Antimicrobial Activity of WCK 4282 (High-Dose Cefepime-Tazobactam) Tested against Gram-negative Organisms from Medical Centers Located in Europe and the Asia-Pacific Region

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HS SADER, DJ FARRELL, RK FLAMM, M CASTANHEIRA, RN JONES
JMI Laboratories, North Liberty, IA, USA

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JMI Laboratories
North Liberty, IA, USA
www.jmilabs.com
319.665.3370, fax 319.665.3371
helio-sader@jmilabs.com

ABSTRACT

Background: WCK4282 (cefepime-tazobactam) is currently under clinical development at 2g/2g q8 as well as q12 hours dosage. We evaluated the spectrum of activity of WCK 4282 (cefepime-tazobactam) tested against contemporary Gram-negative isolates collected as part of the SENTRY Antimicrobial Surveillance Program.

Methods: A total of 4,326 unique patient isolates, including 2,926 from Europe (EU; 44 centers in 19 nations), 983 from Asia-Pacific (APAC; 15 centers in 8 nations) and 417 from China (10 centers), were susceptibility tested against cefepime-tazobactam (tazobactam at fixed 8 mg/L) and comparators by reference broth microdilution method. The isolates were collected in 2014, except China (2013).

Results: The most common infection types were pneumonia (31.8%), bacteremia (31.6%) and skin/soft tissue (15.5%). Against Enterobacteriaceae, cefepime-tazobactam inhibited 93.8-98.7% of strains at ≤8 mg/L [high dose, CLSI; see Tables] and 92.6-97.8 at ≤2 mg/L [low dose, CLSI]), and showed activity similar to that of meropenem (94.2-98.6% susceptible [CLSI]). Further, cefepime-tazobactam was more active than piperacillin-tazobactam (84.2-89.2% susceptible [CLSI]) against Enterobacteriaceae [79.3-85.0% by EUCAST]. Extended-spectrum β-lactamase (ESBL)-phenotype rates were (EU/APAC/China) 19.3/18.8/66.3% among *E. coli*; and 44.8/28.7/41.7% among *Klebsiella* spp.; 100.0 and 71.8% of ESBL-phenotype *E. coli* and *Klebsiella* spp. from EU were inhibited at cefepime-tazobactam MIC of ≤8 mg/L, respectively. Cefepime-tazobactam inhibited 97.4-100.0% of *Enterobacter* spp. (EBS) at ≤8 mg/L; and exhibited good activity against ceftazidime-non-susceptible isolates ($MIC_{50/90}$, 0.25/2 mg/L and 95.5% inhibited at ≤8 mg/L in EU). When tested against *P. aeruginosa*, cefepime-tazobactam activity ($MIC_{50/90}$ of 4/16 mg/L and 79.8% inhibited at ≤8 mg/L in EU) was similar to that of cefepime ($MIC_{50/90}$ of 4/32 mg/L and 78.3% susceptible in EU), and greater than ceftazidime and meropenem (73.1-73.9% susceptible in EU). Cefepime-tazobactam and all β-lactams showed limited activity against *Acinetobacter* spp.

Conclusion: WCK 4282 demonstrated potent activity against Enterobacteriaceae, including ESBL-phenotype *E. coli* and ceftazidime-non-susceptible EBS strains, and *P. aeruginosa* isolated in hospitals from EU, APAC and China. WCK 4282 may represent a valuable option for the treatment of serious infections caused by Gram-negative bacilli, including some multidrug-resistant isolates.

INTRODUCTION

WCK 4282 is a combination agent consisting of cefepime and the β-lactamase inhibitor tazobactam. Cefepime is a parenteral fourth-generation oxyimino-cephalosporin that has a broad-spectrum of 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 the 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 doses are administered as a 30 min infusion.

After reviewing clinical and pharmacokinetic/pharmacodynamics (PK-PD) data and contemporary MIC distributions for cefepime, the Clinical and Laboratory Standards Institute (CLSI) revised its clinical breakpoints in 2014 and introduced the "susceptible-dose dependent" (SDD) interpretive criteria for cefepime. According to the current CLSI breakpoint criteria for Enterobacteriaceae published in the M100-S26 document, the susceptible and resistant breakpoints are ≤2 and ≥16 mg/L, respectively. Furthermore, the SDD interpretative criteria essentially provides three susceptible breakpoints for cefepime according to the dosage, i.e. ≤2 mg/L for 1g q12 hours dosage (low-dosage), ≤4 mg/L for 1g q 8 hours or 2g q12 hours dosages and ≤8 mg/L for 2g q8 hours (high-dosage).

Cefepime-tazobactam is currently under clinical development at 2g/2g q8 hours as well as q12 hours dosage as a 90 min infusion. In this investigation, we evaluated the in vitro potency and the spectrum of activity of cefepime-tazobactam when tested against Gram-negative isolates collected worldwide in 2013-2014 as part of the SENTRY Antimicrobial Surveillance Program, coordinated by JMI Laboratories (North Liberty, Iowa USA).

MATERIALS AND METHODS

Organism collection: A total of 4,326 unique patient isolates collected as part of a global surveillance program (SENTRY Program) were evaluated. The collection included 2,926 from 44 medical centres located in 19 European nations, 983 isolates from 15 medical centres located in eight nations from the Asia-Pacific region (APAC) and 417 isolates from 10 medical centres located in China. All isolates were collected in 2014, except those from China, which were collected in 2013.

Antimicrobial susceptibility testing: MIC values for cefepime-tazobactam and comparator agents were determined using CLSI broth microdilution methodology as described in CLSI document M07-A10 (2015). Cefepime was combined with tazobactam at fixed concentrations of 4 and 8 mg/L. Cefepime susceptible breakpoints published in the CLSI document M100-S26 (2016) for low dosage (≤2 mg/L; 1g every 12 h) and high dosage (≤8 mg/L; 2g every 8 h) were applied for comparison purposes only. Susceptibility interpretations published by CLSI (document M100-S26; 2016) and EUCAST (http://www.eucast.org/clinical_breakpoints/; 2016) were applied for comparator agents, when available. Quality control (QC) was performed using *Escherichia coli* ATCC 25922, ATCC 35218 and NCTC 13353, *Klebsiella pneumoniae* ATCC 700603 and ATCC BAA-1705, and *P. aeruginosa* ATCC 27853. All QC MIC results were within acceptable ranges as published in CLSI documents, including WCK 4282 (see Poster # P0806).

RESULTS

- The most common monitored infection types were pneumonia (31.8%), bacteremia (31.6%) and skin/soft tissue (15.5%). These three types of infections accounted for almost 80% of the organisms.
- Susceptibility rates were generally higher in the APAC region (excluding China), followed by Europe and China (**Tables 1** and **2**).
- Against Enterobacteriaceae, cefepime-tazobactam tested at fixed tazobactam concentration of 8 mg/L inhibited 93.8 (China) to 98.7% (APAC) of strains at ≤8/8 mg/L (high-dose, CLSI) and 92.6 to 97.8% at ≤2 mg/L (low-dose, CLSI; **Tables 1** and **2**). Results were very similar when cefepime-tazobactam was tested at fixed tazobactam concentration of 4 mg/L, with 93.4 (China) to 98.1% (APAC) of strains inhibited at ≤8/4 mg/L (**Table 2**).
- Cefepime-tazobactam in vitro activity against Enterobacteriaceae ($MIC_{50/90}$, ≤0.03-0.06/0.25-0.5 mg/L and 93.8-98.7% inhibited at ≤8/8 mg/L) was similar to that of meropenem ($MIC_{50/90}$, ≤0.06/≤0.06 mg/L; 94.2-98.6% susceptible [CLSI; 94.2-98.7% by EUCAST]) and greater than that of piperacillin-tazobactam ($MIC_{50/90}$, 2-32->64 mg/L; 84.2-89.2% susceptible [CLSI; 79.3-85.0% by EUCAST]; **Tables 1** and **2**).
- Extended-spectrum β-lactamase (ESBL)-phenotype rates were (EU/APAC/China) 19.3/18.8/66.3% among *E. coli*; and 44.8/28.7/41.7% among *Klebsiella* spp.; 100.0 and 69.5% of ESBL-phenotype *E. coli* and *K. pneumoniae* from Europe were inhibited at cefepime-tazobactam MIC of ≤8/8 mg/L, respectively (**Table 3**).
- Cefepime-tazobactam tested at fixed 8 mg/L inhibited 97.4-100.0% of *Enterobacter* spp. at ≤8/8 mg/L; and exhibited good activity against ceftazidime-non-susceptible isolates (95.5% inhibited at ≤8/8 mg/L in Europe; **Table 3**).
- All (100.0%) *P. mirabilis, P. vulgaris, M. morganii* and *S. marcescens* isolates from all three geographic regions were inhibited at ≤8/8 mg/L of cefepime-tazobactam (**Table 1**).
- When tested against *P. aeruginosa*, the in vitro activities of the cefepime-tazobactam combination tested at fixed 4 and 8 mg/L ($MIC_{50/90}$ of 2-4/16-32 mg/L) were similar to that observed for cefepime ($MIC_{50/90}$ of 2-4/32 mg/L).
- Cefepime-tazobactam inhibited 79.9/85.8/73.8% of *P. aeruginosa* isolates from Europe/APAC/China at ≤8/8 mg/L, and *P. aeruginosa* susceptibility rates were 78.3/84.8/72.6% for cefepime, 74.7/81.7/66.7% for piperacillin-tazobactam and 73.8/83.2/69.0% for meropenem (Europe/APAC/China by CLSI and EUCAST criteria; **Table 2**).
- Cefepime-tazobactam and all β-lactams tested exhibited limited activity against *P. aeruginosa* isolates non-susceptible to ceftazidime and/or meropenem, as well as against *Acinetobacter* spp. (**Tables 1**, **2** and **3**).

Table 1. Summary of cefepime-tazobactam activity stratified by geographic region.

Organism (n: Europe/APAC/China)	Cefepime-tazobactam MIC_{50}/MIC_{90} (% inhibited at ≤8 mg/L [high dose, CLSI])[a]		
	Europe	APAC[b]	China
Enterobacteriaceae (2,351/693/243)	≤0.03/0.5 (95.8)	≤0.03/0.25 (98.7)	0.06/0.5 (93.8)
E. coli (883/325/104)	≤0.03/0.12 (100.0)	≤0.03/0.06 (99.7)	0.06/0.25 (96.2)
ESBL-phenotype (170/61/69)	0.12/1 (100.0)	0.06/0.25 (98.4)	0.06/0.25 (94.2)
Klebsiella spp. (737/230/72)	0.06/32 (87.4)	≤0.03/0.25 (96.5)	0.06/64 (86.1)
ESBL-phenotype (330/230/30)	0.5/>64 (71.8)	0.12/64 (87.9)	0.12/64 (66.7)
K. pneumoniae (612/208/67)	0.06/64 (85.0)	≤0.03/0.5 (96.2)	0.06/64 (85.1
MER-non-susceptible (96/8/10)	64/>64 (14.6)	>64/- (0.0)	64/>64 (0.0)
Klebsiella oxytoca (12422/5)	≤0.03/1 (99.2)	≤0.03/0.12 (100.0)	≤0.03/- (100.0)
P. mirabilis (94/14/5)	0.06/0.12 (100.0)	0.06/0.06 (100.0)	0.06/- (100.0)
ESBL-phenotype (14/-/1)	0.12/0.25 (100.0)	-	0.06/- (100.0)
Enterobacter spp. (228/68/38)	0.06/0.5 (98.7)	0.06/1 (100.0)	0.06/1 (97.4)
CAZ-non-susceptible (66/23/15)	0.25/2 (95.5)	0.25/2 (100.0)	0.25/8 (93.3)
Morganella morganii (76/10/3)	≤0.03/0.06 (100.0)	≤0.03/≤0.03 (100.0)	≤0.03/- (100.0)
Citrobacter spp. (132/15/6)	≤0.03/0.25 (99.2)	≤0.03/0.25 (100.0)	0.12/- (100.0)
S. marcescens (93/25/11)	0.06/0.25 (100.0)	0.06/0.12 (100.0)	0.06/0.25 (100.0)
Proteus vulgaris (55/1/4)	0.06/0.12 (100.0)	0.06/- (100.0)	0.06/- (100.0)
Providencia spp. (53/2/-)	≤0.03/0.06 (98.1)	≤0.03/- (100.0)	-
P. aeruginosa (391/197/84)	4/16 (79.8)	2/16 (85.8)	4/32 (73.8)
CAZ-non-susceptible (105/40/25)	16/32 (31.4)	16/>64 (35.0)	32/>64 (20.0)
MER-non-susceptible (102/33/26)	16/32 (42.2)	16/>64 (39.4)	32/>64 (15.6)
A. baumannii (184/93/90)	64/>64 (18.5)	>64/>64 (18.3)	>64/>64 (15.6)

a. According to cefepime susceptible breakpoint for high dosage (2g q8 h) as published in the CLSI document M100-S26.
b. APAC = Asia-Pacific region excluding China.

Table 3. Cumulative frequency distributions of MIC results for cefepime and cefepime plus tazobactam at fixed concentration of 8 mg/L (FEP-TAZ fixed 8) when tested against 2,926 bacterial isolates from Europe.

Organism/ antimicrobial	No. of organisms (cumulative percentage) inhibited at MIC (μg/mL) of:										
	≤0.06	0.12	0.25	0.5	1	2	4	8	16	32	>32
Enterobacteriaceae (2,351)											
FEP-TAZ fixed 8	1,762 (74.9)	203 (83.6)	117 (88.6)	67 (91.4)	35 (92.9)	32 (94.3)	19 (95.1)	18 (95.8)	13 (96.4)	14 (97.0)	71 (100.0)
Cefepime	1,495 (63.6)	173 (70.9)	102 (75.3)	55 (77.6)	38 (79.2)	43 (81.1)	28 (82.3)	63 (84.9)	64 (87.7)	59 (90.2)	231 (100.0)
E. coli (883)											
FEP-TAZ fixed 8	743 (84.1)	71 (92.2)	36 (96.3)	13 (97.7)	3 (98.1)	7 (98.9)	6 (99.5)	4 (100.0)			
Cefepime	637 (72.1)	54 (78.3)	24 (81.0)	15 (82.7)	10 (83.8)	14 (85.4)	13 (86.9)	26 (89.8)	21 (92.2)	22 (94.7)	47 (100.0)
ESBL-phenotype (170)											
FEP-TAZ fixed 8	83 (48.8)	37 (70.6)	22 (83.5)	10 (89.4)	2 (90.6)	7 (94.7)	5 (97.6)	4 (100.0)			
Cefepime	10 (5.9)	7 (10.0)	4 (12.4)	5 (15.3)	6 (18.8)	11 (25.3)	12 (32.4)	25 (47.1)	21 (59.4)	22 (72.4)	47 (100.0)
K. pneumoniae (612)											
FEP-TAZ fixed 8	364 (59.5)	44 (66.7)	32 (71.9)	28 (76.5)	16 (79.1)	15 (81.5)	10 (83.2)	11 (85.0)	12 (86.9)	12 (88.9)	68 (100.0)
Cefepime	267 (43.6)	21 (47.1)	20 (50.3)	11 (52.1)	9 (53.6)	5 (54.4)	6 (55.4)	29 (60.1)	36 (66.0)	35 (71.7)	173 (100.0)
ESBL-phenotype (302)											
FEP-TAZ fixed 8	85 (28.1)	29 (37.7)	23 (45.4)	22 (52.6)	15 (57.6)	15 (62.6)	10 (65.9)	11 (69.5)	12 (73.5)	12 (77.5)	68 (100.0)
Cefepime		2 (0.7)	3 (1.7)	7 (4.0)	6 (6.0)	5 (7.6)	6 (9.6)	29 (19.2)	36 (31.1)	35 (42.7)	173 (100.0)
MER-non-susceptible (96)											
FEP-TAZ fixed 8						2 (2.1)	5 (7.3)	7 (14.6)	11 (26.0)	7 (33.3)	64 (100.0)
Cefepime							1 (1.0)	0 (1.0)	2 (3.1)	5 (8.3)	88 (100.0)
P. mirabilis (94)											
FEP-TAZ fixed 8	80 (85.1)	11 (96.8)	2 (98.9)	1 (100.0)							
Cefepime	69 (73.4)	8 (81.9)	5 (87.2)	1 (88.3)	7 (95.7)	1 (96.8)	1 (97.9)	0 (97.9)	0 (97.9)	0 (97.9)	2 (100.0)
Enterobacter spp. (228)											
FEP-TAZ fixed 8	138 (60.5)	35 (75.9)	21 (85.1)	18 (93.0)	8 (96.5)	2 (97.4)	2 (98.2)	1 (98.7)	1 (99.1)	1 (99.6)	1 (100.0)
Cefepime	129 (56.6)	30 (69.7)	24 (80.3)	12 (85.5)	5 (87.7)	11 (92.5)	3 (93.9)	6 (96.5)	3 (97.8)	1 (98.2)	4 (100.0)
CAZ-non-susceptible (66)											
FEP-TAZ fixed 8	2 (3.0)	18 (30.3)	15 (53.0)	16 (77.3)	7 (87.9)	2 (90.9)	2 (93.9)	1 (95.5)	1 (97.0)	1 (98.5)	1 (100.0)
Cefepime	2 (3.0)	6 (12.1)	16 (36.4)	10 (51.5)	5 (59.1)	11 (75.8)	3 (80.3)	5 (87.9)	3 (92.4)	1 (93.9)	4 (100.0)
P. aeruginosa (391)											
FEP-TAZ fixed 8	1 (0.3)	1 (0.5)	1 (0.8)	7 (2.6)	64 (18.9)	120 (49.6)	63 (65.7)	55 (79.8)	46 (91.6)	23 (97.4)	10 (100.0)
Cefepime		2 (0.5)	0 (0.5)	13 (3.8)	52 (17.1)	128 (49.9)	56 (64.2)	55 (78.3)	44 (89.5)	27 (96.4)	14 (100.0)
CAZ-non-susceptible (105)											
FEP-TAZ fixed 8					2 (1.9)	2 (3.8)	9 (12.4)	20 (31.4)	40 (69.5)	22 (90.5)	10 (100.0)
Cefepime					1 (1.0)	2 (2.9)	6 (8.6)	19 (26.7)	37 (61.9)	26 (86.7)	14 (100.0)
MER-non-susceptible (102)											
FEP-TAZ fixed 8					2 (2.0)	3 (4.9)	14 (18.6)	24 (42.2)	31 (72.5)	18 (90.2)	10 (100.0)
Cefepime					1 (1.0)	3 (3.9)	12 (15.7)	21 (36.3)	30 (65.7)	21 (86.3)	14 (100.0)
A. baumannii (184)											
FEP-TAZ fixed 8	14 (7.6)	5 (10.3)	2 (11.4)	1 (12.0)	3 (13.6)	6 (16.8)	1 (17.4)	2 (18.5)	10 (23.9)	16 (32.6)	124 (100.0)
Cefepime				5 (2.7)	1 (3.3)	6 (6.5)	11 (12.5)	7 (16.3)	5 (19.0)	14 (26.6)	135 (100.0)

Table 2. Activity of cefepime-tazobactam (FEP-TAZ) combinations (tazobactam at fixed 4 and 8 mg/L) and comparator agents tested against bacterial isolates from Europe, Asia-Pacific region and China.

Region/organisms/ Antimicrobial (no. tested)	MIC_{50}	MIC_{90}	CLSI[a] %S	CLSI[a] %R	EUCAST[a] %S	EUCAST[a] %R
Europe						
Enterobacteriaceae (2,351)						
FEP-TAZ (fixed 8 mg/L)	≤0.03	0.5	(95.8/94.3)[b]	-	-	-
FEP-TAZ (fixed 4 mg/L)	≤0.03	1	(94.7/93.2)[b]	-	-	-
Cefepime	0.06	32	81.1	15.1	79.2	17.7
Ceftazidime	0.25	32	78.4	18.3	74.6	21.6
Ceftriaxone	0.12	>8	72.1	26.5	72.1	26.5
Piperacillin-tazobactam	2	>64	84.2	10.7	79.5	15.8
Meropenem	0.03	0.06	95.5	4.1	95.9	3.0
Levofloxacin	≤0.12	>4	78.0	19.6	75.9	22.0
Gentamicin	≤1	>8	85.3	13.8	84.1	14.7
P. aeruginosa (391)						
FEP-TAZ (fixed 8 mg/L)	4	16	(79.8)[c]	-	-	-
FEP-TAZ (fixed 4 mg/L)	2	16	(78.5)[c]	-	-	-
Cefepime	4	32	78.3	10.5	78.3	21.7
Ceftazidime	2	>32	73.1	20.2	73.1	26.9
Piperacillin-tazobactam	4	>64	74.7	13.8	74.7	25.3
Meropenem	0.5	16	73.9	18.4	73.9	11.0
Levofloxacin	0.5	>4	71.1	23.8	63.7	28.9
Amikacin	2	16	91.0	4.9	86.7	9.0
A. baumannii (184)						
FEP-TAZ (fixed 8 mg/L)	64	>64	(18.5)[c]	-	-	-
FEP-TAZ (fixed 4 mg/L)	64	>64	(17.4)[c]	-	-	-
Cefepime	>64	>64	16.3	81.0	-	-
Ceftazidime	>32	>32	17.4	79.3	-	-
Piperacillin-tazobactam	>64	>64	19.6	76.6	-	-
Ampicillin-sulbactam	>32	>32	24.5	70.7	-	-
Meropenem	>32	>32	26.1	72.8	26.1	69.6
Levofloxacin	>4	>4	18.5	69.0	17.4	81.5
Amikacin	>32	>32	28.8	70.1	26.6	71.2
Asia-Pacific region (excluding China)						
Enterobacteriaceae (693)						
FEP-TAZ (fixed 8 mg/L)	≤0.03	0.25	(98.7/97.8)[b]	-	-	-
FEP-TAZ (fixed 4 mg/L)	≤0.03	0.25	(98.1/96.5)[b]	-	-	-
Cefepime	0.06	16	86.3	10.7[b]	83.8	12.7
Ceftazidime	0.25	16	82.5	15.4	78.2	17.5
Ceftriaxone	≤0.06	>8	77.3	20.6	77.3	20.6
Piperacillin-tazobactam	2	32	89.2	6.2	85.0	10.8
Meropenem	≤0.015	0.06	98.6	1.3	98.7	1.0
Levofloxacin	≤0.12	>4	82.7	16.7	81.1	17.3
Gentamicin	≤1	>8	84.6	15.2	84.3	15.4
P. aeruginosa (197)						
FEP-TAZ (fixed 8 mg/L)	2	16	(85.8)[c]	-	-	-
FEP-TAZ (fixed 4 mg/L)	2	16	(85.8)[c]	-	-	-
Cefepime	2	32	84.8	10.2	84.8	15.2
Ceftazidime	2	>16	79.7	13.7	79.7	20.3
Piperacillin-tazobactam	4	64	81.7	9.6	81.7	18.3
Meropenem	0.25	8	83.2	12.2	83.2	7.6
Levofloxacin	0.5	>4	80.7	11.7	72.6	19.3
Amikacin	2	8	94.4	4.1	91.9	5.6
A. baumannii (93)						
FEP-TAZ (fixed 8 mg/L)	>64	>64	(18.3)[c]	-	-	-
FEP-TAZ (fixed 4 mg/L)	>64	>64	(18.3)[c]	-	-	-
Cefepime	>64	>64	17.2	81.7	-	-
Ceftazidime	>16	>16	19.4	78.5	-	-
Piperacillin-tazobactam	>64	>64	17.2	82.8	-	-
Ampicillin-sulbactam	>32	>32	16.1	80.6	-	-
Meropenem	>8	>8	17.2	81.7	17.2	81.7
Levofloxacin	>4	>4	18.3	74.2	18.3	81.7
Amikacin	>32	>32	30.1	68.8	26.9	69.9

Region/organisms/ Antimicrobial (no. tested)	MIC_{50}	MIC_{90}	CLSI[a] %S	CLSI[a] %R	EUCAST[a] %S	EUCAST[a] %R
China						
Enterobacteriaceae (243)						
FEP-TAZ (fixed 8 mg/L)	0.06	0.5	(93.8/92.6)[b]	-	-	-
FEP-TAZ (fixed 4 mg/L)	0.06	1	(93.4/91.8)[b]	-	-	-
Cefepime	0.25	>64	60.5	27.2	56.4	33.3
Ceftazidime	0.5	>32	68.7	25.1	58.8	31.3
Ceftriaxone	4	>8	49.0	50.6	49.0	50.6
Piperacillin-tazobactam	2	64	84.6	8.7	79.3	15.4
Meropenem	≤0.06	≤0.06	94.2	5.8	94.2	5.3
Levofloxacin	0.5	>4	63.2	31.8	61.2	36.8
Gentamicin	≤1	>8	63.0	36.2	62.6	37.0
P. aeruginosa (84)						
FEP-TAZ (fixed 8 mg/L)	4	32	(73.8)[c]	-	-	-
FEP-TAZ (fixed 4 mg/L)	4	32	(73.8)[c]	-	-	-
Cefepime	4	32	72.6	19.0	72.6	27.4
Ceftazidime	4	>32	70.2	25.0	70.2	29.8
Piperacillin-tazobactam	8	>64	66.7	25.0	66.7	33.3
Meropenem	1	>8	69.0	21.4	69.0	10.7
Levofloxacin	0.5	>4	76.2	21.4	67.9	23.8
Amikacin	2	16	91.7	7.1	88.1	8.3
A. baumannii (90)						
FEP-TAZ (fixed 8 mg/L)	>64	>64	(15.6)[c]	-	-	-
FEP-TAZ (fixed 4 mg/L)	>64	>64	(15.6)[c]	-	-	-
Cefepime	>64	>64	14.4	85.6	-	-
Ceftazidime	>32	>32	14.4	85.6	-	-
Piperacillin-tazobactam	>64	>64	12.4	85.4	-	-
Ampicillin-sulbactam	>32	>32	15.6	84.4	-	-
Meropenem	>8	>8	16.7	83.3	16.7	82.2
Levofloxacin	>4	>4	15.6	68.9	15.6	84.4
Amikacin	>32	>32	21.1	78.9	18.9	78.9

a. Criteria as published by CLSI [2016] and EUCAST [2016].
b. Percentage inhibited at ≤8/≤2 mg/L, according cefepime susceptible breakpoint for high/low dosage (2g q8 h / 1g q12 h) as published in the CLSI document M100-S26.
c. Percentage inhibited at ≤8 mg/L, according cefepime susceptible breakpoint as published by the CLSI (M100-S26; 2016) and EUCAST (2016; *P. aeruginosa* only).

CONCLUSIONS

- Cefepime-tazobactam combinations demonstrated potent activity against Enterobacteriaceae, including ESBL-phenotype *E. coli*, ceftazidime-non-susceptible *Enterobacter* spp. and *P. aeruginosa* isolates from Europe, APAC and China.
- MIC results for cefepime-tazobactam tested at a fixed 8 mg/L of tazobactam were similar to those obtained with tazobactam at fixed 4 mg/L.
- The cefepime-tazobactam combination may represent a valuable option for the treatment of serious infections caused by Gram-negative bacilli, including multidrug-resistant isolates.

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