stenotrophomonas maltophilia* and *Burkholderia cepacia* isolates collected worldwide during 2018

Antimicrobial agent	*S. maltophilia* (n=326)			*B. cepacian* (n=42)		
	MIC_{50}	MIC_{90}	%S[a]	MIC_{50}	MIC_{90}	%S[a]
Cefepime-zidebactam	4	16	[79.8/99.7][b]	4	16	[88.1/100.0][b]
Ceftazidime-avibactam	32	>32	[35.0][c]	2	4	[92.9][c]
Ceftolozane-tazobactam	>16	>16	[19.6][c]	2	>16	[71.4][c]
Piperacillin-tazobactam	>128	>128	[0.0][c]	8	64	[71.4][c]
Ceftazidime	>32	>32	21.5	4	16	78.6
Meropenem	>32	>32	[1.5][c]	2	4	92.9
Levofloxacin	1	8	76.1	2	8	71.4
Colistin	4	>8	[48.5][c]	>8	>8	[0.0][c]
TMP-SMX	≤0.12	1	96.0	NT	NT	NT

[a] Criteria as published by CLSI (2018).
[b] Percentage inhibited at ≤8/≤64 mg/L for comparison purposes.
[c] Percentage inhibited at CLSI susceptible breakpoint established for *P. aeruginosa* for comparison purposes.
Abbreviations: %S, percentage susceptible; TMP-SMX, trimethoprim-sulfamethoxazole; NT, not tested.

Conclusions

- Cefepime-zidebactam demonstrated potent *in vitro* activity against contemporary isolates of non-fermentative bacteria collected worldwide in 2018
- Cefepime-zidebactam retained good activity against MDR and XDR *P. aeruginosa* isolates, including most isolates nonsusceptible to ceftolozane-tazobactam and/or ceftazidime-avibactam
- These *in vitro* results support further development of cefepime-zidebactam for treatment of systemic infections caused by NF-GNB

Acknowledgements

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