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Antimicrobial Activity of Cefepime-Zidebactam (WCK 5222) When Tested against Bacterial Isolates from Patients Hospitalized with Pneumonia

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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 against gram-negative (GN) bacterial isolates from patients hospitalized with pneumonia.

Methods: A total of 2,503 isolates from the US (944), Europe (842), Latin America (LA; 168), Asia-Pacific (APAC; 549), and China (164) were collected in 2015 (except China, 2013) by the SENTRY Antimicrobial Surveillance Program and susceptibility (S) tested by a reference broth microdilution method against FEP-ZID (1:1 ratio) and comparator agents. The collection included 1,468 *Enterobacteriaceae* (ENT), 687 *P. aeruginosa* (PSA), and 348 *Acinetobacter* spp. (ASP).

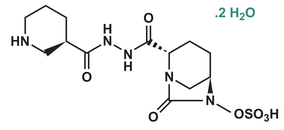
Results: FEP-ZID was the most active compound tested against ENT with $MIC_{50/90}$ of 0.06/0.25 μg/mL and 100.0% inhibited at ≤8/8 μg/mL. Amikacin (AMK; $MIC_{50/90}$, 2/4 μg/mL; 97.5% S) and meropenem (MEM; $MIC_{50/90}$, 0.03/0.12 μg/mL; 95.3% S) were also very active. FEP-ZID was active against individual ENT species ($MIC_{50/90}$, ≤0.03-0.06/0.06-0.5 μg/mL) and retained potent activity against carbapenem-resistant ENT (CRE; n=64; $MIC_{50/90}$, 0.5/2 μg/mL), colistin (COL)-non-S *K. pneumoniae* (KPN; $MIC_{50/90}$, 0.5/1 μg/mL), and ceftazidime (CAZ)-non-S *Enterobacter* spp. ($MIC_{50/90}$, 0.12/0.5 μg/mL; highest MIC, 1 μg/mL). S rates for MEM among KPN were lower in LA (76.2%) compared to other regions (85.9% [EU] to 92.9% [APAC]). FEP-ZID was very active against PSA with $MIC_{50/90}$ of 1/4 μg/mL and 99.7% of isolates inhibited at ≤8/8 μg/mL; highest MIC, 32/32 μg/mL. Among the comparators, COL ($MIC_{50/90}$ of ≤0.5/1 μg/mL; 100.0% S) and AMK ($MIC_{50/90}$, 4/16 μg/mL; 90.9% S) were the most active compounds against PSA. FEP-ZID exhibited consistent activity against PSA from all regions (98.1% [LA] -100.0% [EU, APAC, and China] inhibited at ≤8/8 μg/mL) and retained potent activity against CAZ-non-S and MEM-non-S PSA (98.5%-98.9% inhibited at ≤8/8 μg/mL) and multidrug-resistant isolates (MDR; $MIC_{50/90}$, 4/8 μg/mL; 98.9% inhibited at ≤8/8 μg/mL). FEP-ZID ($MIC_{50/90}$, 16/32 μg/mL) was 4-fold more active than FEP against ASP. The most active compounds tested against ASP were COL ($MIC_{50/90}$, ≤0.5/2 μg/mL; 93.0%S) and AMK ($MIC_{50/90}$, >32/>32 μg/mL; 39.1%S).

Conclusion: FEP-ZID (WCK 5222) was very active against this worldwide collection of GN isolates from patients with pneumonia, including MDR isolates. Importantly, FEP-ZID showed potent activity against CRE, COL-non-S KPN, and MEM-non-S PSA.

Introduction

- Zidebactam, a bicyclo-acyl hydrazide ($C_{13}H_{21}N_5O_7S$ [Figure 1]), is a non-β-lactam agent 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 broad-spectrum activity against aerobic gram-positive and gram-negative bacteria, including *P. 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
- 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 a large worldwide collection of contemporary gram-negative organisms isolated from patients hospitalized worldwide with pneumonia

Figure 1 Chemical structure of zidebactam



Materials and Methods

Organism collection

- 2,503 isolates were collected as part of a global surveillance program, mostly in 2015 (except those from China collected in 2013)
- The organism collection included 1,468 *Enterobacteriaceae*, 687 *P. aeruginosa,* and 348 *Acinetobacter* spp.
- Isolates were consecutively collected from 124 medical institutions worldwide, including Europe (842 isolates from 34 medical centers), United States (US; 944 isolates from 58 medical centers), Latin America (168 isolates from 8 medical centers), the Asia-Pacific (APAC) region (excluding China, 385 isolates from 14 medical centers), and China (164 isolates from 10 medical centers)
- Each participating center was requested to collect consecutive bacterial isolates from lower respiratory tract sites determined to be significant by local criteria as the reported probable cause of pneumonia, and only isolates from invasive sampling (transtracheal aspiration, bronchoalveolar lavage, protected brush samples, qualified sputum samples, etc.) were accepted

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; tested at ratio concentrations of 1:1), both compounds alone, and various comparator agents were tested in 96-well, frozen-form panels produced by JMI Laboratories (North Liberty, Iowa, USA)
- Cefepime breakpoint for high dose (2g q8hs; CLSI), ie, ≤8 μg/mL, was applied for cefepime-zidebactam for comparison purpose only. However, a pharmacokinetic/pharmacodynamic (PK/PD) susceptible breakpoint of ≤64 μg/mL has been proposed based on the results of phase 1 studies where 2g of cefepime plus 1g of zidebactam q8 hours provided >99% PK/PD target attainment for *Enterobacteriaceae*, *P. aeruginosa*, and *Acinetobacter baumannii* isolates with cefepime-zidebactam MICs up to 64 μg/mL (Wockhardt data on file) (Bhagwat et al., 2017a and 2017b)
- Tested QC strains included *Escherichia coli* ATCC 25922, ATCC 35218, and NCTC 13353; *Klebsiella pneumoniae* ATCC 700603 and ATCC BAA-1705; and *Pseudomonas aeruginosa* ATCC 27853

Results

- Cefepime-zidebactam was the most active compound tested against *Enterobacteriaceae* with $MIC_{50/90}$ of 0.06/0.25 μg/mL and 100.0% inhibited at ≤8/8 μg/mL (Tables 1-3 and Figure 2)
- Amikacin ($MIC_{50/90}$, 2/4 μg/mL; 97.5% susceptible), meropenem ($MIC_{50/90}$, 0.03/0.12 μg/mL; 95.3% susceptible), and doripenem ($MIC_{50/90}$, ≤0.06/0.25 μg/mL; 95.6% susceptible) were also very active against *Enterobacteriaceae* (Table 3)
- Cefepime-zidebactam was active against individual *Enterobacteriaceae* species ($MIC_{50/90}$, ≤0.03-0.06/0.06-0.5 μg/mL), and retained potent activity against carbapenem-resistant *Enterobacteriaceae* (CRE; n=64; $MIC_{50/90}$, 0.5/2 μg/mL), colistin-nonsusceptible *K. pneumoniae* ($MIC_{50/90}$, 0.5/1 μg/mL), and ceftazidime-nonsusceptible *Enterobacter* spp. ($MIC_{50/90}$, 0.12/0.5 μg/mL; highest MIC, 1/1 μg/mL; Table 1)
- Susceptibility rates for meropenem among *K. pneumoniae* were lower in Latin America (76.2%) compared to other regions (85.9% [Europe] to 93.1% [APAC]; data not shown)
- Cefepime-zidebactam was very active against *P. aeruginosa* with $MIC_{50/90}$ of 1/4 μg/mL and 99.7% of isolates inhibited at ≤8/8 μg/mL; highest MIC, 32/32 μg/mL (Tables 1-3 and Figure 2)
- Among the comparators, colistin ($MIC_{50/90}$ of ≤0.5/1 μg/mL; 100.0% susceptible) and amikacin ($MIC_{50/90}$, 4/16 μg/mL; 90.9% susceptible) were the most active compounds against *P. aeruginosa* (Table 3)
- Cefepime-zidebactam exhibited consistent activity against *P. aeruginosa* from all regions (98.1% [Latin America] to 100.0% [Europe, APAC, and China] inhibited at ≤8/8 μg/mL) and retained potent activity against ceftazidime-nonsusceptible and meropenem-nonsusceptible *P. aeruginosa* (98.5%-98.9% inhibited at ≤8/8 μg/mL), and multidrug-resistant isolates (MDR; $MIC_{50/90}$, 4/8 μg/mL; 98.9% inhibited at ≤8/8 μg/mL; Table 1)
- Cefepime-zidebactam ($MIC_{50/90}$, 16/32 μg/mL) was 4-fold more active than cefepime against *Acinetobacter* spp. The most active compounds tested against *Acinetobacter* spp. were colistin ($MIC_{50/90}$, ≤0.5/2 μg/mL; 93.0%S) and amikacin ($MIC_{50/90}$, >32/>32 μg/mL; 39.1% susceptible; Table 3)

Table 1 Summary of cefepime-zidebactam 1:1 activity against isolates collected from patients hospitalized with pneumonia

Organism	No.	MIC (μg/mL)			% inhibited
		Range	50%	90%	at ≤8/8 μg/mL*
Enterobacteriaceae	1,468	≤0.03 to 8	0.06	0.25	100.0%
CRE	64	0.06 to 8	0.5	2	100.0%
Escherichia coli	288	≤0.03 to 0.25	0.06	0.12	100.0%
ESBL-phenotype	84	≤0.03 to 0.25	0.12	0.12	100.0%
Klebsiella pneumoniae	456	≤0.03 to 8	0.06	0.5	100.0%
ESBL-phenotype	175	0.06 to 8	0.25	1	100.0%
ESBL-phenotype non-CRE	126	0.06 to 4	0.25	1	100.0%
Meropenem-nonsusceptible	55	0.12 to 8	1	4	100.0%
Colistin-nonsusceptible	23	0.06 to 8	0.5	1	100.0%
Klebsiella oxytoca	82	≤0.03 to 1	≤0.03	0.12	100.0%
Proteus mirabilis	97	≤0.03 to 0.5	0.06	0.12	100.0%
Enterobacter spp.	270	≤0.03 to 1	≤0.03	0.12	100.0%
Ceftazidime-nonsusceptible	70	≤0.03 to 1	0.12	0.5	100.0%
Morganella morganii	20	≤0.03 to 0.12	≤0.03	0.06	100.0%
Citrobacter spp.	58	≤0.03 to 0.25	≤0.03	0.12	100.0%
Serratia marcescens	149	≤0.03 to 1	0.06	0.12	100.0%
Proteus vulgaris	2	≤0.03 to 0.06	≤0.03		100.0%
Providencia spp.	14	≤0.03 to 0.12	≤0.03	0.06	100.0%
Other *Enterobacteriaceae*	28	≤0.03 to 0.12	≤0.03	0.12	100.0%
Pseudomonas aeruginosa	687	0.06 to 32	1	4	99.7%
Ceftazidime-nonsusceptible	136	0.5 to 32	4	8	98.5%
Meropenem-nonsusceptible	185	0.5 to 32	4	8	98.9%
MDR	181	0.5 to 32	4	8	98.9%
Acinetobacter spp.	348	0.5 to >64	16	32	39.9%

* Cefepime breakpoint for high dose (2g q8hs; CLSI), ie, ≤8 μg/mL, was applied for cefepime-zidebactam for comparison purpose only. However, a pharmacokinetic/pharmacodynamic (PK/PD) susceptible breakpoint of ≤64 μg/mL has been proposed based on the results of phase 1 studies where 2g of cefepime plus 1g of zidebactam q8 hours provided >99% PK/PD target attainment for *Enterobacteriaceae*, *P. aeruginosa*, and *Acinetobacter baumannii* isolates with cefepime-zidebactam MICs up to 64 μg/mL (Wockhardt data on file) (Bhagwat et al., 2017a and 2017b)

Figure 2 Cefepime-zidebactam MIC distributions for *Enterobacteriaceae* (n= 1,468) and *P. aeruginosa* (n= 687) from patients hospitalized worldwide with pneumonia

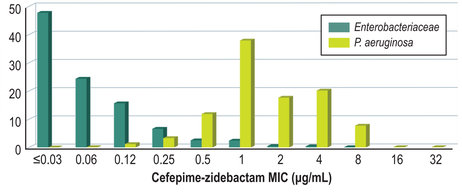


Table 2 Antimicrobial activity of cefepime-zidebactam 1:1, cefepime, and zidebactam tested against the main organisms and organism groups of isolates

Organism / organism group (no. of isolates)	No. of isolates at MIC (μg/mL) and cumulative %													MIC_{50}	MIC_{90}
	≤0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	>64		
Enterobacteriaceae (1,468)															
Cefepime-zidebactam 1:1	699 47.6	356 71.9	229 87.5	97 94.1	37 96.6	35 99.0	8 99.5	6 99.9	1 100.0					0.06	0.25
Cefepime	533 36.3	356 60.6	137 69.9	58 73.8	41 76.6	36 79.1	25 80.8	24 82.4	25 84.1	43 87.1	51 90.5	35 92.9	104 100.0	0.06	32
Zidebactam	2 0.1	137 9.5	458 40.8	148 50.9	71 55.7	44 58.7	22 60.2	18 61.4	13 62.3	8 62.9	29 64.8	41 67.6	474 100.0	0.25	>64
P. aeruginosa (687)															
Cefepime-zidebactam 1:1		1 0.1	8 1.3	23 4.7	81 16.4	260 54.3	121 71.9	138 92.0	53 99.7	1 99.9	1 100.0			1	4
Cefepime			2 0.3	9 1.6	21 4.7	100 19.2	204 48.9	106 64.3	99 78.7	71 89.1	42 95.2	15 97.4	18 100.0	4	32
Zidebactam			2 0.3	4 0.9	22 4.1	69 14.1	216 45.6	213 76.6	107 92.1	31 96.7	3 97.1	2 97.4	18 100.0	4	8
Acinetobacter spp. (348)															
Cefepime-zidebactam 1:1				1 0.3	9 2.9	27 10.6	39 21.8	63 39.9	118 73.9	71 94.3	16 98.9	4 100.0		16	32
Cefepime				1 0.3	9 2.9	30 10.9	28 19.5	15 23.9	16 28.4	53 43.7	75 65.2	121 100.0		64	>64
Zidebactam													348 100.0	>64	>64

Table 3 Activity of cefepime-zidebactam 1:1 and comparator antimicrobial agents

Antimicrobial agent (no. isolates)	MIC_{50}	MIC_{90}	CLSI*		EUCAST*	
			%S	%R	%S	%R
Enterobacteriaceae (1,468)						
Cefepime-zidebactam 1:1	0.06	0.25				
Cefepime	0.06	32	80.8	15.9	79.1	17.6
Ceftazidime	0.25	>32	78.0	20.7	74.8	22.0
Ceftriaxone	0.12	>8	73.3	25.4	73.3	25.4
Piperacillin-tazobactam	2	64	84.6	9.3	79.9	15.4
Imipenem	0.25	1	90.6	5.0	95.0	2.5
Meropenem	0.03	0.12	95.3	4.2	95.8	2.8
Doripenem	≤0.06	0.25	95.6	3.6	95.6	3.6
Levofloxacin	≤0.12	>4	80.1	17.5	74.6	22.0
Gentamicin	≤1	>8	85.1	13.5	84.2	14.9
Amikacin	2	4	97.5	1.4	95.5	2.5
Colistin	0.12	>8			75.9	24.1
Pseudomonas aeruginosa (687)						
Cefepime-zidebactam 1:1	1	4				
Cefepime	4	32	78.7	10.9	78.7	21.3
Ceftazidime	2	32	80.1	15.2	80.1	19.9
Piperacillin-tazobactam	4	>64	76.5	11.8	76.5	23.5
Imipenem	1	>8	71.4	23.4	76.6	11.7
Meropenem	0.5	16	73.1	20.4	73.1	15.3
Levofloxacin	0.5	>4	73.1	20.4	62.6	37.4
Gentamicin	2	>8	81.5	13.0	81.5	18.5
Amikacin	4	16	90.9	6.7	83.9	9.1
Colistin	≤0.5	1	100.0	0.0	100.0	0.0
Acinetobacter spp. (348)						
Cefepime-zidebactam 1:1	16	32				
Cefepime	64	>64	23.9	71.6		
Ceftazidime	>32	>32	25.7	71.4		
Ampicillin-sulbactam	32	>32	31.0	56.4		
Piperacillin-tazobactam	>64	>64	22.1	70.6		
Imipenem	>8	>8	32.1	65.0	32.1	63.3
Meropenem	>32	>32	31.3	67.5	31.3	65.2
Levofloxacin	>4	>4	26.5	67.1	24.8	74.1
Gentamicin	>8	>8	34.7	62.1	34.7	65.3
Amikacin	>32	>32	39.1	57.4	37.0	60.9
Colistin	≤0.5	2	93.0	7.0	93.0	7.0

* Criteria as published by CLSI [2017] and EUCAST [2017]

Conclusions

- Cefepime-zidebactam (WCK 5222) was very active against this worldwide collection of gram-negative bacteria from patients with pneumonia, including MDR isolates
- Importantly, cefepime-zidebactam showed potent activity against CRE, colistin-nonsusceptible *K. pneumoniae*, and meropenem-nonsusceptible *P. aeruginosa*

Acknowledgements

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