WCK4282 (High-Dose Cefepime-Tazobactam) Antimicrobial Activity against Gram-negative Organisms from United States and Latin American Medical Centers (2014)

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ECCMID 2016
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ABSTRACT

Background: WCK4282 (cefepime-tazobactam) is currently under clinical development at 2g/2g q8 as well as q12 hours dosage. We evaluated the in vitro activity of FEP/TAZ8 against clinical bacteria.

Methods: 3,008 isolates from USA and 647 from 4 Latin American (LA) countries (Argentina, Brazil, Chile, Mexico) were collected in 2014 by the SENTRY Antimicrobial Surveillance Program and susceptibility tested by a reference broth microdilution method against cefepime-tazobactam (tazobactam at fixed 8 mg/L) and comparator agents.

Results: Isolates were mainly from pneumonia (26.8%), urinary tract infection (23.8%) and bacteremia (21.2%). Cefepime-tazobactam and cefepime inhibited (USA/LA) 98.3/94.4% and 94.7/72.5% of Enterobacteriaceae strains at ≤8 mg/L (high dose, CLSI; **Table**), and 97.6/91.4% and 92.2/64.8% at ≤2 mg/L (low dose), respectively. Cefepime-tazobactam activity against Enterobacteriaceae was comparable to that of meropenem (97.9/94.8% susceptible in USA/LA) and greater than that of piperacillin-tazobactam (92.0/82.6% susceptible [CLSI] in USA/LA). Except *Klebsiella* spp. (KSP), all Enterobacteriaceae species from USA had ≥98.9% of isolates inhibited at ≤8 mg/L of cefepime-tazobactam. Extended-spectrum β-lactamase (ESBL)-phenotype rates among *E. coli* and KSP were higher in LA (37.4 and 53.9%, respectively) compared to USA (14.4 and 15.6%, respectively). Cefepime-tazobactam inhibited 99.0-100.0% of ESBL-phenotype *E. coli* at ≤8 mg/L, and retained activity against some ESBL-phenotype KSP (72.2-78.8% inhibited at ≤8 mg/L). Meropenem (67.6-73.3% susceptible) also showed more limited activity against ESBL-phenotype KSP. Cefepime-tazobactam inhibited 99.2/98.2% of *Enterobacter* spp. from USA/LA at ≤8 mg/L, and retained activity against most ceftazidime-non-susceptible *Enterobacter* spp. (96.2/95.2% from USA/LA inhibited at ≤8 mg/L). Cefepime-tazobactam, cefepime, piperacillin-tazobactam and meropenem exhibited similar activity against *P. aeruginosa* from USA (84.4-86.2% susceptible) and LA (75.2-79.8% susceptible). *Acinetobacter* spp. exhibited low susceptibility rates for all β-lactams tested.

Conclusion: Resistance rates were higher among isolates from LA compared to USA. Cefepime-tazobactam was highly active against Enterobacteriaceae, including ESBL-phenotype *E. coli* and ceftazidime-non-susceptible *Enterobacter* spp. and *P. aeruginosa*. These in vitro results support the further clinical development of WCK 4282.

Organism (n)		MIC$_{50}$/MIC$_{90}$ (% susceptible[a])			
		CefTaz	Cefepime	Pip-taz	Meropenem
Enterobacteriaceae	USA (2,466)	≤0.03/0.25 (98.3)[b]	0.06/1 (92.2)	2/16 (92.0)	0.03/0.06 (97.9)
	LA (466)	0.06/1 (94.4)[b]	0.06/64 (64.8)	4/>64 (82.6)	0.03/0.06 (94.8)
E. coli	USA (720)	≤0.03/0.12 (99.9)[b]	0.06/2 (90.6)	2/8 (95.0)	≤0.015/0.03 (100.0)
	LA (179)	0.06/0.25 (100.0)[b]	0.06/>64 (65.9)	2/16 (94.4)	≤0.015/0.03 (100.0)
Klebsiella spp.	USA (932)	≤0.03/0.25 (95.9)[b]	≤0.03/4 (88.9)	2/32 (89.6)	0.03/0.03 (95.0)
	LA (167)	0.06/64 (85.0)[b]	4/>64 (49.7)	8/>64 (64.7)	0.03/8 (85.6)
Enterobacter spp.	USA (239)	0.06/0.5 (99.2)[b]	0.06/2 (94.6)	2/64 (82.8)	0.03/0.06 (98.7)
	LA (56)	0.06/1 (98.2)[b]	0.06/16 (78.6)	4/64 (78.6)	0.03/0.06 (100.0)
P. aeruginosa	USA (390)	2/16 (85.9)[c]	2/16 (84.4)	4/32 (86.2)	0.5/4 (85.6)
	LA (109)	4/32 (79.8)[b]	4/32 (77.1)	4/>64 (76.1)	0.5/16 (75.2)

a. According to CLSI breakpoints. b. % inhibited at ≤8/8 mg/L (high dose, CLSI).

INTRODUCTION

WCK 4282 consists of cefepime combined with tazobactam. Cefepime is a parenteral fourth-generation oxyimino-cephalosporin that was initially approved by the United States (USA) Food and Drug Administration (FDA) in 1997. Cefepime has a broad-spectrum of activity against aerobic Gram-positive and Gram-negative bacteria, including *Pseudomonas aeruginosa*. Cefepime clinical indications in the current 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.

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 mg/L, respectively, and Enterobacteriaceae isolates with cefepime MIC of 4 and 8 mg/L 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 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).

WCK 4282 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 in USA and Latin American hospitals in 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 3,655 unique patient isolates collected as part of a global surveillance program (SENTRY Program) were evaluated. The collection included 3,008 from 69 medical centres located in the USA and 647 isolates from eight medical centres located in four Latin American countries: Argentina, Brazil, Chile and Mexico. All isolates were collected in 2014 as part of the SENTRY Antimicrobial Surveillance Program.

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 to cefepime-tazobactam for comparison purposes only. Susceptibility interpretations published by CLSI (document M100-S26; 2016) and EUCAST (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 bacterial isolates from USA hospital were collected mainly from patients with urinary tract infections (28.9%), pneumonia (26.6%) and bloodstream infections (18.6%); whereas the isolates from Latin American hospitals were from skin and soft tissue infections (34.8%), bloodstream infections (33.7%) and pneumonia (27.8%).
- Susceptibility rates were generally much higher in the USA compared to Latin America (**Tables 1** and **2**).
- Against Enterobacteriaceae, cefepime-tazobactam tested at fixed tazobactam concentration of 8 mg/L inhibited 98.3% of strains from USA and 94.4% of strains from Latin America at ≤8/8 mg/L [high-dose, CLSI]. Percentages of Enterobacteriaceae isolates inhibited at ≤2/8 mg/L [low-dose, CLSI]) were 97.6% in the USA and 91.4% in Latin America; and results were very similar when cefepime-tazobactam was tested at fixed tazobactam concentration of 4 mg/L, with 98.1/92.9% and 97.1/90.3% of strains (USA/Latin America) inhibited at ≤8/4 and ≤2/4 mg/L, respectively (**Table 2**).
- Cefepime-tazobactam in vitro activity against Enterobacteriaceae (MIC$_{50/90}$, ≤0.03-0.06/0.25-1 mg/L and 98.3-94.4% inhibited at ≤8/8 mg/L) was comparable to that of meropenem (MIC$_{50/90}$, 0.03/0.06 mg/L and 97.9/94.8% susceptible in USA/Latin America) and greater than that of piperacillin-tazobactam (MIC$_{50/90}$, 2-4/16->64 mg/L and 92.0/82.6% susceptible [CLSI] in USA/Latin America; **Table 2**).
- Except *Klebsiella* spp., all Enterobacteriaceae species from the USA had ≥98.9% of isolates inhibited at ≤8/8 mg/L of cefepime-tazobactam (**Table 1**).
- Extended-spectrum β-lactamase (ESBL)-phenotype rates among *E. coli* and *Klebsiella* spp. were higher in Latin America (37.4 and 53.9%, respectively) compared to USA (14.4 and 15.6%, respectively; data not shown).
- Cefepime-tazobactam inhibited 99.0-100.0% of ESBL-phenotype *E. coli* at ≤8/8 mg/L; and retained activity against some ESBL-phenotype *Klebsiella* spp. (72.2-73.8% inhibited at ≤8/8 mg/L; **Table 1**). Meropenem also showed more limited activity against ESBL-phenotype *Klebsiella* spp. (67.6-73.3% susceptible [CLSI]; data not shown).
- Cefepime-tazobactam inhibited 99.2/98.2% of *Enterobacter* spp. from USA/Latin America at ≤8/8 mg/L; and retained activity against most ceftazidime-non-susceptible *Enterobacter* spp. (96.2/95.5% from USA/Latin America inhibited at ≤8/8 mg/L; **Table 1** [USA]).
- When tested against *P. aeruginosa*, the in vitro activities of the cefepime-tazobactam combinations (tested at fixed 8 and 4 mg/L) were similar to that observed for cefepime, with MIC$_{50/90}$ of 2/16 mg/L in the USA and 4/32 mg/L in Latin America for the three compounds (**Table 2**).
- Cefepime-tazobactam (fixed 8 mg/L) inhibited 85.9/79.8% of *P. aeruginosa* isolates from USA/Latin America at ≤8/8 mg/L, and *P. aeruginosa* susceptibility rates were 84.4/77.1% for cefepime, 86.2/76.1% for piperacillin-tazobactam and 85.6/75.2% for meropenem (USA/Latin America 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 (tazobactam at fixed 8 mg/L) activity stratified by geographic region.

Organism (n: USA/Latin America)	Cefepime-tazobactam MIC$_{50}$/MIC$_{90}$ (% inhibited at ≤8/8 mg/L [high dose, CLSI])[a]	
	USA	Latin America
Enterobacteriaceae (2,466/466)	≤0.03/0.25 (98.3)	0.06/1 (94.4)
E. coli (720/179)	≤0.03/0.12 (99.9)	0.06/0.25 (100.0)
ESBL-phenotype (104/67)	0.12/0.25 (99.0)	0.12/0.5 (100.0)
Klebsiella spp. (932/167)	≤0.03/0.25 (95.9)	0.06/64 (85.0)
ESBL-phenotype (145/90)	0.5/32 (78.8)	1/>64 (72.2)
K. pneumoniae (751/150)	≤0.03/0.25 (94.9)	0.06/64 (83.3)
MER-non-susceptible (45/24)	16/>64 (20.0)	64/>64 (20.8)
Klebsiella oxytoca (178/16)	≤0.03/0.12 (100.0)	≤0.03/1 (100.0)
P. mirabilis (89/23)	0.06/0.12 (100.0)	0.06/0.12 (100.0)
ESBL-phenotype (1/3)	0.12/- (100.0)	0.25 (100.0)
Enterobacter spp. (239/56)	0.06/0.5 (99.2)	0.06/1 (98.2)
CAZ-non-susceptible (53/22)	0.25/2 (96.2)	0.25/2 (95.2)
Morganella morganii (68/8)	≤0.03/0.06 (100.0)	≤0.03/- (100.0)
Citrobacter spp. (153/5)	≤0.03/0.12 (100.0)	0.06/- (100.0)
S. marcescens (93/23)	0.12/0.25 (100.0)	0.06/0.12 (100.0)
Proteus vulgaris (81/3)	0.06/0.12 (100.0)	≤0.03/- (100.0)
Providencia spp. (91/2)	≤0.03/0.12 (98.9)	≤0.03/- (100.0)
P. aeruginosa (390/109)	2/16 (85.9)	4/32 (79.8)
CAZ-non-susceptible (50/32)	16/64 (22.0)	16/>64 (37.5)
MER-non-susceptible (56/27)	16/64 (37.5)	16/>64 (44.4)
A. baumannii (152/72)	4/>64 (53.9)	>64/>64 (9.7)

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 2. Activity of cefepime-tazobactam (WCK 4282) combinations (tazobactam at fixed 4 and 8 mg/L) and comparator agents tested against bacterial isolates from USA and Latin America.

Antimicrobial Agent	MIC$_{50}$	MIC$_{90}$	CLSI[a] %S	CLSI[a] %R	EUCAST[a] %S	EUCAST[a] %R
USA						
Enterobacteriaceae (2,466)						
CefTaz8	≤0.03	0.25	(98.3/97.6)[b]	-	-	-
CefTaz4	0.06	0.25	(98.1/97.1)[b]	-	-	-
Cefepime	0.06	1	92.2	5.3	90.4	6.6
Ceftazidime	0.12	8	88.9	9.5	86.4	11.1
Ceftriaxone	≤0.06	>8	84.5	14.3	84.5	14.3
Pip-taz	2	16	92	4.9	88.9	8
Meropenem	0.03	0.06	97.9	1.8	98.2	1.3
Levofloxacin	≤0.12	>4	84.4	14.1	83.1	15.6
Gentamicin	≤1	4	90.1	9	88.4	9.9
P. aeruginosa (390)						
CefTaz8	2	16	(85.9)[c]	-	-	-
CefTaz4	2	16	(86.2)[c]	-	-	-
Cefepime	2	16	84.4	5.9	84.4	15.6
Ceftazidime	2	16	87.2	10	87.2	12.8
Pip-taz	4	32	86.2	6.7	86.2	13.8
Meropenem	0.5	4	85.6	9.5	85.6	3.3
Levofloxacin	0.5	>4	79	15.6	67.7	21
Amikacin	2	8	97.2	1.8	92.8	2.8
Acinetobacter spp. (152)						
CefTaz8	4	>64	(53.9)[c]	-	-	-
CefTaz4	8	>64	(53.3)[c]	-	-	-
Cefepime	16	>64	46.7	44.7	-	-
Ceftazidime	8	>32	54.6	41.4	-	-
Pip-taz	8	>64	53.9	42.8	-	-
Amp-sulbactam	4	>32	63.6	22.5	-	-
Meropenem	1	>32	56.6	42.8	56.6	38.8
Levofloxacin	0.25	>4	53.3	44.7	52.6	46.7
Amikacin	4	>32	78.1	19.2	74.8	21.9
Latin America						
Enterobacteriaceae (466)						
CefTaz8	0.06	1	(94.4/91.4)[b]	-	-	-
CefTaz4	0.06	2	(92.9/90.3)[b]	-	-	-
Cefepime	0.06	64	64.8	27.5[b]	63.3	32.6
Ceftazidime	0.25	>16	65.9	28.5	60.3	34.1
Ceftriaxone	0.25	>8	58.4	40.8	58.4	40.8
Pip-taz	4	>64	82.6	11.8	78.8	17.4
Meropenem	0.03	0.06	94.8	4.5	95.5	3.4
Levofloxacin	0.25	>4	63.5	35.4	62.7	36.5
Gentamicin	≤1	>8	72.7	26.2	71.9	27.3
P. aeruginosa (109)						
CefTaz8	4	32	(79.8)[c]	-	-	-
CefTaz4	4	32	(78.9)[c]	-	-	-
Cefepime	4	32	77.1	12.8	77.1	22.9
Ceftazidime	4	>16	70.6	21.1	70.6	29.4
Pip-taz	4	>64	76.1	11.9	76.1	23.9
Meropenem	0.5	4	75.2	19.3	75.2	14.7
Levofloxacin	0.5	>4	67	28.4	59.6	33
Amikacin	4	16	90.8	7.3	89.9	9.2
Acinetobacter spp. (72)						
CefTaz8	>64	>64	(9.7)[c]	-	-	-
CefTaz4	>64	>64	(8.3)[c]	-	-	-
Cefepime	>64	>64	6.9	90.3	-	-
Ceftazidime	>16	>16	9.7	88.9	-	-
Pip-taz	>64	>64	6.9	91.7	-	-
Amp-sulbactam	32	>32	18.1	59.7	-	-
Meropenem	32	>32	11.1	88.9	11.1	87.5
Levofloxacin	>4	>4	11.1	87.5	9.7	88.9
Amikacin	>32	>32	13.9	84.7	12.5	86.1

Abbreviations: CefTaz8 = Cefepime-tazobactam Fixed 8; CefTaz4 = Cefepime-tazobactam Fixed 4; Pip-taz = Piperacillin-tazobactam; Amp-sulbactam = Ampicillin-sulbactam.
a. Criteria as published by CLSI [2016] and EUCAST [2016].
b. Percentage inhibited at ≤8/≤2 mg/L, according to cefepime susceptible breakpoint for high/low dosage (2g q8 h / 1g q12) as published in the CLSI document M100-S26.
c. Percentage inhibited at ≤8 mg/L, according to cefepime susceptible breakpoint as published by the CLSI (M100-S26; 2016) and EUCAST (2016; *P. aeruginosa* only).

Table 3. Cumulative frequency distributions of cefepime and WCK 4282 (CefTaz8; cefepime + tazobactam at fixed concentrations of 8 µg/mL) MIC results when tested against 3,008 bacterial isolates (USA)

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	MIC$_{50}$	MIC$_{90}$
Enterobacteriaceae (2,466)													
Cefepime	1,772 (71.9)	255 (82.2)	101 (86.3)	66 (89.0)	35 (90.4)	45 (92.2)	30 (93.4)	31 (94.7)	22 (95.6)	29 (96.8)	80 (100.0)	0.06	1
CefTaz8	1,953 (79.2)	260 (89.7)	104 (94.0)	42 (95.7)	26 (96.7)	23 (97.6)	8 (98.0)	8 (98.3)	21 (99.1)	8 (99.5)	13 (100.0)	≤0.03	0.25
E. coli (720)													
Cefepime	523 (72.6)	79 (83.6)	16 (85.8)	12 (87.5)	7 (88.5)	15 (90.6)	6 (91.4)	14 (93.3)	11 (94.9)	11 (96.4)	26 (100.0)	0.06	2
CefTaz8	600 (83.3)	79 (94.3)	25 (97.8)	5 (98.5)	4 (99.0)	6 (99.9)	0 (99.9)	0 (99.9)	1 (100.0)	--	--	≤0.03	0.12
ESBL-phenotype (104)													
Cefepime	2 (1.9)	9 (10.6)	4 (14.4)	6 (20.2)	4 (24.0)	11 (34.6)	6 (40.4)	14 (53.8)	11 (64.4)	11 (75.0)	26 (100.0)	8	>64
CefTaz8	45 (43.3)	30 (72.1)	16 (87.5)	4 (91.3)	2 (93.3)	6 (99.0)	0 (99.0)	0 (99.0)	1 (100.0)	--	--	0.12	0.5
K. pneumoniae (751)													
Cefepime	545 (72.6)	61 (80.7)	21 (83.5)	11 (85.0)	7 (85.9)	8 (87.0)	11 (88.4)	12 (90.0)	11 (91.5)	14 (93.3)	50 (100.0)	0.06	8
CefTaz8	593 (79.0)	62 (87.2)	23 (90.3)	13 (92.0)	8 (93.1)	3 (93.5)	7 (94.4)	4 (94.9)	19 (97.5)	6 (98.3)	13 (100.0)	≤0.03	0.25
ESBL-phenotype (122)													
Cefepime	--	--	4 (3.3)	5 (7.4)	7 (13.1)	8 (19.7)	11 (28.7)	12 (38.5)	11 (47.5)	14 (59.0)	50 (100.0)	32	>64
CefTaz8	37 (30.3)	10 (38.5)	9 (45.9)	8 (52.5)	6 (57.4)	3 (59.8)	7 (65.6)	4 (68.9)	19 (84.4)	6 (89.3)	13 (100.0)	0.5	64
MER-non-susceptible (45)													
Cefepime	--	--	--	--	--	--	--	5 (11.1)	4 (20.0)	7 (35.6)	29 (100.0)	64	>64
CefTaz8	--	--	--	--	--	1 (2.2)	4 (11.1)	4 (20.0)	17 (57.8)	6 (71.1)	13 (100.0)	16	>64
Klebsiella oxytoca (178)													
Cefepime	280 (81.2)	16 (85.8)	10 (88.7)	7 (90.7)	9 (93.3)	8 (95.7)	4 (96.8)	4 (98.0)	3 (98.8)	2 (99.4)	2 (100.0)	≤0.03	0.5
CefTaz8	294 (85.2)	12 (88.7)	9 (91.3)	7 (93.3)	9 (95.9)	6 (97.7)	3 (98.6)	4 (99.7)	0 (99.7)	1 (100.0)	--	≤0.03	0.25
P. mirabilis (89)													
Cefepime	66 (74.2)	21 (97.8)	1 (98.9)	0 (98.9)	0 (98.9)	0 (98.9)	0 (98.9)	0 (98.9)	0 (98.9)	1 (100.0)	0.06	0.12	
CefTaz8	72 (80.9)	17 (100.0)	--	--	--	--	--	--	--	--	--	0.06	0.12
Enterobacter spp. (239)													
Cefepime	147 (61.5)	26 (72.4)	20 (80.8)	18 (88.3)	4 (90.0)	11 (94.6)	9 (98.3)	2 (99.2)	0 (99.2)	1 (99.6)	1 (100.0)	0.06	2
CefTaz8	154 (64.4)	30 (77.0)	27 (88.3)	11 (92.9)	6 (95.4)	9 (99.2)	0 (99.2)	0 (99.2)	1 (99.6)	1 (100.0)	--	0.06	0.5
CAZ-non-susceptible (53)													
Cefepime	1 (1.9)	2 (5.7)	11 (26.4)	12 (49.1)	4 (56.6)	10 (75.5)	9 (92.5)	2 (96.2)	0 (96.2)	1 (98.1)	1 (100.0)	1	4
CefTaz8	3 (5.7)	8 (20.8)	19 (56.6)	7 (69.8)	6 (81.1)	8 (96.2)	0 (96.2)	0 (96.2)	1 (98.1)	1 (100.0)	--	0.25	2
Citrobacter spp. (153)													
Cefepime	128 (83.7)	3 (85.6)	7 (90.2)	4 (92.8)	6 (96.7)	4 (99.3)	0 (99.3)	0 (99.3)	0 (99.3)	1 (100.0)	--	≤0.03	0.25
CefTaz8	128 (83.7)	10 (90.2)	9 (96.1)	1 (96.7)	3 (98.7)	1 (99.3)	0 (99.3)	1 (100.0)	--	--	--	≤0.03	0.12
S. marcescens (93)													
Cefepime	33 (35.5)	34 (72.0)	13 (86.0)	7 (93.5)	2 (95.7)	2 (97.8)	1 (98.9)	1 (100.0)	--	--	--	0.12	0.5
CefTaz8	38 (40.9)	29 (72.0)	16 (89.2)	6 (95.7)	0 (95.7)	3 (98.9)	0 (98.9)	1 (100.0)	--	--	--	0.12	0.5
Morganella morganii. (68)													
Cefepime	62 (91.2)	2 (94.1)	2 (97.1)	0 (97.1)	0 (97.1)	1 (98.5)	1 (100.0)	--	--	--	--	≤0.03	0.06
CefTaz8	66 (97.1)	2 (100.0)	--	--	--	--	--	--	--	--	--	≤0.03	0.06
Proteus vulgaris (81)													
Cefepime	43 (53.1)	20 (77.8)	8 (87.7)	6 (95.1)	1 (96.3)	2 (98.8)	1 (100.0)	--	--	--	--	0.06	0.5
CefTaz8	62 (76.5)	19 (100.0)	--	--	--	--	--	--	--	--	--	0.06	0.12
Providencia spp. (91)													
Cefepime	72 (79.1)	3 (82.4)	7 (90.1)	4 (94.5)	2 (96.7)	1 (97.8)	0 (97.8)	0 (97.8)	1 (98.9)	--	--	≤0.03	0.25
CefTaz8	81 (89.0)	6 (95.6)	0 (95.6)	0 (95.6)	2 (97.8)	1 (98.9)	0 (98.9)	0 (98.9)	0 (98.9)	1 (100.0)	--	≤0.03	0.12
P. aeruginosa (390)													
Cefepime	--	2 (0.5)	2 (1.0)	2 (1.5)	47 (13.6)	154 (53.1)	65 (69.7)	57 (84.4)	38 (94.1)	12 (97.2)	11 (100.0)	2	16
CefTaz8	--	2 (0.5)	3 (1.3)	4 (2.3)	51 (15.4)	156 (55.4)	57 (70.0)	62 (85.9)	35 (94.9)	14 (98.5)	6 (100.0)	2	16
Acinetobacter spp. (152)													
Cefepime	--	--	1 (0.7)	0 (0.7)	6 (4.6)	23 (19.7)	29 (38.8)	12 (46.7)	13 (55.3)	18 (67.1)	50 (100.0)	16	>64
CefTaz8	39 (25.7)	4 (28.3)	7 (32.9)	3 (34.9)	9 (40.8)	9 (46.7)	5 (50.0)	6 (53.9)	12 (61.8)	20 (75.0)	38 (100.0)	4	>64

CONCLUSIONS

- Cefepime-tazobactam combinations demonstrated potent activity against Enterobacteriaceae, including ESBL-phenotype *E. coli*, ceftazidime-non-susceptible *Enterobacter* spp. and *P. aeruginosa* isolates from hospitals from USA and Latin America.
- 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.
- These in vitro results support the further clinical development of WCK 4282 for the treatment of serious infections caused by Gram-negative bacilli, including multidrug-resistant isolates.

ACKNOWLEDGEMENTS

This study was supported by Wockhardt Limited.

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