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Antimicrobial Activity of WCK 5222 (Cefepime-Zidebactam) Tested against Clinical Isolates of *Pseudomonas aeruginosa* and *Acinetobacter* spp. Collected Worldwide (2015)

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Amended Abstract*

Background: WCK 5222 consists of cefepime (FEP) combined with zidebactam (ZID), a bicyclo-acyl hydrazide with a dual mechanism of action involving selective and high binding affinity to Gram-negative PBP2 and β-lactamase inhibition.

Methods: 1,291 *P. aeruginosa* (PSA) and 639 *Acinetobacter* spp. (ASP) isolates were collected from 146 medical centers (21 countries) in 2015 by the SENTRY Antimicrobial Surveillance Program and susceptibility (S) tested by a reference broth microdilution method against FEP-ZID (1:1 and 2:1 ratios) and comparator agents.

Results: FEP-ZID was very active against PSA with $MIC_{50/90}$ of 1/4 μg/mL and 99.5% of isolates inhibited at ≤8 μg/mL (1:1 ratio; Table). FEP-ZID (1:1 ratio) MIC values were generally 2-fold lower than those for FEP-ZID 2:1 ratio ($MIC_{50/90}$, 2/8 μg/mL) and ZID alone ($MIC_{50/90}$, 4/8 μg/mL). Colistin (COL; $MIC_{50/90}$ of ≤0.5/1 μg/mL; 100.0% S) and amikacin (AMK; $MIC_{50/90}$, 4/16 μg/mL; 92.2% S) were also active against PSA. FEP-ZID exhibited consistent activity against PSA from all continents (99.2%-100.0% inhibited at ≤8/8 μg/mL) and retained potent activity against ceftazidime (CAZ)-non-S and meropenem (MEM)-non-S PSA (97.4%-98.1% inhibited at ≤8/8 μg/mL). FEP-ZID 1:1 and 2:1 ratios ($MIC_{50/90}$, 16/32 μg/mL for both) were 4-fold more active than FEP against ASP. The most active compounds tested against ASP were COL ($MIC_{50/90}$, ≤0.5/1 μg/mL; 94.8% S) and AMK ($MIC_{50/90}$, >32/>32 μg/mL; 44.4% S).

Conclusion: FEP-ZID (WCK 5222) demonstrated potent *in vitro* activity against this worldwide collection of PSA, including isolates resistant to CAZ and/or MEM, and moderate activity against ASP. These *in vitro* results support further development of WCK 5222 for treatment of systemic PSA and ASP infections.

Antimicrobial agent	MIC_{50}/MIC_{90} (% susceptible[a])			
	P. aeruginosa			ASP
	All (1,291)	CAZ-NS (235)	MEM-NS (310)	(639)
FEP-ZID (1:1)	1/4	4/8	4/8	16/32
Cefepime	2/32 (81.6)	32/>64 (18.3)	16/64 (46.5)	64/>64 (29.6)
Zidebactam	4/8 (94.6)[b]	8/16 (84.7)[b]	8/16 (84.8)[b]	>64/>64 (0.3)[b]
Ceftazidime	2/32 (81.7)	32/>32 (0.0)	16/>32 (47.2)	>32/>32 (32.8)
PIP-TAZ[b]	4/64 (79.0)	64/>64 (7.2)	32/>64 (40.5)	>64/>64 (28.5)
Meropenem	0.5/16 (76.0)	16/>32 (30.6)	16/>32 (0.0)	32/>32 (37.2)

a. According to CLSI breakpoints; b. PIP-TAZ = piperacillin-tazobactam.

* Abstract has been updated with results of additional isolates tested after its submission.

Introduction

Zidebactam is a novel β-lactamase inhibitor that possesses potent intrinsic antimicrobial activity against many bacterial species, including *Pseudomonas aeruginosa*, 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*. Cefepime was initially approved by the United States Food and Drug Administration (US-FDA) in 1997 and clinical indications in the current US-FDA product package insert include the treatment of moderate to severe pneumonia, complicated and uncomplicated urinary tract infections, complicated intraabdominal infections and uncomplicated skin and skin structure infections, as well as empiric therapy for febrile neutropenic patients.

Cefepime combined with zidebactam (WCK 5222) is under clinical development for treatment of Gram-negative infections (NCT02707107 and NCT02674347; www.clinicaltrials.gov). We evaluated the *in vitro* activity of cefepime combined with zidebactam against contemporary clinical isolates of *P. aeruginosa* and *Acinetobacter* spp. collected worldwide.

Methods

Susceptibility testing: MIC values were determined using Clinical and Laboratory Standards Institute (CLSI) broth microdilution methodology as described in CLSI document M07-A10 (2015). The combination of cefepime-zidebactam (WCK 5222; two ratio concentrations, 1:1 and 2:1), both compounds alone and various comparator agents were tested in 96-well, frozen-form panels produced by JMI Laboratories (North Liberty, Iowa, USA). Quality control (QC) isolates were tested in each test batch and the inoculum density was monitored by colony counts. QC ranges and interpretive criteria for the comparator compounds were as published in CLSI M100-S26 (2016). The tested QC strains included the following: *P. aeruginosa* ATCC 27853, *Escherichia coli* ATCC 25922, ATCC 35218 and NCTC 13353, and *Klebsiella pneumoniae* ATCC 700603 and ATCC BAA-1705.

Organism collection: A total of 1,291 *P. aeruginosa* and 639 *Acinetobacter* spp. isolates were consecutively collected from 134 medical centers (21 countries) as part of the SENTRY Antimicrobial Surveillance Program. All isolates were collected in 2015, except those from China (198 isolates) which were collected in 2013. Isolates were collected from medical centers located in the United States (USA; 747 isolates from 64 medical centers), Europe (519 isolates from 38 medical centers), Latin America (176 isolates from eight medical centers), Asia Pacific (APAC) region, excluding China (290 isolates from 14 medical centers) and China (198 isolates from 10 medical centers).

Results

- Cefepime-zidebactam 1:1 ratio was very active against *P. aeruginosa* with $MIC_{50/90}$ of 1/4 μg/mL and exhibited consistent activity against *P. aeruginosa* from all continents (**Tables 1** and **2** and **Figure 1**).
- Cefepime-zidebactam retained potent *in vitro* activity against ceftazidime-non-susceptible ($MIC_{50/90}$, 4/8 μg/mL [1:1]) and meropenem-non-susceptible *P. aeruginosa* ($MIC_{50/90}$, 4/8 μg/mL [1:1]; **Table 2**).
- Cefepime-zidebactam 1:1 ratio ($MIC_{50/90}$, 1/4 μg/mL) MIC values were slightly lower (≤2-fold) than those for cefepime-zidebactam 2:1 ratio ($MIC_{50/90}$, 2/8 μg/mL; **Table 2** and **Figure 1**).
- Zidebactam alone exhibited potent *in vitro* activity against *P. aeruginosa* ($MIC_{50/90}$, 4/8 μg/mL) and inhibited 94.6% of isolates at ≤8 μg/mL (**Table 2**).
- Colistin ($MIC_{50/90}$ of ≤0.5/1 μg/mL; 100.0% susceptible) and amikacin ($MIC_{50/90}$, 4/16 μg/mL; 92.2% susceptible) were also very active against *P. aeruginosa*. In contrast, meropenem ($MIC_{50/90}$, 0.5/16 μg/mL), piperacillin-tazobactam ($MIC_{50/90}$, 4/64 μg/mL) and ceftazidime ($MIC_{50/90}$, 2/32 μg/mL) were active against only 76.0%, 79.0% and 81.7% of isolates at the current CLSI susceptible breakpoint, respectively (**Table 3**).
- Among *P. aeruginosa* isolates, susceptibility rates for the antimicrobial agents tested were generally lower in Europe compared to the other geographic regions (**Table 3**).
- Cefepime-zidebactam 1:1 and 2:1 ratios ($MIC_{50/90}$, 16/32 μg/mL for both) were at least 4-fold more active than cefepime ($MIC_{50/90}$, 64/>64 μg/mL) against *Acinetobacter* spp. (**Table 2**).
- The most active compounds tested against *Acinetobacter* spp. were colistin ($MIC_{50/90}$, ≤0.5/1 μg/mL; 94.8% susceptible) and amikacin ($MIC_{50/90}$, >32/>32 μg/mL; 44.4% susceptible; **Table 3**).
- Susceptibility rates of *Acinetobacter* spp. isolates collected from USA medical centers were substantially higher for most antimicrobial agents tested when compared to those from other geographic regions (**Table 3**).

Table 1. Summary of cefepime-zidebactam 1:1 activity against isolates included in this study.

Organisms	No.	MIC (μg/mL)		
		Range	50%	90%
Pseudomonas aeruginosa	1,291	0.06 to 32	1	4
ceftazidime-non-susceptible[a]	235	0.5 to 32	4	8
meropenem-non-susceptible[b]	310	0.5 to 32	4	8
Acinetobacter spp.	639	0.06 to >64	16	32

a. MIC, ≥16 μg/mL.
b. MIC, ≥4 μg/mL.

Table 2. Antimicrobial activity of cefepime-zidebactam 1:1, cefepime-zidebactam 2:1, cefepime, and zidebactam tested against *P. aeruginosa* and *Acinetobacter* spp.

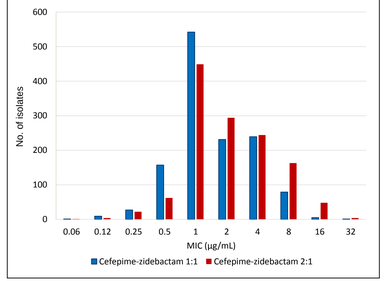
Organisms (no.) / antimicrobials	No. of isolates (cumulative %) inhibited at MIC (μg/mL) of:													MIC_{50}	MIC_{90}
	≤0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	>64		
***Pseudomonas aeruginosa* (1,291)**															
Cefepime-zidebactam 1:1	0 (0.0%)	1 (0.1%)	9 (0.8%)	27 (2.9%)	157 (15.0%)	542 (57.0%)	231 (74.9%)	239 (93.4%)	79 (99.5%)	5 (99.9%)	1 (100.0%)			1	4
Cefepime-zidebactam 2:1	0 (0.0%)	1 (0.1%)	4 (0.4%)	22 (2.1%)	62 (6.9%)	449 (41.7%)	294 (64.4%)	244 (83.3%)	163 (96.0%)	48 (99.7%)	4 (100.0%)			2	8
Cefepime		0 (0.0%)	2 (0.2%)	11 (1.0%)	28 (3.2%)	222 (20.4%)	423 (53.1%)	181 (67.2%)	187 (81.6%)	106 (89.9%)	76 (95.7%)	26 (97.8%)	29 (100.0%)	2	32
Zidebactam		0 (0.0%)	2 (0.2%)	5 (0.5%)	28 (2.7%)	128 (12.6%)	460 (48.3%)	410 (80.0%)	188 (94.6%)	42 (97.8%)	4 (98.1%)	3 (98.4%)	21 (100.0%)	4	8
ceftazidime-non-susceptible (MIC, ≥ 16 μg/mL) (235)															
Cefepime-zidebactam 1:1				0 (0.0%)	3 (1.3%)	7 (4.3%)	44 (23.0%)	109 (69.4%)	66 (97.4%)	5 (99.6%)	1 (100.0%)			4	8
Cefepime-zidebactam 2:1				0 (0.0%)	2 (0.9%)	3 (2.1%)	7 (5.1%)	69 (34.5%)	107 (80.0%)	43 (98.3%)	4 (100.0%)			8	16
Cefepime					0 (0.0%)	1 (0.4%)	5 (2.6%)	37 (18.3%)	72 (48.9%)	69 (78.3%)	22 (87.7%)	29 (100.0%)		32	>64
Zidebactam				0 (0.0%)	2 (1.7%)	2 (1.7%)	11 (6.4%)	91 (45.1%)	93 (84.7%)	25 (95.3%)	2 (96.2%)	2 (97.0%)	7 (100.0%)	8	16
meropenem-non-susceptible (MIC, ≥ 4 μg/mL) (310)															
Cefepime-zidebactam 1:1				0 (0.0%)	4 (1.3%)	27 (10.0%)	69 (32.3%)	138 (76.8%)	66 (98.1%)	5 (99.7%)	1 (100.0%)			4	8
Cefepime-zidebactam 2:1				0 (0.0%)	1 (0.3%)	13 (4.5%)	31 (14.5%)	110 (50.0%)	109 (85.2%)	42 (98.7%)	4 (100.0%)			4	16
Cefepime					0 (0.0%)	7 (2.3%)	20 (8.7%)	29 (18.1%)	88 (46.5%)	55 (64.2%)	59 (83.2%)	26 (91.6%)	26 (100.0%)	16	64
Zidebactam				0 (0.0%)	2 (0.6%)	5 (2.3%)	33 (12.9%)	114 (49.7%)	109 (84.8%)	31 (94.8%)	3 (95.8%)	3 (96.8%)	10 (100.0%)	8	16
***Acinetobacter* spp. (639)**															
Cefepime-zidebactam 1:1	0 (0.0%)	3 (0.5%)	0 (0.5%)	0 (0.5%)	8 (1.7%)	19 (4.7%)	68 (15.3%)	70 (26.3%)	115 (44.3%)	205 (76.4%)	121 (95.3%)	25 (99.2%)	5 (100.0%)	16	32
Cefepime-zidebactam 2:1	0 (0.0%)	2 (0.3%)	1 (0.5%)	0 (0.5%)	8 (1.7%)	19 (4.7%)	70 (15.6%)	66 (26.0%)	86 (39.4%)	195 (70.0%)	154 (94.1%)	34 (99.4%)	4 (100.0%)	16	32
Cefepime			0 (0.0%)	2 (0.3%)	5 (1.1%)	16 (3.6%)	65 (13.8%)	66 (24.1%)	35 (29.6%)	38 (35.5%)	76 (47.4%)	129 (67.6%)	207 (100.0%)	64	>64
Zidebactam	0 (0.0%)	1 (0.2%)	0 (0.2%)	0 (0.2%)	0 (0.2%)	1 (0.3%)	0 (0.3%)	0 (0.3%)	0 (0.3%)	0 (0.3%)	1 (0.5%)	0 (0.5%)	636 (100.0%)	>64	>64

Table 3. Activity of cefepime-zidebactam 1:1, cefepime-zidebactam 2:1 and comparator antimicrobial agents when tested against *Pseudomonas aeruginosa* and *Acinetobacter* spp. isolates collected worldwide.

Organism (no.)/ Antimicrobial Agent	MIC_{50}	MIC_{90}	All regions combined (CLSI[a])			% S by region[b]				
			%S	%I	%R	USA	Europe	LA	APAC	China
***P. aeruginosa* (1,291)**										
Cefepime-zidebactam 1:1	1	4	-	-	-	-	-	-	-	-
Cefepime-zidebactam 2:1	2	8	-	-	-	-	-	-	-	-
Cefepime	2	32	81.6	8.2	10.1	85.0	72.1	83.1	87.0	78.0
Ceftazidime	2	32	81.7	4.7	13.6	86.4	71.5	83.1	85.5	76.0
Meropenem	0.5	16	76.0	5.9	18.1	82.6	62.4	73.7	81.0	69.8
Imipenem	1	>8	74.5	4.3	21.2	80.3	61.4	74.6	80.0	70.0
Piperacillin-tazobactam	4	64	79.0	11.4	9.6	83.7	68.8	83.1	83.0	68.0
Aztreonam	4	>16	72.0	11.4	16.5	76.3	63.8	71.2	77.0	62.9
Levofloxacin	0.5	>4	74.6	6.1	19.3	75.7	66.8	76.3	82.5	74.2
Gentamicin	2	>8	84.4	4.0	11.6	88.0	72.1	83.9	91.5	86.6
Amikacin	4	16	92.2	1.8	6.1	96.7	82.9	87.3	95.0	93.8
Colistin	≤0.5	1	100.0	0.0	0.0	100.0	100.0	100.0	100.0	100.0
***Acinetobacter* spp. (639)[c]**										
Cefepime-zidebactam 1:1	16	32	-	-	-	-	-	-	-	-
Cefepime-zidebactam 2:1	16	32	-	-	-	-	-	-	-	-
Cefepime	64	>64	29.6	5.9	64.5	52.9	26.2	19.0	14.4	16.3
Ceftazidime	>32	>32	30.6	3.9	65.4	51.7	28.1	20.7	19.1	15.1
Meropenem	32	>32	37.2	1.7	61.0	59.9	38.0	20.7	21.1	20.4
Imipenem	>8	>8	39.5	2.1	58.5	62.8	40.7	20.7	20.2	23.7
Piperacillin-tazobactam	>64	>64	28.5	6.2	65.3	47.8	28.1	15.8	14.8	15.1
Ampicillin-sulbactam	32	>32	36.1	12.3	51.6	63.2	33.0	22.4	18.0	19.4
Levofloxacin	>4	>4	31.8	6.2	62.1	52.9	29.9	20.7	18.0	17.2
Gentamicin	>8	>8	39.7	3.3	57.0	63.4	37.1	37.9	22.5	19.4
Amikacin	>32	>32	44.4	3.9	51.7	80.2	35.7	34.5	22.5	25.8
Colistin	≤0.5	1	94.8	-	5.2	93.6	94.1	100.0	89.9	100.0

a. Criteria as published by CLSI [2016].
b. LA = Latin America and APAC = Asia Pacific region, excluding China.
c. Organisms include: *Acinetobacter baumannii-calcoaceticus* species complex (593), *A. berezinae* (2), *A. guillouiae* (3), *A. haemolyticus* (7), *A. johnsonii* (6), *A. junii* (3), *A. lwoffii* (8), *A. pittii* (2), *A. radioresistens* (2), *A. soli* (1), *A. towneri* (1), *A. ursingii* (6), Unspeciated *Acinetobacter* (5).

Figure 1. MIC distributions for cefepime-zidebactam 1:1 and 2:1 ratios when tested against 1,291 clinical isolates of *P. aeruginosa* collected worldwide in 2015.



Conclusions

- **Cefepime-zidebactam (WCK 5222) demonstrated potent *in vitro* activity against this worldwide collection of *P. aeruginosa* isolates, including isolates resistant to ceftazidime and/or meropenem.**
- **Zidebactam exhibited robust antimicrobial activity ($MIC_{50/90}$, 4/8 μg/mL) against *P. aeruginosa*.**
- ***Acinetobacter* spp. isolates showed high rates of resistance to all antimicrobial agents tested, except colistin.**
- **These *in vitro* results support further development of cefepime-zidebactam (WCK 5222) for treatment of systemic infections caused by *P. aeruginosa* and *Acinetobacter* spp.**

Acknowledgements

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