ECCMID 2019 | Poster #P1174

Antimicrobial Activity of High-Dose Extended-Infusion Cefepime-Tazobactam (WCK 4282) Tested against Gram-Negative Organisms Collected from Medical Centres in Europe and the Asia-Pacific Region (2018)

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Introduction

- Cefepime was initially approved by the United States Food and Drug Administration (US FDA) in 1997, and the clinical indications in the current US FDA product package insert include the treatment for 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 dosages vary from 1g q12 hours to 2g q8 hours administered as a 30-minute infusion
- Cefepime-tazobactam is currently under clinical development at 2g/2g q8 hours dosage as a 90-minute infusion
- Cefepime-tazobactam combination was demonstrated to be active against several isolates producing extended-spectrum β-lactamases (ESBLs) and AmpC β-lactamases
- We evaluated the potency and spectrum of activity of cefepime-tazobactam against contemporary gram-negative isolates collected by the SENTRY Antimicrobial Surveillance Program in the year 2018

Materials and Methods

- A total of 3,607 *Enterobacterales* and 830 *Pseudomonas aeruginosa* isolates (1/patient) were consecutively collected in 2018
  - 3,038 *Enterobacterales* and 680 *P. aeruginosa* from Europe (EUR; 29 centres in 14 nations)
  - 569 *Enterobacterales* and 150 *P. aeruginosa* from Asia-Pacific excluding China (APAC; 9 centres in 5 nations)
- Isolates were from bloodstream (34.0%), pneumonia (29.3%), urinary tract (25.7%), and intra-abdominal infections (11.0%)
- Susceptibility testing against cefepime-tazobactam (tazobactam at fixed 8 mg/L) and comparators was performed by reference broth microdilution method
- Percentage of isolates inhibited at cefepime ≤8 mg/L (Clinical and Laboratory Standards Institute [CLSI], cefepime high dose breakpoint) and at ≤16 mg/L (pharmacokinetic/pharmacodynamic [PK/PD]-susceptible breakpoint based on high-dose extended infusion) in presence of tazobactam were evaluated
- European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints were applied for categorizing multidrug-resistant (MDR) subsets, and EUCAST and CLSI breakpoints were applied for comparators

Results

- Cefepime-tazobactam inhibited 98.3/97.9% of *Enterobacterales* isolates from EUR/APAC (98.2% overall) at ≤16 mg/L (97.8/97.4% at ≤8 mg/L; CLSI breakpoint for high dose), with spectrum of activity similar to meropenem (97.6% susceptible [S]) and greater than ceftolozane-tazobactam (89.2%S) and piperacillin-tazobactam (82.9%S; EUCAST) (Tables 1 and 2 and Figure 1)
- Among MDR *Enterobacterales* (n=550), 84.0% were meropenem-S EUCAST; 81.3% per CLSI and cefepime-tazobactam inhibited 88.4% at ≤16 mg/L and 85.3% at ≤8 mg/L (Table 2 and Figure 2)
- ESBL-phenotype rates were 17.2/24.6% among *Escherichia coli* and 39.9/19.8% among *Klebsiella pneumoniae* in EUR/APAC (data not shown)
- Among ESBL-phenotype *E. coli* and *K. pneumoniae* from EUR, 99.6% and 81.1% of isolates were inhibited at a cefepime-tazobactam MIC of ≤16 mg/L (Table 1), 86.1%and 35.5% were ceftolozane-tazobactam-S, and 63.7% and 23.5% were piperacillin-tazobactam-S, respectively (data not shown)
- Overall, 91.2% of *Enterobacterales* isolates displaying an ESBL phenotype (n=634) were inhibited at cefepime-tazobactam MIC values of ≤16 mg/L (89.1% at ≤8 mg/L; $MIC_{50/90}$, 0.12/16 mg/L), whereas susceptibility rates for meropenem ($MIC_{50/90}$, 0.03/8 mg/L) and ceftolozane-tazobactam ($MIC_{50/90}$, 1/>16 mg/L) were 87.5% and 63.3%, respectively (Table 2 and Figure 2)
- Cefepime-tazobactam inhibited 99.3/95.5% of *Enterobacter* spp. from EUR/APAC at ≤16 mg/L and exhibited good activity against ceftazidime-nonsusceptible isolates (n=140; $MIC_{50/90}$, 0.25/4 mg/L; 96.4% inhibited at ≤16 mg/L; Table 2 and Figure 2)
- When tested against *P. aeruginosa*, cefepime-tazobactam activity ($MIC_{50/90}$, 2/16 mg/L; 94.0/92.0% inhibited at ≤16 mg/L for EUR/APAC; 93.6% overall) was similar to that of ceftolozane-tazobactam ($MIC_{50/90}$, 1/4 mg/L; 92.5/94.0%S for EUR/APAC; 92.7% overall) and greater than those of piperacillin-tazobactam ($MIC_{50/90}$, 4/128 mg/L; 70.7/81.3%S for EUR/APAC; 72.6% overall) and meropenem ($MIC_{50/90}$, 0.5/16 mg/L; 71.8/81.3%S for EUR/APAC and 73.5% overall; Tables 1 and 3 and Figure 3)
- Cefepime-tazobactam retained good activity against meropenem-nonsusceptible *P. aeruginosa* (n=220; $MIC_{50/90}$, 8/32 mg/L; 79.5% inhibited at ≤16 mg/L) with coverage similar to ceftolozane-tazobactam ($MIC_{50/90}$, 2/>16 mg/L; 75.5%S; Table 3)

Conclusions

- Cefepime-tazobactam demonstrated potent activity against *Enterobacterales*, including MDR, ESBL-phenotype, and ceftazidime-nonsusceptible isolates
- Cefepime-tazobactam spectrum of activity against *P. aeruginosa* was similar to that of ceftolozane-tazobactam and greater than those of meropenem and piperacillin-tazobactam
- Cefepime-tazobactam may represent a valuable option for treating serious infections caused by gram-negative bacilli, including MDR isolates

Acknowledgements

This study was supported by Wockhardt Bio Ag.

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Table 1 Summary of cefepime-tazobactam activity against the main species and resistant subsets

Organism (no. of isolates from EUR/APAC)	Cefepime-tazobactam $MIC_{50/90}$ (% inhibited at ≤8 mg/L [CLSI high dose]/≤16 mg/L [proposed PK/PD breakpoint])	
	EUR	APAC
Enterobacterales (3,038/569)	0.06/0.25 (97.8/98.3)	0.03/0.25 (97.4/97.9)
E. coli (1,590/276)	0.03/0.12 (99.9/99.9)	0.03/0.12 (99.3/99.3)
ESBL-phenotype *E. coli* (273/68)	0.06/0.5 (99.3/99.6)	0.06/0.25 (97.1/97.1)
K. pneumoniae (596/116)	0.06/8 (90.4/92.4)	0.03/0.25 (95.7/95.7)
ESBL-phenotype *K. pneumoniae* (238/23)	0.25/128 (76.1/81.1)	0.12/64 (78.3/78.3)
Enterobacter spp. (280/67)	0.06/1 (98.9/99.3)	0.06/8 (91.0/95.5)
Proteus mirabilis (158/21)	0.06/0.12 (100.0/100.0)	0.06/0.12 (100.0/100.0)
S. marcescens (114/31)	0.06/0.25 (99.1/99.1)	0.12/0.25 (100.0/100.0)
P. aeruginosa (680/150)	4/16 (81.0/94.0)	2/16 (89.3/92.0)

[a] According to cefepime-susceptible breakpoint for high dosage (2g q8 h) as published in the CLSI M100 document (2019).
[b] EUR, Europe; APAC, Asia-Pacific region excluding China; ESBL, extended-spectrum β-lactamase; PK/PD, pharmacokinetic/pharmacodynamic.

Table 2 Activity of cefepime-tazobactam and comparator antimicrobial agents when tested against *Enterobacterales* from medical centres in Europe and Asia-Pacific region during 2018

Antimicrobial agent / Antimicrobial (no. tested)	MIC_{50}	MIC_{90}	CLSI[a] %S	CLSI[a] %R	EUCAST[a] %S	EUCAST[a] %R
Enterobacterales (3,607)						
Cefepime-tazobactam	0.06	0.25	[98.2][b]			
Cefepime	0.06	64	83.1	13.9	81.6	15.4
Ceftriaxone	≤0.06	>8	77.4	21.9	77.4	21.9
Ceftazidime	0.25	>32	81.2	16.9	78.3	18.8
Ceftolozane-tazobactam	0.25	2	91.9	6.4	89.2	10.8
Cefoperazone-sulbactam	1	16	93.0[c]	3.9		
Piperacillin-tazobactam	2	64	86.7	7.9	82.9	13.3
Meropenem	0.03	0.06	97.1	2.4	97.6	1.8
Amikacin	2	4	98.8	0.8	97.0	1.2
Gentamicin	0.5	>16	88.1	11.5	87.6	11.9
Levofloxacin	0.06	16	77.1	20.2	77.1	20.2
MDR (550)[d]						
Cefepime-tazobactam	0.25	32	[88.4][b]			
Cefepime	128	>256	21.5	70.5	17.1	74.2
Ceftriaxone	>8	>8	10.2	87.8	10.2	87.8
Ceftazidime	32	>32	20.2	75.6	13.5	79.8
Ceftolozane-tazobactam	2	>16	60.5	33.2	48.9	51.1
Cefoperazone-sulbactam	16	>32	65.6[c]	22.2		
Piperacillin-tazobactam	32	>128	40.5	36.7	25.5	59.5
Meropenem	0.06	16	81.3	16.0	84.0	12.0
Amikacin	4	16	92.4	5.1	82.4	7.6
Gentamicin	>16	>16	44.0	54.0	42.2	56.0
Levofloxacin	8	>32	16.9	75.4	16.9	75.4
ESBL-phenotype (634)[e]						
Cefepime-tazobactam	0.12	16	[91.2][b]			
Cefepime	64	>256	16.7	72.1	13.2	78.5
Ceftriaxone	>8	>8	6.3	92.7	6.3	92.7
Ceftazidime	32	>32	20.0	70.8	7.1	80.0
Ceftolozane-tazobactam	1	>16	72.8	23.2	63.3	36.7
Cefoperazone-sulbactam	8	>32	72.7[c]	18.6		
Piperacillin-tazobactam	16	>128	59.0	26.7	48.9	41.0
Meropenem	0.03	8	86.6	12.5	87.5	9.6
Amikacin	4	16	94.3	3.9	87.2	5.7
Gentamicin	1	>16	61.4	38.2	60.9	38.6
Levofloxacin	8	>32	27.8	66.8	27.8	66.8
Ceftazidime-nonsusceptible *Enterobacter* spp. (140)[f]						
Cefepime-tazobactam	0.25	4	[96.4][b]			
Cefepime	2	256	57.9	28.6	42.9	32.1
Ceftriaxone	>8	>8	1.4	97.1	1.4	97.1
Ceftazidime	>32	>32	7.1	91.4	0.0	92.9
Ceftolozane-tazobactam	4	>16	27.0	49.6	15.3	84.7
Cefoperazone-sulbactam	16	>32	66.4[c]	10.7		
Piperacillin-tazobactam	64	>128	22.1	42.1	12.1	77.9
Meropenem	0.06	1	90.0	5.0	95.0	2.9
Amikacin	2	4	97.9	1.4	94.3	2.1
Gentamicin	0.5	>16	71.4	26.4	70.0	28.6
Levofloxacin	0.25	16	67.6	27.3	67.6	27.3

MDR, multidrug-resistant; ESBL, extended-spectrum β-lactamase
[a] Criteria as published by CLSI (2019) and EUCAST (2019).
[b] Values in brackets indicate percentage inhibited at ≤16 mg/L, which is the proposed breakpoints for high dosage.
[c] Sulperazone Package Insert.
[d] Organisms include: *Citrobacter freundii* species complex (5), *C. koseri* (1), *Enterobacter aerogenes* (4), *E. cloacae* species complex (60), *E. coli* (197), *Hafnia alvei* (9), *Klebsiella oxytoca* (5), *K. pneumoniae* (213), *Morganella morganii* (8), *Proteus mirabilis* (27), *Providencia stuartii* (3), *Serratia marcescens* (18).
[e] Organisms include: *Escherichia coli* (340), *Klebsiella oxytoca* (19), *K. pneumoniae* (261), *Proteus mirabilis* (14).
[f] Organisms include: *Enterobacter aerogenes* (27), *E. asburiae* (1), *E. cloacae* species complex (112).

Table 3 Activity of cefepime-tazobactam and comparator antimicrobial agents when tested against *Pseudomonas aeruginosa* isolates from medical centres in Europe and Asia-Pacific region during 2018

Antimicrobial agent / Antimicrobial (no. tested)	MIC_{50}	MIC_{90}	CLSI[a] %S	CLSI[a] %R	EUCAST[a] %S	EUCAST[a] %R
P. aeruginosa (830)						
Cefepime-tazobactam	2	16	[93.6][b]			
Cefepime	4	16	81.0	7.1	81.0	19.0
Ceftazidime	2	32	76.0	17.1	76.0	24.0
Ceftolozane-tazobactam	1	4	92.7	3.9	92.7	7.3
Cefoperazone-sulbactam	8	>32	78.2	10.3[c]		
Piperacillin-tazobactam	4	128	72.6	14.0	72.6	27.4
Meropenem	0.5	16	73.5	20.5	73.5	13.9
Amikacin	4	16	90.0	6.5	85.4	10.0
Tobramycin	0.5	>16	85.4	13.8	85.4	14.6
Levofloxacin	0.5	32	70.9	20.8	63.0	37.0
Meropenem-nonsusceptible *P. aeruginosa* (220)						
Cefepime-tazobactam	8	32	[79.5][b]			
Cefepime	16	32	45.0	22.7	45.0	55.0
Ceftazidime	16	>32	36.8	48.2	36.8	63.2
Ceftolozane-tazobactam	2	>16	75.5	17.3	75.5	24.5
Cefoperazone-sulbactam	32	>32	39.1[c]	33.2		
Piperacillin-tazobactam	64	>128	28.8	40.2	28.8	71.2
Meropenem	16	>32	0.0	77.3	0.0	52.3
Amikacin	8	>32	69.1	22.3	60.9	30.9
Tobramycin	2	>16	57.7	40.9	57.7	42.3
Levofloxacin	8	>32	22.3	67.3	22.3	77.7

[a] Criteria as published by CLSI (2019) and EUCAST (2019).
[b] Percentage inhibited at ≤16 mg/L, which is the proposed pharmacokinetic/pharmacodynamic-susceptible breakpoint for high dose.
[c] Sulperazone Package Insert.

Figure 1 MIC distributions for cefepime-tazobactam and cefepime when testing *Enterobacterales* isolates from Europe and the Asia-Pacific region (2018)

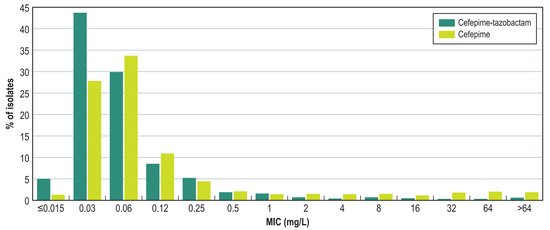
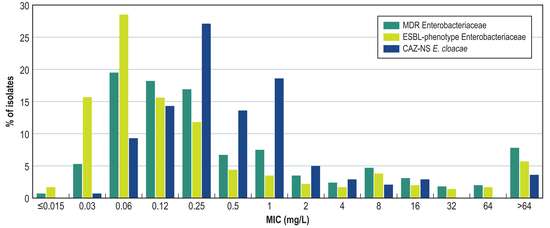
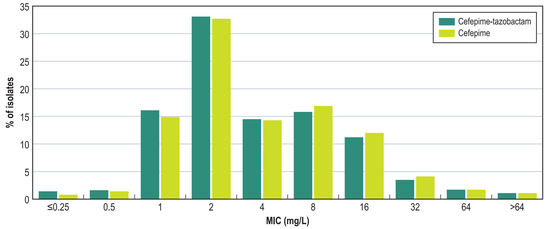


Figure 2 MIC distributions for cefepime-tazobactam when testing *Enterobacterales*-resistant subsets from Europe and the Asia-Pacific region (2018)



MDR, multidrug-resistant; ESBL, extended-spectrum β-lactamase; CAZ-NS, ceftazidime-nonsusceptible.

Figure 3 MIC distributions for cefepime-tazobactam and cefepime when testing *P. aeruginosa* isolates from Europe and the Asia-Pacific region (2018)



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