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Cefepime-Zidebactam (WCK 5222) Activity When Tested against Gram-Negative Organisms Isolated from Patients Hospitalized in Europe and the Asia-Pacific Region in 2018

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Introduction

- Zidebactam, a bicyclo-acyl hydrazide ($C_{15}H_{24}N_6O_7S$), is a non-β-lactam agent with a dual mechanism of action involving selective and high-affinity gram-negative penicillin-binding-protein (PBP) 2 binding and β-lactamase inhibition
- Due to PBP2 binding, zidebactam demonstrates antibacterial activity against various *Enterobacterales* and nonfermentative gram-negative bacilli (NF-GNB)
- 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 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 Europe and the Asia-Pacific region (APAC)

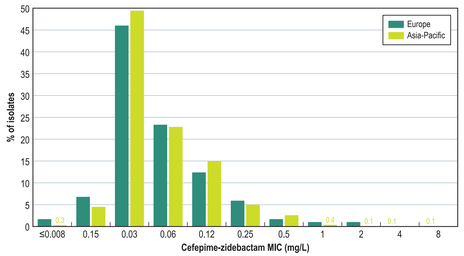
Materials and Methods

- A total of 5,077 isolates were collected by the 2018 SENTRY Antimicrobial Surveillance Program from medical centres in Europe (n=4,135; 29 centres in 14 nations) and APAC (n=942; 10 centres in 6 nations)
- The collection included 3,939 *Enterobacterales* and 1,138 NF-GNB 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 (PK-PD) target attainment and was applied for NF-GNB
- EUCAST breakpoints were applied for comparators, when available
- Multidrug-resistant (MDR) and extensively drug-resistant (XDR) *Enterobacterales* and *P. aeruginosa* strains were classified according to recommended guidelines (Magiorakos et al., 2012) as follows
  - MDR: 3 or more drug classes have a nonsusceptible (EUCAST) drug
  - XDR: all but 2 or fewer classes have a nonsusceptible (EUCAST) drug

Results

- Cefepime-zidebactam was very active against *Enterobacterales* with $MIC_{50/90}$ values of 0.03/0.12 mg/L in Europe and APAC, and the highest MIC values were 8 mg/L in Europe and 2 mg/L in APAC (Table 1 and Figure 1)
- The most active comparators against *Enterobacterales* were ceftazidime-avibactam ($MIC_{50/90}$, 0.12/0.5mg/L; 99.2% susceptible [S]), the carbapenems (meropenem $MIC_{50/90}$, 0.03/0.06mg/L; 97.6%S), and amikacin ($MIC_{50/90}$, 2/4mg/L; 97.0%S; Table 1)
- Cefepime-zidebactam retained good activity against MDR (n=632; $MIC_{50/90}$, 0.12/1 mg/L), XDR (n=88; $MIC_{50/90}$, 1/2mg/L), and carbapenem-resistant *Enterobacterales* (CRE; n=92; $MIC_{50/90}$, 1/2mg/L; Table 2 and Figure 2)
- The most active compounds tested against CRE isolates were cefepime-zidebactam (100.0% inhibited at ≤8 mg/L), ceftazidime-avibactam (81.8%S/6.7%S in Europe/APAC), colistin (70.1%S/86.7%S in Europe/APAC), and amikacin (51.9%S/73.3%S in Europe/APAC; Table 2 and Figure 2)
- Cefepime-zidebactam was also very active against *P. aeruginosa* ($MIC_{50/90}$ of 1/4 mg/L and 99.3%/98.8% of isolates from Europe/APAC inhibited at ≤8 mg/L; Table 1 and Figure 3)
- Cefepime-zidebactam retained activity against *P. aeruginosa* displaying an MDR phenotype ($MIC_{50/90}$, 4/8mg/L; 97.4%/93.1% isolates from Europe/APAC inhibited at ≤8 mg/L) and against isolates nonsusceptible to meropenem, ceftazidime, and piperacillin-tazobactam ($MIC_{50/90}$, 4/8mg/L; 96.7%/86.7% isolates from Europe/APAC inhibited at ≤8mg/L; Table 2 and Figure 4)
- Cefepime-zidebactam inhibited 37.6%/40.5% of *Acinetobacter* spp. isolates (Europe/APAC; overall $MIC_{50/90}$, 16/32 mg/L) at ≤8 mg/L and 98.9%/100.0% at ≤64 mg/L, which is the proposed PK/PD breakpoint for these organisms (Table 1 and Figure 5)
- Cefepime-zidebactam inhibited 77.9%/90.6% of *Stenotrophomonas maltophilia* (Europe/APAC; overall $MIC_{50/90}$, 4/16 mg/L) at ≤8 mg/L (highest MIC, 64 mg/L; which is the proposed PK/PD breakpoint for these organisms (Table 1 and Figure 5)

Figure 1 Antimicrobial activity of cefepime-zidebactam against *Enterobacterales* stratified by geographic region



Conclusions

- Cefepime-zidebactam demonstrated potent *in vitro* activity against GNB isolates collected in European and APAC medical centres in 2018
- Cefepime-zidebactam retained potent *in vitro* activity against CRE, *P. aeruginosa* isolates nonsusceptible to meropenem, ceftazidime, and piperacillin-tazobactam, and MDR *Enterobacterales* and *P. aeruginosa*
- Cefepime-zidebactam was highly active against *S. maltophilia* (80.5% inhibited at ≤8 mg/L)
- Cefepime-zidebactam demonstrated good activity against *Acinetobacter* spp. ($MIC_{50/90}$, 16/32 mg/L) and retained activity against carbapenem-resistant isolates due to the β-lactam enhancer effect of zidebactam as zidebactam is not an inhibitor of class D OXA carbapenemases
- These *in vitro* results support further development of cefepime-zidebactam for treatment of systemic gram-negative infections

Table 1 Activity of cefepime-zidebactam and comparator antimicrobial agents when tested against gram-negative bacilli from Europe and the Asia-Pacific region (APAC)

Organism / Antimicrobial agent (no. tested)	MIC_{50}	MIC_{90}	Europe[a] %S	Europe[a] %R	Asia-Pacific[a] %S	Asia-Pacific[a] %R
Enterobacterales			(3,234)		(705)	
Cefepime-zidebactam	0.03	0.12	[100.0][b]		[100.0][b]	
Ceftazidime-avibactam	0.12	0.5	97.7	2.3	99.5	0.5
Ceftolozane-tazobactam	0.25	2	89.7	10.3	88.9	11.1
Cefoperazone-sulbactam	1	16	92.8[c]	4.1[c]	93.8	3.0
Piperacillin-tazobactam	2	64	86.5	10.1	81.7[c]	14.2[c]
Cefepime	0.06	64	80.7	16.3	80.8	16.1
Ceftriaxone	≤0.06	>8	75.9	23.4	76.7	22.6
Ceftazidime	0.25	>32	77.0	19.7	77.5	19.4
Meropenem	0.03	0.06	97.9	1.8	97.6	1.8
Amikacin	2	4	97.4	0.7	96.8	1.3
Gentamicin	0.5	>16	87.8	11.6	86.9	12.6
Tobramycin	1	16	83.3	13.5	82.3	15.3
Levofloxacin	0.06	16	77.5	19.1	76.4	20.9
Colistin	0.12	>8	86.3	13.7	87.0	13.0
P. aeruginosa			(684)		(165)	
Cefepime-zidebactam	1	4	[99.3][b]		[98.8][b]	
Ceftazidime-avibactam	2	8	94.6	5.4	96.4	3.6
Ceftolozane-tazobactam	1	4	92.3	7.7	94.5	5.5
Cefoperazone-sulbactam	8	>32	76.1[c]	11.0[c]	87.3[c]	6.7[c]
Piperacillin-tazobactam	4	128	70.7	29.3	80.0	20.0
Cefepime	4	16	79.2	20.8	88.5	11.5
Ceftazidime	2	32	74.1	25.9	84.2	15.8
Meropenem	0.5	16	71.6	15.4	82.4	6.7
Amikacin	4	16	84.2	10.5	90.9	7.3
Gentamicin	2	>16	78.5	21.5	87.3	12.7
Tobramycin	0.5	>16	84.4	15.6	90.9	9.1
Levofloxacin	0.5	32	60.1	39.9	75.2	24.8
Colistin	0.5	1	99.6	0.4	98.2	1.8
Acinetobacter spp.			(93)		(42)	
Cefepime-zidebactam	16	32	[37.6/98.9][b]		[40.5/100.0][b]	
Ceftazidime-avibactam	32	>32				
Ceftolozane-tazobactam	16	>16				
Cefoperazone-sulbactam	16	>32	49.5[c]	28.0[c]	52.4[c]	14.3[c]
Piperacillin-tazobactam	>128	>128	25.8[d]	68.8[d]	30.8[d]	64.1[d]
Cefepime	128	256	28.0[d]	69.9[d]	35.7[d]	61.9[d]
Ceftazidime	>32	>32	29.0[d]	66.7[d]	38.1[d]	52.4[d]
Meropenem	>32	>32	32.3	66.7	40.5	59.5
Amikacin	>32	>32	39.8	58.1	50.0	50.0
Gentamicin	>16	>16	34.4	65.6	42.9	57.1
Tobramycin	>16	>16	40.9	59.1	45.2	54.8
Levofloxacin	16	>32	29.0	71.0	40.5	57.1
Colistin	0.25	1	89.2	10.8	95.2	4.8
S. maltophilia[f]			(122)[f]		(32)[f]	
Cefepime-zidebactam	4	16	[77.9/100.0][b]		[90.6/100.0][b]	
Ceftazidime-avibactam	32	>32				
Ceftolozane-tazobactam	>16	>16				
Cefoperazone-sulbactam	32	>32				
Piperacillin-tazobactam	>128	>128				
Ceftazidime	>32	>32	12.3[d]	79.5[d]	25.0[d]	68.8[d]
Levofloxacin	1	4	84.4[d]	7.4[d]	84.4[d]	6.2[d]
TMP-SMX[e]	≤0.12	0.5	96.7	3.3	100.0	0.0

[a] Criteria as published by EUCAST unless noted. MIC_{50} and MIC_{90} values are for the Europe and Asia-Pacific isolates combined.
[b] Percentage inhibited at ≤8 mg/L in brackets for comparison purposes.
[c] Criteria as published in the Sulperazone Package Insert.
[d] CLSI breakpoints were applied due to the absence of EUCAST breakpoints.
[e] Percentages inhibited at ≤8/≤64 mg/L in brackets for comparison purposes.
[f] The number of isolates tested was adjusted because additional isolates were tested after the submission of the abstract.
[g] TMP-SMX, trimethoprim-sulfamethoxazole.

Table 2 Activity of cefepime-zidebactam and comparator antimicrobial agents when tested against carbapenem-resistant *Enterobacterales* (CRE) multidrug-resistant (MDR) *Enterobacterales* and *P. aeruginosa* from medical centres in Asia-Pacific and Europe during 2018

Organism / Antimicrobial agent (no. tested)	MIC_{50}	MIC_{90}	Europe[a] %S	Europe[a] %R	Asia-Pacific[a] %S	Asia-Pacific[a] %R
CRE			(77)		(15)	
Cefepime-zidebactam	1	2	[100.0][c]		[100.0][c]	
Ceftazidime-avibactam	2	>32	81.8	18.2	6.7	93.3
Ceftolozane-tazobactam	>16	>16	0.0	100.0	0.0	100.0
Cefoperazone-sulbactam	>32	>32	0.0[d]	96.1[d]	0.0[d]	100.0[d]
Piperacillin-tazobactam	>128	>128	0.0	100.0	0.0	100.0
Amikacin	8	>32	51.9	32.5	73.3	6.7
Gentamicin	4	>16	48.1	49.4	46.7	53.3
Tobramycin	16	>16	22.1	76.6	26.7	66.7
Levofloxacin	32	>32	13.0	85.7	20.0	66.7
Colistin	0.25	>8	70.1	29.9	86.7	13.3
MDR *Enterobacterales*[b]			(525)		(107)	
Cefepime-zidebactam	0.12	1	[100.0][c]		[100.0][c]	
Ceftazidime-avibactam	0.25	2	97.1	2.9	85.0	15.0
Ceftolozane-tazobactam	2	>16	48.6	51.4	51.7	48.3
Cefoperazone-sulbactam	16	>32	66.7[d]	21.4[d]	70.1[d]	17.8[d]
Piperacillin-tazobactam	32	>128	23.4	59.6	43.0	43.0
Cefepime	64	>256	16.4	74.9	17.8	72.9
Meropenem	0.03	16	85.0	11.0	86.0	12.1
Amikacin	4	16	82.5	8.2	86.9	3.7
Gentamicin	>16	>16	41.3	56.6	40.2	58.9
Tobramycin	16	>16	18.1	76.0	17.8	70.1
Levofloxacin	8	>32	17.8	75.0	19.8	69.8
Colistin	0.25	>8	82.4	17.6	84.0	16.0
MDR *P. aeruginosa*[b]			(195)		(29)	
Cefepime-zidebactam	4	8	[97.4][c]		[93.1][c]	
Ceftazidime-avibactam	4	32	82.1	17.9	79.3	20.7
Ceftolozane-tazobactam	2	>16	75.4	24.6	69.0	31.0
Cefoperazone-sulbactam	32	>32	29.2[d]	35.9[d]	41.4[d]	27.6[d]
Piperacillin-tazobactam	64	>128	10.8	89.2	13.8	86.2
Cefepime	16	64	35.9	64.1	48.3	51.7
Ceftazidime	32	>32	21.5	78.5	31.0	69.0
Meropenem	8	>32	22.1	47.7	27.6	37.9
Amikacin	8	>32	55.4	32.8	55.2	37.9
Gentamicin	16	>16	38.5	61.5	44.8	55.2
Tobramycin	4	>16	49.7	50.3	55.2	44.8
Levofloxacin	8	>32	19.5	80.5	10.3	89.7
Colistin	0.5	1	99.5	0.5	89.7	10.3

[a] Criteria as published by EUCAST unless noted. MIC_{50} and MIC_{90} values are for the Europe and Asia-Pacific isolates combined.
[b] MDR *Enterobacterales* and *P. aeruginosa* strains were classified according to recommended guidelines (Magiorakos et al., 2012) as follows: nonsusceptible (EUCAST criteria) to at least 3 antimicrobial classes.
[c] Percentage inhibited at ≤8 mg/L in brackets for comparison purposes.
[d] Criteria as published in the Sulperazone Package Insert.

Figure 2 Antimicrobial activity of cefepime-zidebactam against multidrug-resistant (MDR), extensively drug-resistant (XDR), and carbapenem-resistant *Enterobacterales* (CRE) isolates

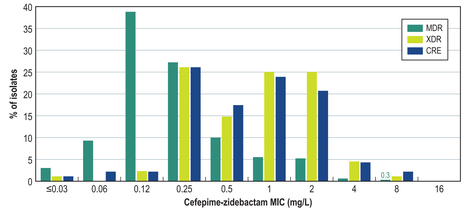


Figure 3 Antimicrobial activity of cefepime-zidebactam against *P. aeruginosa* stratified by geographic region

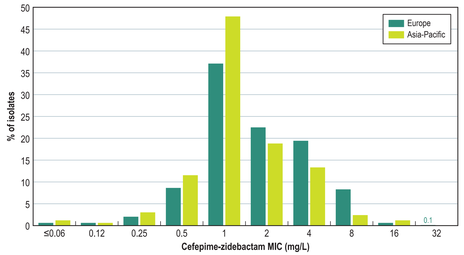
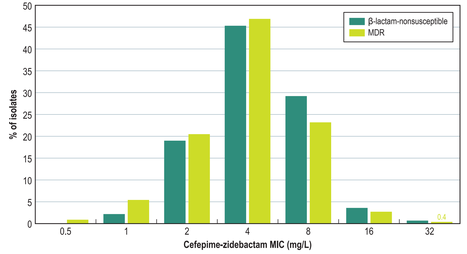
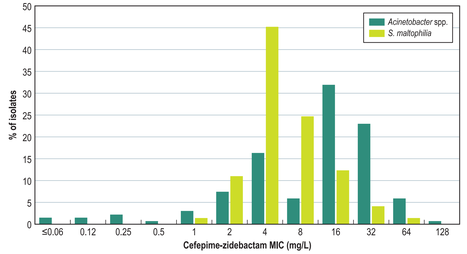


Figure 4 Antimicrobial activity of cefepime-zidebactam against β-lactam-nonsusceptible and multidrug-resistant (MDR) *P. aeruginosa*



β-lactam nonsusceptible defined as nonsusceptible to ceftazidime, meropenem, and piperacillin-tazobactam.

Figure 5. Antimicrobial activity of cefepime-zidebactam against *Acinetobacter* spp. and *S. maltophilia*



Acknowledgements

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