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In Vitro Activity of WCK 5222 (Cefepime-Zidebactam) Tested against Clinical Isolates of Antimicrobial Resistant Gram-negative Bacilli

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Amended Abstract*

Background: Zidebactam (ZID) is a bicyclo-acyl hydrazide with a dual mechanism of action: selective Gram-negative PBP2 binding and β-lactamase inhibition. We evaluated the *in vitro* activity of cefepime (FEP) combined with ZID (FEP-ZID [WCK 5222]) against contemporary clinical isolates of Enterobacteriaceae (ENT) and *P. aeruginosa* (PSA) with various resistant (R) phenotypes.

Methods: Isolates were collected from 134 medical centers from 32 countries worldwide in 2015 by the SENTRY Antimicrobial Surveillance Program. Susceptibility testing was performed in a central laboratory by a reference broth microdilution method against FEP-ZID (1:1 and 2:1 ratios) and comparator agents.

Results: FEP-ZID (1:1 ratio) was very active against all R subsets (see Table). The highest FEP-ZID (1:1) MIC value among ENT was 64 μg/mL (only one isolate at >8 μg/mL), and >99% of isolates would be considered susceptible (S) when the CLSI high dose FEP breakpoint (≤8 μg/mL) is applied. Further, 86.9-100.0% of ENT were inhibited at FEP-ZID (1:1) MIC of ≤2 μg/mL (low dose FEP breakpoint, CLSI). MIC values for FEP-ZID at a 2:1 ratio were slightly higher (less than one doubling dilution overall) compared to the 1:1 ratio. Among ESBL-phenotype *E. coli* (EC) / *Klebsiella* spp. (KSP), meropenem (MEM) and amikacin (AMK) were active against 98.6/69.7% and 97.4/82.1%, respectively. Only 74.1-83.7% of multidrug-R (MDR) ENT were S to MEM, AMK or colistin (COL). Carbapenem-R ENT (CRE) and extensively drug R (XDR) ENT exhibited low S to AMK (59.2 and 48.7% S, respectively), COL (71.7 and 61.3% S, respectively) and all antimicrobials tested except for FEP-ZID. COL and the FEP-ZID combinations were the most active compounds tested against MDR and XDR PSA. ZID tested alone was also active *in vitro* against MDR and XDR PSA ($MIC_{50/90}$, 8/16 μg/mL for both), whereas only 65.3 and 52.4% of strains were S to AMK, respectively.

Conclusion: FEP-ZID (WCK 5222) showed potent *in vitro* activity against R subsets of Gram-negative bacilli with high rates of R to most antimicrobial agents currently available for clinical use.

Resistant subset (no.)	MIC_{50}/MIC_{90} (% susceptible[a])				
	FEP-ZID (1:1)	ZID	Meropenem	Amikacin	Colistin
ESBL-phenotype EC (503)	0.12 / 0.25 (100.0 / 100.0)[b]	0.12 / 0.25	0.03 / 0.06 (98.6)	4 / 8 (97.4)	0.12 / 0.25 (99.4)[c]
ESBL-phenotype KSP (446)	0.25 / 2 (95.5 / 99.3)[b]	1 / >64	0.06 / >32 (69.7)	4 / >32 (82.1)	0.12 / 4 (88.7)[c]
Ceftazidime-non-S EBS (222)	0.12 / 0.5 (99.1 / 100.0)[b]	0.25 / 16	0.06 / 0.25 (92.8)	1 / 4 (96.8)	0.12 / >8 (87.3)[c]
CRE (153)	1 / 4 (86.9 / 99.3)[b]	2 / >64	32 / >32 (2.0)	16 / >32 (59.2)	0.12 / >8 (71.7)[c]
MDR ENT (707)	0.25 / 1 (96.9 / 99.9)[b]	0.5 / >64	0.06 / 32 (76.7)	4 / >32 (83.7)	0.25 / >8 (74.1)[c]
XDR ENT (119)	1 / 4 (88.2 / 100.0)[b]	2 / >64	16 / >32 (5.0)	32 / >32 (48.7)	0.25 / >8 (61.3)[c]
MDR PSA (251)	4 / 8 (97.6)[d]	8 / 16	16 / >32 (15.9)	8 / >32 (65.3)	1 / 1 (100.0)
XDR PSA (170)	4 / 8 (96.5)[d]	8 / 16	16 / >32 (9.4)	16 / >32 (52.4)	1 / 1 (100.0)

a. According to CLSI breakpoints
b. % inhibited at ≤2/≤8 μg/mL for comparison purposes only
c. According to EUCAST breakpoints
d. CLSI and EUCAST S breakpoint for FEP

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

Introduction

Zidebactam is a bicyclo-acyl hydrazide ($C_{13}H_{21}N_5O_7S$ [**Figure 1**]) with a dual mechanism of action involving selective and high-affinity Gram-negative PBP2 binding and β-lactamase inhibition. Due to PBP2 binding, zidebactam demonstrates antibacterial activity against various Enterobacteriaceae and *Pseudomonas aeruginosa*. Cefepime is a parenteral fourth-generation oxyimino-cephalosporin with a broad-spectrum of activity against aerobic Gram-positive and Gram-negative bacteria, including *P. aeruginosa*, which was initially approved by the United States Food and Drug Administration (US-FDA) in 1997. Clinical indications for treatment with cefepime in the current US-FDA product package insert 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 clinical breakpoints have recently (2014) been revised by the Clinical and Laboratory Standards Institute (CLSI) based on results from clinical and pharmacokinetic/pharmacodynamics (PK-PD) studies and contemporary MIC distributions. According to the current CLSI breakpoint criteria for Enterobacteriaceae published in the M100-S26 document, cefepime susceptible and resistant breakpoints are ≤2 and ≥16 μg/mL, respectively, and Enterobacteriaceae isolates with cefepime MIC values of 4 and 8 μg/mL should be reported as "susceptible-dose dependent" (SDD). The SDD interpretative criteria essentially provides three susceptible breakpoints for cefepime according to the dosage: i.e., ≤2 μg/mL for 1g of cefepime q12 hours (low-dosage), ≤4 μg/mL for 1g q8 hours or 2g q12 hours, and ≤8 μg/mL for 2g q8 hours (high-dosage).

Zidebactam combined with cefepime (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 Enterobacteriaceae and *P. aeruginosa* with various resistant phenotypes.

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 daily 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 sponsor provided available MIC information for cefepime-zidebactam and zidebactam alone tested against the listed QC organisms. The tested QC strains included the following: *Escherichia coli* ATCC 25922, ATCC 35218 and NCTC 13353, *Klebsiella pneumoniae* ATCC 700603 and ATCC BAA-1705, and *Pseudomonas aeruginosa* ATCC 27853.

Organism collection: All isolates were collected in 2015 as part of a global surveillance program, except those from China, which were collected in 2013. Isolates were collected from 134 medical institutions worldwide, including Europe (EU; 38 medical centers), United States (USA; 64), Latin America (LA; eight), Asia-West Pacific (APAC) region (excluding China, 14), and China (10).

Resistant subsets: An ESBL-screen-positive phenotype was defined according to CLSI: i.e., a MIC of ≥2 μg/mL for ceftazidime and/or ceftriaxone and/or aztreonam. Carbapenem-resistant Enterobacteriaceae (CRE) was defined as resistant (MIC, ≥4 μg/mL [CLSI]) to imipenem (excluding *P. mirabilis* and indole-positive Proteeae) or meropenem or doripenem. Isolates were further categorized as multidrug-resistant (MDR) and extensively drug-resistant (XDR) according to criteria published by Magiorakos *et al.* (2012): i.e., MDR = nonsusceptible to ≥1 agent in ≥3 antimicrobial classes, and XDR = nonsusceptible to ≥1 agent in all but ≤2 antimicrobial classes. Class representatives used in the analysis were: ceftriaxone, meropenem, piperacillin-tazobactam, levofloxacin, gentamicin, tigecycline and colistin for Enterobacteriaceae (seven classes), and ceftazidime, meropenem, piperacillin-tazobactam, levofloxacin, gentamicin and colistin for *P. aeruginosa*.

Results

- The highest cefepime-zidebactam MIC values among ESBL-phenotype *E. coli* isolates was only 2/2 μg/mL for the 1:1 ratio and 4/2 μg/mL for the 2:1 ratio combinations. Zidebactam tested alone was also active against these organisms ($MIC_{50/90}$, 0.12/0.25 μg/mL; 97.4% inhibited at ≤2 μg/mL), whereas only 24.7% of isolates were susceptible to cefepime (**Table 1**). Meropenem (98.6% susceptible), amikacin (97.4% susceptible) and colistin (99.4% susceptible [EUCAST]) exhibited good activity against ESBL-phenotype *E. coli* (**Table 2** and **Figure 2**).
- Cefepime-zidebactam 1:1 ($MIC_{50/90}$, 0.25/2 μg/mL) and 2:1 ratio ($MIC_{50/90}$, 0.5/4 μg/mL) were highly active against ESBL-phenotype *Klebsiella* spp., with 99.8 and 99.3% of isolates inhibited at ≤8/8 (1:1 ratio) and ≤8/4 μg/mL (2:1 ratio), respectively (high-dose cefepime breakpoint [CLSI], **Table 1**). In contrast, these organisms exhibited low susceptibility to meropenem (69.7% susceptible), amikacin (82.1% susceptible) and even colistin (88.7% susceptible [EUCAST]; **Table 2** and **Figure 2**).
- All ceftazidime-non-susceptible *Enterobacter* spp. isolates were inhibited at ≤4/4 μg/mL of cefepime-zidebactam (1:1 ratio; $MIC_{50/90}$, 0.12/0.5 μg/mL), and susceptibility rates for meropenem, gentamicin and colistin were 92.8, 77.9 and 87.3%, respectively (**Table 2** and **Figure 2**).
- Zidebactam showed variable intrinsic antimicrobial activity (bimodal MIC distribution) against *Klebsiella* spp. ($MIC_{50/90}$, 1/>64 μg/mL; 68.2% inhibited at ≤8 μg/mL) and *Enterobacter* spp. ($MIC_{50/90}$, 0.25/16 μg/mL; 89.2% inhibited at ≤8 μg/mL; **Table 1**).
- Among CRE, 99.3% of isolates (152/153) were inhibited at ≤8/8 μg/mL of cefepime-zidebactam (1:1 ratio; $MIC_{50/90}$, 1/4 μg/mL). After the cefepime-zidebactam combinations, the most active compounds tested against CRE were colistin ($MIC_{50/90}$, 0.12/>8 μg/mL; 71.7% susceptible [EUCAST] and amikacin ($MIC_{50/90}$, 16/>32 μg/mL; 59.2% susceptible; **Table 2** and **Figure 2**).
- Cefepime-zidebactam (1:1 ratio) inhibited 99.9% (706/707) of MDR Enterobacteriaceae isolates at ≤8/8 μg/mL (1:1 ratio; $MIC_{50/90}$, 0.25/1 μg/mL; **Table 1** and **Figure 2**). Only one MDR isolate, which was also a CRE, had a MIC value >8/8 μg/mL. This *K. pneumoniae* isolate was from a patient with a urinary tract infection in a hospital located in Ankara, Turkey.
- All XDR Enterobacteriaceae isolates were inhibited at ≤8/8 μg/mL of cefepime-zidebactam (1:1 ratio; $MIC_{50/90}$, 1/4 μg/mL). The most active agents among the comparators tested against XDR Enterobacteriaceae were colistin (61.3% susceptible), amikacin (48.7% susceptible) and gentamicin (25.2% susceptible; **Table 2** and **Figure 2**).
- The cefepime-zidebactam combinations and colistin were the most active compounds tested against MDR and XDR *P. aeruginosa*. Cefepime-zidebactam 1:1 and 2:1 ratios inhibited, respectively, 97.6 and 79.7% of MDR, and 96.5 and 72.9% of XDR *P. aeruginosa* at ≤8 μg/mL (cefepime concentration), which is the CLSI and EUCAST susceptible breakpoint for cefepime when tested against *P. aeruginosa* (**Table 1** and **Figure 2**).
- Zidebactam tested alone was also active *in vitro* against MDR and XDR *P. aeruginosa* ($MIC_{50/90}$, 8/16 μg/mL for both), whereas only 65.3% of MDR and 52.4% of XDR *P. aeruginosa* isolates were susceptible to amikacin (**Table 2** and **Figure 2**).
- MIC values for cefepime-zidebactam at a 2:1 ratio were slightly higher (less than one doubling dilution overall) compared to the 1:1 ratio (**Table 1**).

Table 1. Antimicrobial activity of cefepime-zidebactam 1:1, cefepime-zidebactam 2:1, cefepime, and zidebactam when tested against resistant subsets of Enterobacteriaceae and *P. aeruginosa* isolates.

	No. of isolates at MIC (μg/mL; cumulative %)														
Organisms / organism (no.)	≤0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	>64	MIC_{50}	MIC_{90}
Enterobacteriaceae															
ESBL-phenotype *E. coli* (503)															
Cefepime-zidebactam 1:1	20 (4.0%)	143 (32.4%)	286 (89.3%)	44 (98.0%)	6 (99.2%)	1 (99.4%)	3 (100.0%)							0.12	0.25
Cefepime-zidebactam 2:1	14 (2.8%)	31 (8.9%)	159 (40.6%)	243 (88.9%)	48 (98.4%)	4 (99.2%)	2 (99.6%)	2 (100.0%)						0.25	0.5
Cefepime	4 (0.8%)	10 (2.8%)	16 (6.0%)	29 (11.7%)	16 (14.9%)	20 (18.9%)	29 (24.7%)	45 (33.6%)	47 (42.9%)	66 (56.1%)	57 (67.4%)	66 (80.5%)	98 (100.0%)	16	>64
Zidebactam	0 (0.0%)	61 (12.1%)	346 (80.9%)	66 (94.0%)	11 (96.2%)	4 (97.0%)	2 (97.4%)	2 (97.8%)	0 (97.8%)	0 (97.8%)	2 (98.2%)	1 (98.4%)	8 (100.0%)	0.12	0.25
ESBL-phenotype *Klebsiella* spp. (446)															
Cefepime-zidebactam 1:1	3 (0.7%)	25 (6.3%)	124 (34.1%)	124 (61.9%)	62 (75.8%)	56 (88.3%)	32 (95.5%)	15 (98.9%)	4 (99.8%)	0 (99.8%)	0 (99.8%)	1 (100.0%)		0.25	2
Cefepime-zidebactam 2:1	2 (0.4%)	6 (1.8%)	35 (9.6%)	128 (38.3%)	117 (64.6%)	60 (78.0%)	45 (88.1%)	36 (96.2%)	14 (99.3%)	2 (99.8%)	0 (99.8%)	1 (100.0%)		0.5	4
Cefepime	1 (0.2%)	2 (0.7%)	7 (2.2%)	6 (3.6%)	16 (7.2%)	16 (10.8%)	15 (14.1%)	18 (18.2%)	28 (24.4%)	47 (35.0%)	53 (46.9%)	55 (59.2%)	182 (100.0%)	64	>64
Zidebactam	0 (0.0%)	5 (1.1%)	61 (15.0%)	90 (35.5%)	52 (47.3%)	37 (55.7%)	26 (61.6%)	20 (66.1%)	9 (68.2%)	7 (69.8%)	12 (72.5%)	15 (75.9%)	106 (100.0%)	1	>64
ceftazidime-non-susceptible (MIC, ≥ 8 μg/mL) *Enterobacter* spp. (222)															
Cefepime-zidebactam 1:1	6 (2.7%)	40 (20.7%)	90 (61.3%)	56 (86.5%)	20 (95.5%)	5 (97.7%)	3 (99.1%)	2 (100.0%)						0.12	0.5
Cefepime-zidebactam 2:1	3 (1.4%)	22 (11.3%)	48 (32.9%)	80 (68.9%)	45 (89.2%)	14 (95.5%)	8 (99.1%)	0 (99.1%)	2 (100.0%)					0.25	1
Cefepime	2 (0.9%)	5 (3.2%)	23 (13.5%)	27 (25.7%)	20 (34.7%)	31 (48.6%)	27 (60.8%)	24 (71.6%)	8 (75.2%)	14 (81.5%)	18 (89.6%)	12 (95.0%)	11 (100.0%)	2	64
Zidebactam	0 (0.0%)	4 (1.8%)	42 (20.7%)	75 (54.5%)	51 (77.5%)	17 (85.1%)	4 (86.9%)	4 (88.7%)	1 (89.2%)	3 (90.5%)	3 (91.9%)	1 (92.3%)	17 (100.0%)	0.25	16
CRE (153)															
Cefepime-zidebactam 1:1	0 (0.0%)	2 (1.3%)	18 (13.1%)	25 (29.4%)	24 (45.1%)	36 (68.6%)	28 (86.9%)	15 (96.7%)	4 (99.3%)	0 (99.3%)	0 (99.3%)	1 (100.0%)		1	4
Cefepime-zidebactam 2:1		0 (0.0%)	4 (2.6%)	22 (17.0%)	23 (32.0%)	24 (47.7%)	34 (69.9%)	28 (88.2%)	15 (98.0%)	2 (99.3%)	0 (99.3%)	1 (100.0%)		2	8
Cefepime	0 (0.0%)	1 (0.7%)	0 (0.7%)	0 (0.7%)	1 (1.3%)	0 (1.3%)	2 (2.6%)	4 (5.2%)	7 (9.8%)	12 (17.6%)	19 (30.1%)	16 (40.5%)	91 (100.0%)	>64	>64
Zidebactam		0 (0.0%)	13 (8.6%)	18 (20.5%)	12 (28.5%)	18 (40.4%)	18 (52.3%)	13 (60.9%)	2 (62.3%)	1 (62.9%)	5 (66.2%)	3 (68.2%)	48 (100.0%)	2	>64
MDR Enterobacteriaceae (707)															
Cefepime-zidebactam 1:1	11 (1.6%)	70 (11.5%)	263 (48.7%)	157 (70.9%)	82 (82.5%)	64 (91.5%)	38 (96.9%)	17 (99.3%)	4 (99.9%)	0 (99.9%)	0 (99.9%)	1 (100.0%)		0.25	1
Cefepime-zidebactam 2:1	8 (1.1%)	31 (5.5%)	78 (16.5%)	248 (51.6%)	154 (73.4%)	76 (84.2%)	55 (91.9%)	38 (97.3%)	16 (99.6%)	2 (99.9%)	0 (99.9%)	1 (100.0%)		0.25	2
Cefepime	5 (0.7%)	16 (3.0%)	16 (5.2%)	14 (7.2%)	16 (9.5%)	36 (14.6%)	33 (19.2%)	37 (24.5%)	50 (31.5%)	70 (41.4%)	81 (52.9%)	85 (64.9%)	248 (100.0%)	32	>64
Zidebactam	0 (0.0%)	27 (3.8%)	184 (30.0%)	117 (46.6%)	72 (56.8%)	45 (63.2%)	27 (67.0%)	20 (69.9%)	8 (71.0%)	5 (71.7%)	10 (73.2%)	11 (74.7%)	178 (100.0%)	0.5	>64
XDR Enterobacteriaceae (119)															
Cefepime-zidebactam 1:1		0 (0.0%)	11 (9.2%)	20 (26.1%)	21 (43.7%)	30 (68.9%)	23 (88.2%)	11 (97.5%)	3 (100.0%)					1	4
Cefepime-zidebactam 2:1		0 (0.0%)	1 (0.8%)	15 (13.4%)	16 (26.9%)	24 (47.1%)	26 (68.9%)	25 (89.9%)	10 (98.3%)	2 (100.0%)				2	8
Cefepime			0 (0.0%)	1 (0.8%)	0 (0.8%)	1 (1.7%)	7 (7.6%)	14 (19.3%)	14 (31.1%)	14 (42.0%)	14 (53.8%)	14 (65.5%)	79 (100.0%)	>64	>64
Zidebactam		0 (0.0%)	8 (6.8%)	13 (17.9%)	14 (29.9%)	13 (41.0%)	13 (52.1%)	9 (59.8%)	1 (60.7%)	1 (61.5%)	4 (65.0%)	3 (67.5%)	38 (100.0%)	2	>64
P. aeruginosa															
MDR *P. aeruginosa* (251)															
Cefepime-zidebactam 1:1				0 (0.0%)	3 (1.2%)	4 (2.8%)	48 (21.9%)	118 (68.9%)	72 (97.6%)	5 (99.6%)	1 (100.0%)			4	8
Cefepime-zidebactam 2:1				0 (0.0%)	1 (0.4%)	2 (1.2%)	7 (4.0%)	78 (35.1%)	112 (79.7%)	47 (98.4%)	4 (100.0%)			8	16
Cefepime							0 (0.0%)	7 (2.8%)	53 (21.1%)	69 (50.6%)	26 (78.1%)	29 (88.4%)	29 (100.0%)	16	>64
Zidebactam				0 (0.0%)	3 (1.2%)	2 (2.0%)	16 (8.4%)	87 (43.0%)	96 (81.3%)	33 (94.4%)	2 (95.2%)	2 (96.0%)	10 (100.0%)	8	16
XDR *P. aeruginosa* (170)															
Cefepime-zidebactam 1:1				0 (0.0%)	2 (1.2%)	1 (1.8%)	25 (16.5%)	76 (61.2%)	60 (96.5%)	5 (99.4%)	1 (100.0%)			4	8
Cefepime-zidebactam 2:1				0 (0.0%)	1 (0.6%)	1 (1.2%)	2 (2.4%)	39 (25.3%)	81 (72.9%)	42 (97.6%)	4 (100.0%)			8	16
Cefepime							0 (0.0%)	2 (1.2%)	24 (15.3%)	42 (40.0%)	54 (71.8%)	22 (84.7%)	26 (100.0%)	32	>64
Zidebactam				0 (0.0%)	2 (1.2%)	1 (1.8%)	7 (5.9%)	57 (39.4%)	67 (78.8%)	25 (93.5%)	2 (94.7%)	7 (95.9%)	7 (100.0%)	8	16

Abbreviations: ESBL = extended-spectrum β-lactamase, CRE = carbapenem-resistant Enterobacteriaceae, MDR = multidrug-resistant and XDR = extensively drug-resistant.

Table 2. Activity of cefepime-zidebactam 1:1 and comparator antimicrobial agents when tested against resistant subsets of Enterobacteriaceae and *P. aeruginosa* isolates.

Organism/antimicrobial (no.)[b]	MIC_{50}	MIC_{90}	CLSI[a]		
			%S	%I	%R
Enterobacteriaceae					
ESBL-phenotype *E. coli* (503)					
Cefepime-zidebactam 1:1	0.12	0.25	-	-	-
Cefepime	16	>64	24.7	18.3	57.1
Ceftazidime	16	>32	29.2	9.5	61.2
Ceftriaxone	>8	>8	6.2	1.2	92.6
Piperacillin-tazobactam	4	64	83.7	7.4	8.9
Meropenem	0.03	0.06	98.6	0.0	1.4
Levofloxacin	>4	>4	29.2	2.8	68.0
Gentamicin	≤1	>8	59.2	1.0	39.8
Amikacin	4	8	97.4	1.6	1.0
Colistin	0.12	0.25	99.4	-	0.6
ESBL-phenotype *Klebsiella* spp. (446)					
Cefepime-zidebactam 1:1	0.25	2	-	-	-
Cefepime	64	>64	14.1	10.3	75.6
Ceftazidime	>32	>32	11.0	4.3	84.8
Ceftriaxone	>8	>8	4.5	1.6	93.9
Piperacillin-tazobactam	64	>64	34.8	16.6	48.7
Meropenem	0.06	>32	69.7	3.6	26.7
Levofloxacin	>4	>4	35.3	4.5	60.2
Gentamicin	>8	>8	42.8	3.1	54.0
Amikacin	4	>32	82.1	5.6	12.3
Colistin	0.12	4	88.7	-	11.3
Ceftazidime-non-susceptible *Enterobacter* spp. (222)					
Cefepime-zidebactam 1:1	0.12	0.5	-	-	-
Cefepime	2	64	60.8	14.4	24.8
Ceftazidime	>32	>32	0.0	5.0	95.0
Ceftriaxone	>8	>8	0.0	0.5	99.5
Piperacillin-tazobactam	64	>64	30.6	48.2	21.2
Meropenem	0.06	0.25	92.8	1.4	5.9
Levofloxacin	≤0.12	>4	81.5	5.4	13.1
Gentamicin	≤1	>8	77.9	3.6	18.5
Amikacin	1	4	96.8	1.4	1.8
Colistin	0.12	>8	87.3	-	12.7
CRE (153)					
Cefepime-zidebactam 1:1	1	4	-	-	-
Cefepime	>64	>64	2.6	7.2	90.2
Ceftazidime	>32	>32	2.0	0.0	98.0
Ceftriaxone	>8	>8	0.7	0.0	99.3
Piperacillin-tazobactam	>64	>64	2.6	5.9	91.4
Meropenem	32	>32	2.0	2.6	95.4
Levofloxacin	>4	>4	17.8	3.3	78.9
Gentamicin	8	>8	40.8	11.2	48.0
Amikacin	16	>32	59.2	15.8	25.0
Colistin	0.12	>8	71.7	-	28.3
MDR Enterobacteriaceae (707)					
Cefepime-zidebactam 1:1	0.25	1	-	-	-
Cefepime	32	>64	19.2	12.3	68.5
Ceftazidime	>32	>32	19.7	2.7	77.7
Ceftriaxone	>8	>8	7.6	1.3	91.1
Piperacillin-tazobactam	64	>64	39.9	21.2	38.9
Meropenem	0.06	32	76.7	2.8	20.5
Levofloxacin	>4	>4	12.6	7.4	80.1
Gentamicin	>8	>8	28.9	5.7	65.5
Amikacin	4	>32	83.7	5.7	10.6
Colistin	0.25	>8	74.1	-	25.9
XDR Enterobacteriaceae (119)					
Cefepime-zidebactam 1:1	1	4	-	-	-
Cefepime	>64	>64	1.7	2.5	95.8
Ceftazidime	>32	>32	0.8	0.0	99.2
Ceftriaxone	>8	>8	0.0	0.0	100.0
Piperacillin-tazobactam	>64	>64	0.0	6.7	93.3
Meropenem	16	>32	5.0	9.2	85.7
Levofloxacin	>4	>4	0.8	5.0	94.1
Gentamicin	>8	>8	25.2	11.8	63.0
Amikacin	32	>32	48.7	20.2	31.1
Colistin	0.25	>8	61.3	-	38.7
Pseudomonas aeruginosa					
MDR *P. aeruginosa* (251)					
Cefepime-zidebactam 1:1	4	8	-	-	-
Cefepime	16	>64	21.1	29.5	49.4
Ceftazidime	32	>32	23.1	17.9	59.0
Piperacillin-tazobactam	64	>64	16.7	42.6	40.6
Meropenem	16	>32	15.9	11.2	72.9
Levofloxacin	>4	>4	19.1	13.5	67.3
Gentamicin	8	>8	36.7	13.9	49.4
Amikacin	8	>32	65.3	7.2	27.5
Colistin	1	1	100.0	0.0	0.0
XDR *P. aeruginosa* (170)					
Cefepime-zidebactam 1:1	4	8	-	-	-
Cefepime	32	>64	15.3	24.7	60.0
Ceftazidime	32	>32	13.5	20.0	66.5
Piperacillin-tazobactam	64	>64	5.3	51.8	42.9
Meropenem	16	>32	9.4	7.6	82.9
Levofloxacin	>4	>4	7.6	12.4	80.0
Gentamicin	>8	>8	23.5	14.1	62.4
Amikacin	16	>32	52.4	9.4	38.2
Colistin	16	1	100.0	0.0	0.0

a. Criteria as published by CLSI [2016], except colistin for which EUCAST [2016] criteria were applied for Enterobacteriaceae.
b. Abbreviations: ESBL = extended-spectrum β-lactamase, CRE = carbapenem-resistant Enterobacteriaceae, MDR = multidrug-resistant and XDR = extensively drug-resistant.

Figure 1. Chemical structure of zidebactam.

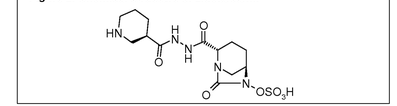
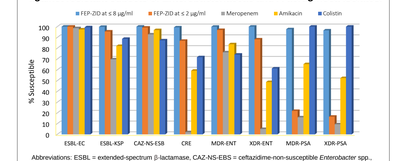


Figure 2. Antimicrobial activity of cefepime-zidebactam 1:1 (% inhibited at ≤8/8 and ≤2/2 μg/mL), meropenem, amikacin and colistin when tested against resistant subsets of Enterobacteriaceae and *P. aeruginosa* isolates.



Abbreviations: ESBL = extended-spectrum β-lactamase, CAZ-NS-EBS = ceftazidime-non-susceptible *Enterobacter* spp., CRE = carbapenem-resistant Enterobacteriaceae, MDR = multidrug-resistant and XDR = extensively drug-resistant

Conclusions

- **Cefepime-zidebactam (WCK 5222) showed potent *in vitro* activity against resistant subsets of Gram-negative bacilli with high rates of resistance to most antimicrobial agents currently available for clinical use.**
- **WCK 5222 exhibited good antimicrobial activity against MDR and XDR *P. aeruginosa* ($MIC_{50/90}$, 4/8 μg/mL [1:1] for both subsets).**
- **WCK 5222 also exhibited potent antimicrobial activity against both XDR ENT ($MIC_{50/90}$, 1/4 μg/mL [1:1]) and CRE ($MIC_{50/90}$, 1/4 μg/mL [1:1]) resistotypes.**
- **Zidebactam alone exhibited good antimicrobial activity against MDR and XDR *P. aeruginosa* ($MIC_{50/90}$, 8/16 μg/mL for both subsets).**
- **These *in vitro* results indicate that cefepime-zidebactam (WCK 5222) may become a valuable option for treatment of serious Gram-negative infections caused by resistant organisms. Additional clinical studies are warranted.**

Acknowledgements

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