Antimicrobial Activity of High-Proportion Cefepime-Tazobactam (WCK 4282) against a Large Number of Gram-Negative Isolates Collected Worldwide in 2014

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ABSTRACT Cefepime-tazobactam (WCK 4282) is currently under clinical development for use at a dosage of 2 g/2 g every 8 h. A total of 7,981 isolates were collected from 146 medical centers (39 countries) in 2014 as a part of the SENTRY Antimicrobial Surveillance Program, and their susceptibilities to cefepime-tazobactam (with tazobactam at fixed concentrations of 4 and 8 $\mu\text{g/ml}$) were tested by a reference broth microdilution method. Isolates were mainly from patients with pneumonia (29.5%) and bloodstream infections (26.9%). Cefepime-tazobactam (with tazobactam at a fixed concentration of 8 $\mu\text{g/ml}$) and cefepime inhibited 96.9 and 87.9% of *Enterobacteriaceae* strains at ≤ 8 $\mu\text{g/ml}$. The activity of cefepime-tazobactam against *Enterobacteriaceae* strains was comparable to that of meropenem (96.7% of isolates were susceptible) and greater than that of piperacillin-tazobactam (87.7% susceptible). All *Enterobacteriaceae* species from the United States except *Klebsiella pneumoniae* had >99.0% of isolates inhibited by cefepime-tazobactam at $\leq 8/8$ $\mu\text{g/ml}$. The prevalence of the extended-spectrum β -lactamase (ESBL)-screening-positive phenotype was the highest among *Escherichia coli* isolates in China (66.3%) and among *K. pneumoniae* isolates (58.0%) in Latin America. Cefepime-tazobactam at $\leq 8/8$ $\mu\text{g/ml}$ inhibited 98.7 and 71.3% of ESBL-screening-positive phenotype *E. coli* strains and *K. pneumoniae* strains, respectively. Meropenem showed limited activity against ESBL-screening-positive phenotype *K. pneumoniae* strains (69.6% susceptible). Cefepime-tazobactam was active against *Enterobacter* spp. (MIC_{50} and MIC_{90} , 0.06 and 0.5 $\mu\text{g/ml}$, respectively), including ceftazidime-nonsusceptible isolates (96.1% of isolates were inhibited by cefepime-tazobactam at $\leq 8/8$ $\mu\text{g/ml}$). The activity of cefepime-tazobactam against *Pseudomonas aeruginosa* (82.4 and 91.6% of isolates were inhibited by cefepime-tazobactam at $\leq 8/8$ and $\leq 16/8$ $\mu\text{g/ml}$, respectively) was comparable to that of meropenem and piperacillin-tazobactam (79.2% susceptible). In summary, cefepime-tazobactam was highly active against *P. aeruginosa* and *Enterobacteriaceae* strains, including ESBL-screening-positive phenotype *E. coli* strains and ceftazidime-nonsusceptible *Enterobacter* spp. These results support the further clinical development of the cefepime-tazobactam combination.

KEYWORDS cefepime-tazobactam

Cefepime-tazobactam is currently under clinical development, with higher-dose regimens of 2 g of cefepime plus 2 g of tazobactam to be administered every 8 h (q8h) via a 90-min infusion. Cefepime is a parenteral oxymino-cephalosporin which was initially approved by the U.S. Food and Drug Administration (FDA) in 1996 (1). Cefepime has a broad spectrum of activity against aerobic Gram-positive and -negative bacteria, including *Pseudomonas aeruginosa* (2, 3), and the clinical indications for treatment with cefepime included in the current FDA product package insert include moderate to

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severe pneumonia, complicated and uncomplicated urinary tract infections, complicated intra-abdominal infections, and uncomplicated skin and skin structure infections, and it is also approved for use for empirical therapy for febrile neutropenic patients. Cefepime doses are administered as a 30-min infusion (1, 4).

The clinical breakpoints for cefepime have been revised by the Clinical and Laboratory Standards Institute (CLSI) on the basis of results from clinical and pharmacokinetic (PK)-pharmacodynamic (PD) studies and contemporary MIC distributions (5, 6). However, according to the current CLSI breakpoint criteria for *Enterobacteriaceae* published in the M100-S26 document (7), the breakpoints for cefepime susceptibility and resistance were further modified to ≤ 2 and ≥ 16 $\mu\text{g/ml}$, respectively, and *Enterobacteriaceae* isolates with cefepime MIC values of 4 and 8 $\mu\text{g/ml}$ should be reported as susceptible-dose dependent (SDD). The SDD interpretative criteria essentially provide three breakpoints for cefepime susceptibility according to the dosage utilized, i.e., ≤ 2 $\mu\text{g/ml}$ for a dosage of 1 g every 12 h (q12h) (low dose), ≤ 4 $\mu\text{g/ml}$ for a dosage of 1 g q8h or 2 g q12h, and ≤ 8 $\mu\text{g/ml}$ for a dosage of 2 g q8h (high dose) (7).

In an attempt to overcome cefepime resistance and enhance the potential of covering organisms for which the MIC values of the cefepime-tazobactam combination are elevated, a dual approach of combining cefepime with tazobactam at a high level and administering the combination as an extended infusion was undertaken. This approach led to the restoration of cefepime activity against multiple β -lactamase-producing pathogens and generated an adequate concentration-time profile to cover isolates with cefepime-tazobactam MICs of 16 $\mu\text{g/ml}$, as established through *in vivo* PK-PD studies, population PK studies, and a Monte Carlo simulation based on phase 1 clinical PK studies (8, 9).

In this investigation, we evaluated the *in vitro* potency and the spectrum of activity of cefepime-tazobactam when it was tested against Gram-negative isolates collected worldwide in 2014 as part of the SENTRY Antimicrobial Surveillance Program.

RESULTS

Isolates were obtained from patients hospitalized with pneumonia (29.5%; $n = 2,355$ patients), bloodstream infections (26.9%; $n = 2,143$), urinary tract infections (18.6%; $n = 1,485$), acute bacterial skin and skin structure infections (e.g., wound swabs or aspirated pus; 16.5%; $n = 1,318$), intra-abdominal infections (6.2%; $n = 498$), and other infection types (2.3%; $n = 182$).

A total of 6,219 *Enterobacteriaceae* isolates were tested, and 84.0% were found to be susceptible to cefepime alone (MIC₅₀ and MIC₉₀, 0.06 and 16 $\mu\text{g/ml}$, respectively) according to the CLSI breakpoint for susceptibility of ≤ 2 $\mu\text{g/ml}$. When the EUCAST breakpoint for susceptibility (≤ 1 $\mu\text{g/ml}$) was applied, the cefepime susceptibility rate was 82.1% (Tables 1 and 2). The MIC₉₀ values of cefepime-tazobactam (0.5 and 0.25 $\mu\text{g/ml}$ when tazobactam was at fixed concentrations of 4 and 8 $\mu\text{g/ml}$, respectively) were substantially lower than those of cefepime alone (16 $\mu\text{g/ml}$; Table 2). Overall, 96.9 and 96.2% of the *Enterobacteriaceae* isolates were inhibited by ≤ 8 $\mu\text{g/ml}$ of cefepime-tazobactam when tazobactam was at fixed 8 $\mu\text{g/ml}$ (MIC₅₀ and MIC₉₀, ≤ 0.03 and 0.25 $\mu\text{g/ml}$, respectively) and by ≤ 8 $\mu\text{g/ml}$ of cefepime-tazobactam when tazobactam was at fixed 4 $\mu\text{g/ml}$ (MIC₅₀ and MIC₉₀, 0.06 and 0.5 $\mu\text{g/ml}$, respectively), respectively (Table 2). The activity of cefepime-tazobactam against the *Enterobacteriaceae* was comparable to that of meropenem (MIC₅₀ and MIC₉₀, 0.03 and 0.06 $\mu\text{g/ml}$, respectively; 96.7% of the isolates were susceptible) and greater than that of piperacillin-tazobactam (MIC₅₀ and MIC₉₀, 2 and 32 $\mu\text{g/ml}$, respectively; 87.7% susceptible). All *Enterobacteriaceae* species except *Klebsiella pneumoniae* had $\geq 98.6\%$ of isolates inhibited by ≤ 8 $\mu\text{g/ml}$ cefepime-tazobactam with tazobactam at a fixed concentration of 8 $\mu\text{g/ml}$ (Tables 1 and 3). At the proposed PK-PD breakpoint of 16 $\mu\text{g/ml}$, cefepime-tazobactam inhibited 92.3% of *K. pneumoniae* isolates.

When the *in vitro* activities of cefepime-tazobactam and cefepime were compared, the reduction of the cefepime MIC values was more pronounced among extended-spectrum β -lactamase (ESBL)-screening-positive phenotype *Enterobacteriaceae* strains

TABLE 1 Cumulative frequency distributions of cefepime and ceftazidime-tazobactam (with tazobactam at fixed concentration of 8 µg/ml) MIC results when tested against bacterial isolates^a

Organism (no. of isolates) and antimicrobial	No. of organisms (cumulative % inhibited) at MIC (µg/ml) of:												
	≤0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	>64
<i>Enterobacteriaceae</i> (6,219)													
Cefepime	2,625 (42.2)	1,469 (65.8)	519 (74.2)	244 (78.1)	155 (80.6)	93 (82.1)	122 (84.0)	92 (85.5)	147 (87.9)	151 (90.3)	131 (92.4)	166 (95.1)	305 (100.0)
Ceftazidime-tazobactam	3,175 (51.1)	1,585 (76.5)	596 (86.1)	304 (91.0)	141 (93.3)	84 (94.6)	68 (95.7)	40 (96.4)	36 (96.9)	42 (97.6)	26 (98.0)	54 (98.9)	68 (100.0)
<i>E. coli</i> (2,211)													
Cefepime	1,000 (45.2)	535 (69.4)	162 (76.8)	48 (78.9)	38 (80.6)	20 (81.5)	44 (83.5)	37 (85.2)	67 (88.2)	65 (91.2)	52 (93.5)	58 (96.2)	85 (100.0)
Ceftazidime-tazobactam	1,290 (58.3)	551 (83.3)	207 (92.6)	93 (96.8)	27 (98.1)	10 (98.5)	14 (99.1)	7 (99.5)	6 (99.7)	3 (99.9)	1 (99.9)	0 (>99.9)	2 (100.0)
<i>E. coli</i> with ESBL phenotype (471)													
Cefepime	5 (1.1)	14 (4.0)	18 (7.9)	10 (10.0)	18 (13.8)	12 (16.3)	33 (23.4)	35 (30.8)	66 (44.8)	65 (58.6)	52 (69.6)	58 (82.0)	85 (100.0)
Ceftazidime-tazobactam	87 (18.5)	148 (49.9)	112 (73.7)	65 (87.5)	22 (92.1)	5 (93.2)	14 (96.2)	6 (97.5)	6 (98.7)	3 (99.4)	1 (99.6)	0 (99.6)	2 (100.0)
<i>Klebsiella</i> spp. (2,138)													
Cefepime	981 (45.9)	343 (61.9)	113 (67.2)	60 (70.0)	39 (71.8)	32 (73.3)	31 (74.8)	27 (76.1)	61 (78.9)	73 (82.3)	72 (85.7)	97 (90.2)	209 (100.0)
Ceftazidime-tazobactam	1,139 (53.3)	410 (72.5)	142 (79.1)	87 (83.2)	58 (85.9)	40 (87.7)	34 (89.3)	29 (90.7)	25 (91.9)	36 (93.5)	22 (94.6)	52 (97.0)	64 (100.0)
<i>Klebsiella</i> spp. with ESBL phenotype (661)													
Cefepime	2 (0.3)	7 (1.4)	12 (3.2)	16 (5.6)	26 (9.5)	28 (13.8)	31 (18.5)	27 (22.5)	61 (31.8)	73 (42.8)	72 (53.7)	97 (68.4)	209 (100.0)
Ceftazidime-tazobactam	103 (15.6)	103 (31.2)	58 (39.9)	53 (48.0)	46 (54.9)	36 (60.4)	34 (65.5)	29 (69.9)	25 (73.7)	36 (79.1)	22 (82.5)	52 (90.3)	64 (100.0)
<i>K. pneumoniae</i> (1,788)													
Cefepime	747 (41.8)	293 (58.2)	96 (63.5)	50 (66.3)	32 (68.1)	23 (69.4)	23 (70.7)	23 (72.0)	57 (75.2)	70 (79.1)	70 (83.0)	95 (88.3)	209 (100.0)
Ceftazidime-tazobactam	879 (49.2)	372 (70.0)	129 (77.2)	78 (81.5)	51 (84.4)	31 (86.1)	28 (87.7)	26 (89.1)	21 (90.3)	36 (92.3)	21 (93.5)	52 (96.4)	64 (100.0)
<i>K. pneumoniae</i> with ESBL phenotype (602)													
Cefepime	1 (0.2)	3 (0.7)	5 (1.5)	8 (2.8)	19 (6.0)	19 (9.1)	23 (13.0)	23 (16.8)	57 (26.2)	70 (37.9)	70 (49.5)	95 (65.3)	209 (100.0)
Ceftazidime-tazobactam	92 (15.3)	96 (31.2)	53 (40.0)	47 (47.8)	39 (54.3)	27 (58.8)	28 (63.5)	26 (67.8)	21 (71.3)	36 (77.2)	21 (80.7)	52 (89.4)	64 (100.0)
MEM-nonsusceptible <i>K. pneumoniae</i> (183)													
Cefepime								1 (0.5)	6 (3.8)	6 (7.1)	17 (16.4)	33 (34.4)	120 (100.0)
Ceftazidime-tazobactam							6 (3.3)	10 (8.7)	12 (15.3)	32 (32.8)	16 (41.5)	49 (68.3)	58 (100.0)
<i>Klebsiella oxytoca</i> (345)													
Cefepime	230 (66.7)	50 (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)	
Ceftazidime-tazobactam	256 (74.2)	38 (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)		
<i>Klebsiella oxytoca</i> with ESBL phenotype (59)													
Cefepime	1 (1.7)	4 (8.5)	7 (20.3)	8 (33.9)	7 (45.8)	9 (61.0)	8 (74.6)	4 (81.4)	4 (88.1)	3 (93.2)	2 (96.6)	2 (100.0)	
Ceftazidime-tazobactam	11 (18.6)	7 (30.5)	5 (39.0)	6 (49.2)	7 (61.0)	9 (76.3)	6 (86.4)	3 (91.5)	4 (98.3)	0 (98.3)	1 (100.0)		
<i>P. mirabilis</i> (228)													
Cefepime	27 (11.8)	144 (75.0)	32 (89.0)	8 (92.5)	1 (93.0)	7 (96.1)	1 (96.5)	1 (96.9)	3 (98.2)	0 (98.2)	0 (98.2)	1 (98.7)	3 (100.0)
Ceftazidime-tazobactam	39 (17.1)	155 (85.1)	29 (97.8)	4 (99.6)	1 (100.0)								
<i>P. mirabilis</i> with ESBL phenotype (19)													
Cefepime		4 (21.1)	10 (73.7)	2 (10.5)	1 (15.8)	7 (52.6)	1 (57.9)	1 (63.2)	3 (78.9)	0 (78.9)	0 (78.9)	1 (84.2)	3 (100.0)
Ceftazidime-tazobactam					1 (100.0)								
<i>Enterobacter</i> spp. (629)													
Cefepime	208 (33.1)	151 (57.1)	78 (69.5)	55 (78.2)	39 (84.4)	15 (86.8)	30 (91.6)	19 (94.6)	11 (96.3)	9 (97.8)	4 (98.4)	5 (99.2)	5 (100.0)
Ceftazidime-tazobactam	233 (37.0)	151 (61.0)	92 (75.7)	63 (85.7)	38 (91.7)	25 (95.7)	13 (97.8)	4 (98.4)	3 (98.9)	3 (99.4)	2 (99.7)	1 (99.8)	1 (100.0)

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TABLE 1 (Continued)

Organism (no. of isolates) and antimicrobial	No. of organisms (cumulative % inhibited) at MIC ($\mu\text{g/ml}$) of:												
	≤ 0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	> 64
CAZ-nonsusceptible <i>Enterobacter</i> spp. (179)													
Cefepime		4 (2.2)	17 (11.7)	33 (30.2)	31 (47.5)	15 (55.9)	28 (71.5)	18 (81.6)	10 (87.2)	9 (92.2)	4 (94.4)	5 (97.2)	5 (100.0)
Cefepime-tazobactam	1 (0.6)	11 (6.7)	41 (29.6)	45 (54.7)	32 (72.6)	23 (85.5)	12 (92.2)	4 (94.4)	3 (96.1)	3 (97.8)	2 (98.9)	1 (99.4)	1 (100.0)
<i>Morganella morganii</i> (165)													
Cefepime	104 (63.0)	47 (91.5)	6 (95.2)	4 (97.6)	1 (98.2)	0 (98.2)	1 (98.8)	2 (100.0)					
Cefepime-tazobactam	129 (78.2)	30 (96.4)	3 (98.2)	3 (100.0)									
<i>Citrobacter</i> spp. (311)													
Cefepime	197 (63.3)	45 (77.8)	12 (81.7)	14 (86.2)	15 (91.0)	10 (94.2)	6 (96.1)	4 (97.4)	1 (97.7)	1 (98.1)	2 (98.7)	3 (99.7)	1 (100.0)
Cefepime-tazobactam	200 (64.3)	57 (82.6)	18 (88.4)	19 (94.5)	7 (96.8)	5 (98.4)	3 (99.4)	0 (99.4)	1 (99.7)	0 (99.7)	0 (99.7)	1 (100.0)	
<i>Serratia marcescens</i> (245)													
Cefepime	8 (3.3)	98 (43.3)	81 (76.3)	31 (89.0)	11 (93.5)	4 (95.1)	4 (96.7)	1 (97.1)	3 (98.4)	2 (99.2)	0 (99.2)	1 (99.6)	1 (100.0)
Cefepime-tazobactam	8 (3.3)	116 (50.6)	72 (80.0)	33 (93.5)	10 (97.6)	2 (98.4)	3 (99.6)	0 (99.6)	1 (100.0)				
<i>Proteus vulgaris</i> (144)													
Cefepime	11 (7.6)	76 (60.4)	31 (81.9)	15 (92.4)	6 (96.5)	1 (97.2)	3 (99.3)	1 (100.0)					
Cefepime-tazobactam	32 (22.2)	84 (80.6)	26 (98.6)	2 (100.0)									
<i>Providencia</i> spp. (148)													
Cefepime	89 (60.1)	30 (80.4)	4 (83.1)	9 (89.2)	5 (92.6)	4 (95.3)	2 (96.6)	0 (96.6)	1 (97.3)	1 (98.0)	1 (98.6)	1 (99.3)	1 (100.0)
Cefepime-tazobactam	105 (70.9)	31 (91.9)	7 (96.6)	0 (96.6)	0 (96.6)	2 (98.0)	1 (98.6)	0 (98.6)	0 (98.6)	0 (98.6)	1 (99.3)	0 (99.3)	1 (100.0)
<i>P. aeruginosa</i> (1,171)													
Cefepime		1 (0.1)	4 (0.3)	4 (0.7)	36 (3.8)	136 (15.4)	414 (50.7)	184 (66.4)	169 (80.9)	110 (90.3)	63 (95.6)	24 (97.7)	27 (100.0)
Cefepime-tazobactam			5 (0.5)	6 (1.0)	17 (2.5)	171 (17.1)	404 (51.6)	184 (67.3)	177 (82.4)	108 (91.6)	61 (96.8)	15 (98.1)	22 (100.0)
CAZ-nonsusceptible <i>P. aeruginosa</i> (252)													
Cefepime						1 (0.4)	3 (1.6)	17 (8.3)	40 (24.2)	79 (55.6)	61 (79.8)	24 (89.3)	27 (100.0)
Cefepime-tazobactam						2 (0.8)	4 (2.4)	24 (11.9)	45 (29.8)	82 (62.3)	58 (85.3)	15 (91.3)	22 (100.0)
MEM-nonsusceptible <i>P. aeruginosa</i> (244)													
Cefepime						1 (0.4)	15 (6.6)	23 (16.0)	52 (37.3)	62 (62.7)	45 (81.1)	20 (89.3)	26 (100.0)
Cefepime-tazobactam						4 (1.6)	13 (7.0)	26 (17.6)	56 (40.6)	65 (67.2)	46 (86.1)	14 (91.8)	20 (100.0)
<i>A. baumannii</i> (591)													
Cefepime				1 (0.2)	5 (1.0)	8 (2.4)	42 (9.5)	54 (18.6)	25 (22.8)	21 (26.4)	42 (33.5)	105 (51.3)	288 (100.0)
Cefepime-tazobactam	53 (9.0)	17 (11.8)	11 (13.7)	14 (16.1)	9 (17.6)	15 (20.1)	18 (23.2)	8 (24.5)	9 (26.1)	31 (31.3)	55 (40.6)	90 (55.8)	261 (100.0)

^aTazobactam was used at a fixed concentration of 8 $\mu\text{g/ml}$, and the results are for 7,981 bacterial isolates from all geographic regions combined. Values in bold indicate MIC₅₀s and MIC₉₀s. Abbreviations: ESBL phenotype, extended-spectrum β -lactamase (ESBL)-screen-positive phenotype, defined as an MIC of ≥ 2 $\mu\text{g/ml}$ for ceftazidime, ceftazidime, and/or aztreonam; CAZ nonsusceptible, ceftazidime nonsusceptible (MICs, ≥ 8 $\mu\text{g/ml}$ for *Enterobacteriaceae* and ≥ 16 $\mu\text{g/ml}$ for *P. aeruginosa*); MEM nonsusceptible, meropenem nonsusceptible (MICs, ≥ 2 $\mu\text{g/ml}$ for *Enterobacteriaceae* and ≥ 4 $\mu\text{g/ml}$ for *P. aeruginosa*) (7).

TABLE 2 Activity of cefepime-tazobactam combination and comparator agents tested against bacterial isolates collected worldwide in 2014

Organism and antimicrobial agent	MIC ₅₀ (μ g/ml)	MIC ₉₀ (μ g/ml)	% susceptible by use of CLSI/EUCAST breakpoint criteria ^a (no. of isolates)					
			United States	Europe	Latin America	APAC ^d	China	All regions
<i>Enterobacteriaceae</i>			(2,466)	(2,351)	(466)	(693)	(243)	(6,219)
Cefepime-tazobactam (tazobactam at fixed 8 μ g/ml)	≤ 0.03	0.25	98.3/97.6 ^b	95.8/94.3 ^b	94.4/91.4 ^b	98.7/97.8 ^b	93.8/92.6 ^b	96.9/95.7 ^b
Cefepime-tazobactam (tazobactam at fixed 4 μ g/ml)	0.06	0.5	98.1/97.1 ^b	94.7/93.2 ^b	92.9/90.3 ^b	98.1/96.5 ^b	93.4/91.8 ^b	96.2/94.9 ^b
Cefepime	0.06	16	92.2/90.4	81.1/79.2	64.8/63.3	86.3/83.8	60.5/56.4	84.0/82.1
Ceftazidime	0.25	>16	88.9/86.4	78.4/74.6	65.9/60.3	82.5/78.2	68.7/58.8	81.7/78.0
Ceftriaxone	≤ 0.06	>8	84.5/84.5	72.1/72.1	58.4/58.4	77.3/77.3	49.0/49.0	75.7/78.0
Piperacillin-tazobactam	2	32	92.0/88.9	84.2/79.5	82.6/78.8	89.2/85.0	84.6/79.3	87.7/83.8
Meropenem	0.03	0.06	97.9/98.2	95.5/95.9	94.8/95.5	98.6/98.7	94.2/94.2	96.7/97.0
Levofloxacin	≤ 0.12	>8	84.4/83.1	78.0/75.9	63.5/62.7	82.7/81.1	63.2/61.2	79.4/77.8
Gentamicin	≤ 1	4	90.1/88.4	85.3/84.1	72.7/71.9	84.6/84.3	63.0/62.6	85.3/84.1
<i>P. aeruginosa</i>			(390)	(391)	(109)	(197)	(84)	(1,171)
Cefepime-tazobactam (tazobactam at fixed 8 μ g/ml)	2	16	85.9 ^c	79.8 ^c	79.8 ^c	85.8 ^c	73.8 ^c	82.4 ^b
Cefepime-tazobactam (tazobactam at fixed 4 μ g/ml)	2	16	86.2 ^c	78.5 ^c	78.9 ^c	85.8 ^c	73.8 ^c	82.0 ^b
Cefepime	2	16	84.4/84.4	78.3/78.3	77.1/77.1	84.8/84.8	72.6/72.6	80.9/80.9
Ceftazidime	2	>16	87.2/87.2	73.1/73.1	70.6/70.6	79.7/79.7	70.2/70.2	78.5/78.5
Piperacillin-tazobactam	4	>64	86.2/86.2	74.7/74.7	76.1/76.1	81.7/81.7	66.7/66.7	79.2/79.2
Meropenem	0.5	8	85.6/85.6	73.9/73.9	75.2/75.2	83.2/53.2	69.0/69.0	79.2/79.2
Levofloxacin	0.5	>4	79.0/67.7	71.1/63.7	67.0/59.6	80.7/72.6	76.2/67.9	75.3/66.4
Amikacin	2	8	97.2/92.8	91.0/86.7	90.8/89.9	94.4/91.9	91.7/88.1	93.7/90.0
<i>Acinetobacter</i> spp.			(152)	(184)	(72)	(93)	(90)	(591)
Cefepime-tazobactam (tazobactam at fixed 8 μ g/ml)	64	>64	53.9 ^c	18.5 ^c	9.7 ^c	18.3 ^c	15.6 ^c	26.1 ^b
Cefepime-tazobactam (tazobactam at fixed 4 μ g/ml)	64	>64	53.3 ^c	17.4 ^c	8.3 ^c	18.3 ^c	15.6 ^c	25.9 ^b
Cefepime	64	>64	46.7/—	16.3/—	6.9/—	17.2/—	14.4/—	22.8/—
Ceftazidime	>32	>32	54.6/—	17.4/—	9.7/—	19.4/—	14.4/—	25.9/—
Piperacillin-tazobactam	>64	>64	53.9/—	19.6/—	6.9/—	17.2/—	12.4/—	25.4/—
Ampicillin-sulbactam	32	>32	63.6/—	24.5/—	18.1/—	16.1/—	15.6/—	31.0/—
Meropenem	>32	>32	56.6/56.6	26.1/26.1	11.1/11.1	17.2/17.2	16.7/16.7	29.3/—
Levofloxacin	>4	>4	53.3/52.6	18.5/17.4	11.1/11.1	18.3/18.3	15.6/15.6	26.1/25.4
Amikacin	>32	>32	78.1/74.8	28.8/26.6	13.9/12.5	30.1/26.9	21.1/18.9	38.6/36.1

^aUnless indicated otherwise, the data are based on the criteria published by CLSI (7) and EUCAST (12). For cefepime-tazobactam, only CLSI criteria were applied. — indicates that breakpoints have not been established.

^bPercentage inhibited by ≤ 8 μ g/ml cefepime/ ≤ 2 μ g/ml cefepime, according to the CLSI breakpoint criteria for cefepime susceptibility for high and low dosages (2 g every 8 h and 1 g every 12 h, respectively), as published in CLSI document M100-S26 (7).

^cPercentage inhibited at ≤ 8 μ g/ml, according to the CLSI breakpoint for cefepime susceptibility published by the CLSI (7) and EUCAST (12) (*P. aeruginosa* only).

^dAPAC, Asia-Pacific region excluding China.

and ceftazidime-nonsusceptible *Enterobacter* strains (Table 3). The MIC₅₀ and MIC₉₀ values of cefepime for ESBL-screening-positive phenotype *Escherichia coli* strains were 16 and >64 μ g/ml, respectively, and those of cefepime-tazobactam with tazobactam at fixed 8 μ g/ml were 0.12 and 0.5 μ g/ml, respectively. The MIC₅₀ and MIC₉₀ values of cefepime for ESBL-screening-positive phenotype *K. pneumoniae* isolates were 64 and >64 μ g/ml, respectively, and those of cefepime-tazobactam with tazobactam at fixed 8 μ g/ml were 0.5 and >64 μ g/ml, respectively. The MIC₅₀ and MIC₉₀ values of cefepime for ceftazidime-nonsusceptible *Enterobacter* spp. were 1 and 16 μ g/ml, respectively, and those of cefepime-tazobactam with tazobactam at fixed 8 μ g/ml were 0.25 and 2 μ g/ml, respectively. Furthermore, there was a tendency for the MIC values of cefepime-tazobactam with tazobactam at fixed 8 μ g/ml to be slightly lower than those of cefepime-tazobactam with tazobactam at fixed 4 μ g/ml (data not shown). Testing of cefepime-tazobactam with tazobactam at fixed 8 μ g/ml increased the susceptibility rate by only 1% for the *Enterobacteriaceae* overall compared to that obtained with cefepime-tazobactam with tazobactam at fixed 4 μ g/ml (Table 2).

TABLE 3 Summary of activity of cefepime-tazobactam with tazobactam at fixed 8 $\mu\text{g/ml}$ stratified by geographic region

Organisms (no. of isolates for all regions combined) ^b	MIC ₅₀ /MIC ₉₀ ($\mu\text{g/ml}$) of cefepime-tazobactam with tazobactam at fixed 8 $\mu\text{g/ml}$ (% isolates inhibited at $\leq 8 \mu\text{g/ml}$) ^a					
	United States	Europe	Latin America	APAC ^b	China	All regions
<i>Enterobacteriaceae</i> (6,219)	$\leq 0.03/0.25$ (98.3)	$\leq 0.03/0.5$ (95.8)	0.06/1 (94.4)	$\leq 0.03/0.25$ (98.7)	0.06/0.5 (93.8)	$\leq 0.03/0.25$ (96.9)
<i>E. coli</i> (2,211)	$\leq 0.03/0.12$ (99.9)	$\leq 0.03/0.12$ (100.0)	0.06/0.25 (100.0)	$\leq 0.03/0.06$ (99.7)	0.06/0.25 (96.2)	$\leq 0.03/0.12$ (99.7)
ESBL phenotype (471)	0.12/0.25 (99.0)	0.12/1 (100.0)	0.12/0.25 (100.0)	0.06/0.25 (98.4)	0.06/0.25 (94.2)	0.12/0.5 (98.7)
<i>Klebsiella</i> spp. (2,138)	$\leq 0.03/0.25$ (95.9)	0.06/32 (87.4)	0.06/64 (85.0)	$\leq 0.03/0.25$ (96.5)	0.06/64 (86.1)	$\leq 0.03/0.4$ (91.9)
ESBL phenotype (661)	0.5/32 (78.8)	0.5/>64 (71.8)	1/>64 (72.2)	0.12/64 (87.9)	0.12/64 (66.7)	0.5/64 (73.7)
<i>K. pneumoniae</i> (1,788)	$\leq 0.03/0.25$ (94.9)	0.06/64 (85.0)	0.06/64 (83.3)	$\leq 0.03/0.5$ (96.2)	0.06/64 (85.1)	0.06/8 (90.3)
MEM-non-susceptible (183)	16/>64 (20.0)	64/>64 (14.6)	64/>64 (20.8)	>64/— (0.0)	64/>64 (0.0)	64/>64 (15.3)
<i>Klebsiella oxytoca</i> (345)	$\leq 0.03/0.12$ (100.0)	$\leq 0.03/1$ (99.2)	$\leq 0.03/1$ (100.0)	$\leq 0.03/0.12$ (100.0)	$\leq 0.03/—$ (100.0)	$\leq 0.03/0.25$ (99.7)
ESBL-phenotype (59)	0.5/4 (100.0)	1/8 (96.4)	1/— (100.0)	0.12/— (100.0)	—	0.5/4 (98.3)
<i>P. mirabilis</i> (228)	0.06/0.12 (100.0)	0.06/0.12 (100.0)	0.06/0.12 (100.0)	0.06/0.06 (100.0)	0.06/— (100.0)	0.06/0.12 (100.0)
ESBL phenotype (19)	0.12/— (100.0)	0.12/0.25 (100.0)	0.25 (100.0)	—	0.06/— (100.0)	0.12/0.25 (100.0)
<i>Enterobacter</i> spp. (629)	0.06/0.25 (99.2)	0.06/0.5 (98.7)	0.06/1 (98.2)	0.06/1 (100.0)	0.06/1 (97.4)	0.06/0.5 (98.9)
CAZ nonsusceptible (179)	0.25/2 (96.2)	0.25/2 (95.5)	0.25/2 (95.2)	0.25/2 (100.0)	0.25/8 (93.3)	0.25/2 (96.1)
<i>Morganella morganii</i> (165)	$\leq 0.03/0.06$ (100.0)	$\leq 0.03/0.06$ (100.0)	$\leq 0.03/—$ (100.0)	$\leq 0.03/\leq 0.03$ (100.0)	$\leq 0.03/—$ (100.0)	$\leq 0.03/0.06$ (100.0)
<i>Citrobacter</i> spp. (311)	$\leq 0.03/0.12$ (100.0)	$\leq 0.03/0.25$ (99.2)	0.06/— (100.0)	$\leq 0.03/0.25$ (100.0)	0.12/— (100.0)	$\leq 0.03/0.25$ (99.7)
<i>Serratia marcescens</i> (245)	0.06/0.25 (100.0)	0.06/0.25 (100.0)	0.06/0.12 (100.0)	0.06/0.12 (100.0)	0.06/0.25 (100.0)	0.06/0.25 (100.0)
<i>Proteus vulgaris</i> (144)	0.06/0.12 (100.0)	0.06/0.12 (100.0)	$\leq 0.03/—$ (100.0)	0.06/— (100.0)	0.06/— (100.0)	0.06/0.12 (100.0)
<i>Providencia</i> spp. (148)	$\leq 0.03/0.12$ (98.9)	$\leq 0.03/0.06$ (98.1)	$\leq 0.03/—$ (100.0)	$\leq 0.03/—$ (100.0)	—	$\leq 0.03/0.06$ (98.6)
<i>P. aeruginosa</i> (1,171)	2/16 (85.9)	4/16 (79.8)	4/32 (79.8)	2/16 (85.8)	4/32 (73.8)	2/16 (82.4)
CAZ nonsusceptible (252)	16/64 (22.0)	16/32 (31.4)	16/>64 (37.5)	16/>64 (35.0)	32/>64 (20.0)	16/64 (29.8)
MEM nonsusceptible (244)	16/64 (37.5)	16/32 (42.2)	16/>64 (44.4)	16/>64 (39.4)	32/>64 (15.6)	16/64 (40.6)
<i>A. baumannii</i> (591)	4/>64 (53.9)	64/>64 (18.5)	>64/>64 (9.7)	>64/>64 (18.3)	>64/>64 (15.6)	64/>64 (26.1)

^aAccording to the breakpoint for cefepime susceptibility for a high dosage (2 g every 8 h) published in CLSI document M100-S26 (7). —, there were too few isolates (<10) with which to calculate the MIC₉₀.

^bAbbreviations: APAC, Asia-Pacific region excluding China; ESBL phenotype, extended-spectrum β -lactamase (ESBL)-screen-positive phenotype, defined as an MIC of $\geq 2 \mu\text{g/ml}$ for ceftazidime, ceftazidime, and/or aztreonam; CAZ nonsusceptible, ceftazidime nonsusceptible (MICs, $\geq 8 \mu\text{g/ml}$ for *Enterobacteriaceae* and $\geq 16 \mu\text{g/ml}$ for *P. aeruginosa*); MEM nonsusceptible, meropenem nonsusceptible (MICs, $\geq 2 \mu\text{g/ml}$ for *Enterobacteriaceae* and $\geq 4 \mu\text{g/ml}$ for *P. aeruginosa*) (7).

Overall, cefepime-tazobactam at $\leq 8/8 \mu\text{g/ml}$ inhibited 98.7% of ESBL-screening-positive phenotype *E. coli* isolates and retained activity against many ESBL-screening-positive phenotype *Klebsiella* spp. (73.7 and 79.1% of isolates were inhibited by cefepime-tazobactam at $\leq 8/8$ and $\leq 16/8 \mu\text{g/ml}$, respectively; Table 3). Meropenem showed more limited activity against ESBL-screening-positive phenotype *Klebsiella* spp. (71.9% of the isolates were susceptible by use of the CLSI breakpoint; data not shown), indicating that a large proportion of isolates categorized as having the ESBL-screening-positive phenotype according to the CLSI ESBL screening criteria (MICs, $\geq 2 \mu\text{g/ml}$ for ceftazidime, ceftazidime, and/or aztreonam) (7) produce carbapenemases and/or carry other resistance mechanisms that affect the activity of the carbapenems. Of note, cefepime-tazobactam exhibited limited activity against meropenem-nonsusceptible *K. pneumoniae* isolates (MIC₅₀, $>64 \mu\text{g/ml}$). When the antimicrobial agents were tested against ceftazidime-nonsusceptible *Enterobacter* strains, the MIC₅₀ and MIC₉₀ values of cefepime were 1 and 16 $\mu\text{g/ml}$, respectively, and the MIC₅₀ and MIC₉₀ values of cefepime-tazobactam with tazobactam at fixed 8 $\mu\text{g/ml}$ were 0.25 and 2 $\mu\text{g/ml}$, respectively (Table 3).

The rate of susceptibility to cefepime (where susceptibility was defined as an MIC of $\leq 2 \mu\text{g/ml}$ [the CLSI breakpoint]) varied substantially among isolates of the *Enterobacteriaceae* from the different geographic regions. The highest rate of susceptibility to cefepime was observed in the United States (92.2%), followed by the Asia-Pacific region excluding China (APAC) (86.3%), Europe (81.1%), Latin America (64.8%), and China (60.5%) (Table 2). Less variation in the percentages of *Enterobacteriaceae* isolates inhibited by cefepime-tazobactam with tazobactam at fixed 4 $\mu\text{g/ml}$ (90.3 to 97.1%) or 8 $\mu\text{g/ml}$ (91.4 to 97.6%) was observed among the geographic regions for isolates for

TABLE 4 Regional occurrence of resistance phenotypes^a

Geographic region	% of isolates							
	ESBL phenotype				MEM-NS		CAZ-NS	
	<i>E. coli</i>	<i>K. pneumoniae</i>	<i>K. oxytoca</i>	<i>P. mirabilis</i>	<i>K. pneumoniae</i>	<i>P. aeruginosa</i>	<i>Enterobacter</i> spp.	<i>P. aeruginosa</i>
United States	14.4	16.2	12.9	1.1	6.0	26.1	22.2	26.9
Europe	19.3	49.3	22.6	14.9	15.7	14.4	28.9	12.8
Latin American	37.4	58.0	18.8	13.3	16.0	24.8	39.3	29.4
APAC	18.8	29.3	22.7	0.0	3.8	16.8	33.8	20.3
China	66.3	44.8	0.0	20.0	14.9	31.0	39.5	29.8
All regions combined	21.3	33.7	17.1	8.3	10.2	20.8	28.5	21.5

^aAbbreviations: ESBL phenotype, extended-spectrum β -lactamase (ESBL)-screen-positive phenotype, defined as an MIC of ≥ 2 $\mu\text{g/ml}$ for ceftriaxone, ceftazidime, and/or aztreonam (20); MEM-NS, meropenem nonsusceptible (MICs, ≥ 2 $\mu\text{g/ml}$ for *K. pneumoniae* and ≥ 4 $\mu\text{g/ml}$ for *P. aeruginosa*) (7); CAZ-NS, ceftazidime nonsusceptible (MICs, ≥ 8 $\mu\text{g/ml}$ for *Enterobacter* spp. and ≥ 16 $\mu\text{g/ml}$ for *P. aeruginosa*) (7); APAC, Asia-West Pacific region excluding China.

which the MIC values were ≤ 2 $\mu\text{g/ml}$ (Table 2). The highest activities of cefepime-tazobactam (with tazobactam at fixed 8 $\mu\text{g/ml}$) against the *Enterobacteriaceae* were observed among isolates from the United States (MIC₅₀ and MIC₉₀, ≤ 0.03 and 0.25 $\mu\text{g/ml}$, respectively, with 97.6% of isolates being inhibited at ≤ 2 $\mu\text{g/ml}$) and APAC (MIC₅₀ and MIC₉₀, ≤ 0.03 and 0.25 $\mu\text{g/ml}$, respectively, with 97.8% of isolates being inhibited at ≤ 2 $\mu\text{g/ml}$), followed by Europe (MIC₅₀ and MIC₉₀, ≤ 0.03 and 0.5 $\mu\text{g/ml}$, respectively, with 94.3% of isolates being inhibited at ≤ 2 $\mu\text{g/ml}$), China (MIC₅₀ and MIC₉₀, 0.06 and 0.5 $\mu\text{g/ml}$, respectively, with 92.6% of isolates being inhibited at ≤ 2 $\mu\text{g/ml}$), and Latin America (MIC₅₀ and MIC₉₀, 0.06 and 1 $\mu\text{g/ml}$, respectively, with 91.4% of isolates being inhibited at ≤ 2 $\mu\text{g/ml}$) (Table 2).

When the *in vitro* activities of the cefepime-tazobactam combinations (with tazobactam at fixed 4 and 8 $\mu\text{g/ml}$) against *P. aeruginosa* were tested, they were found to be similar to those observed for cefepime alone, with the MIC₅₀ and MIC₉₀ values of the three compounds being 2 and 16 $\mu\text{g/ml}$, respectively (Table 2). This observation of a lack of a significant effect of tazobactam on the MICs of the partner cephalosporin has also been reported for the ceftolozane-tazobactam combination (10). Furthermore, the activity of cefepime-tazobactam against *P. aeruginosa* (82.4% of isolates of which were inhibited by cefepime-tazobactam at $\leq 8/8$ $\mu\text{g/ml}$) was slightly greater than the activities of meropenem (79.2% of isolates were susceptible), piperacillin-tazobactam (79.2% susceptible), and ceftazidime (78.5% susceptible) (Table 2). The activity of cefepime against *P. aeruginosa* was the highest in the United States (MIC₅₀ and MIC₉₀, 2 and 16 $\mu\text{g/ml}$, respectively; 84.4% susceptible) and APAC (MIC₅₀ and MIC₉₀, 2 and 32 $\mu\text{g/ml}$, respectively; 84.8% susceptible), followed by Europe (MIC₅₀ and MIC₉₀, 4 and 32 $\mu\text{g/ml}$, respectively; 78.3% susceptible), Latin America (MIC₅₀ and MIC₉₀, 4 and 32 $\mu\text{g/ml}$, respectively; 77.1% susceptible), and China (MIC₅₀ and MIC₉₀, 4 and 32 $\mu\text{g/ml}$; 72.6% susceptible); and the activities of cefepime-tazobactam with tazobactam at fixed 4 and 8 $\mu\text{g/ml}$ were very similar to those of cefepime tested alone in all geographic regions (Table 2).

The frequencies of *E. coli*, *K. pneumoniae*, *Klebsiella oxytoca*, and *Proteus mirabilis* isolates with an ESBL-screening-positive phenotype, as well as the frequencies of meropenem-nonsusceptible *K. pneumoniae* and *P. aeruginosa* isolates and ceftazidime-nonsusceptible *Enterobacter* and *P. aeruginosa* strains, observed in the organism collection evaluated in the present study were stratified by geographic region in Table 4. The rates of positivity for the ESBL-screening-positive phenotype were generally the highest among isolates cultured from patients in China and Latin America, followed by Europe, APAC, and the United States. The highest rate of positivity for the ESBL-screening-positive phenotype among *E. coli* isolates was observed in China (66.3%), followed by Latin America (37.4%), Europe (19.3%), APAC (18.8%), and the United States (14.4%) (Table 4). Among the *K. pneumoniae* isolates, the rates of positivity for the ESBL-screening-positive phenotype were the highest in Latin America (58.0%), followed by Europe (49.3%), China (44.8%), APAC (29.3%), and the United States (16.2%) (Table 4). Furthermore, the rate of occurrence of *K. pneumoniae* strains with decreased susceptibility to meropenem (MIC, ≥ 2 $\mu\text{g/ml}$) was greater in Latin

America (16.0%), Europe (15.7%), and China (14.9%) than in the United States (6.0%) and APAC (3.8%) (Table 4). Among the *P. aeruginosa* isolates, decreased susceptibility to ceftazidime was the most pronounced in China (29.8%), followed by Latin America (29.4%) and then the United States (26.9%). The rates of occurrence of *P. aeruginosa* isolates with decreased susceptibility to meropenem were also higher in these three regions (24.8 to 31.0%) than in Europe and APAC (14.4 to 16.8%) (Table 4). Cefepime and the cefepime-tazobactam combinations (with tazobactam at fixed 4 and 8 $\mu\text{g/ml}$) showed more limited *in vitro* activity against these subsets of resistant isolates (subsets in which $<40.0\%$ of isolates were inhibited by $\leq 8 \mu\text{g/ml}$) than against the susceptible counterparts (subsets in which 92.3 to 96.8% of isolates were inhibited by $\leq 8 \mu\text{g/ml}$) (Table 3). Also, all three compounds exhibited compromised activity when they were tested against *Acinetobacter* spp. (MIC_{50} and MIC_{90} , 64 and $>64 \mu\text{g/ml}$, respectively, for all three compounds; Table 3).

DISCUSSION

Since its introduction to clinical practice more than 2 decades ago, cefepime has been a first-line agent for the empirical treatment of patients with neutropenic fever (1). Furthermore, due to its broad spectrum of antimicrobial activity, its stability against inducible AmpC and some ESBLs, and its higher threshold for selection of strains hyperproducing chromosomally mediated β -lactamases, cefepime has been extensively used for the treatment of severe infections caused by Gram-negative bacteria. Also, cefepime possesses activity against some key Gram-positive pathogens, such as *Streptococcus pneumoniae* and methicillin-susceptible staphylococci, superior to that of other broad-spectrum cephalosporins (2, 11).

Cefepime is generally administered as an intravenous infusion over 30 min. Dosages range from 0.5 to 2 g every 8 to 12 h, depending on the clinical indication, the severity of infection, and patient renal function (1). Because these various dose regimens provide a wide range of pharmacokinetic (PK)-pharmacodynamics (PD) target achievements, in 2013 the CLSI elected to lower the breakpoint for cefepime susceptibility from 8 to 2 $\mu\text{g/ml}$ and to introduce a new susceptibility testing category for cefepime known as susceptible-dose dependent (SDD; MICs, 4 to 8 $\mu\text{g/ml}$) (7). The SDD category addresses concerns that the breakpoint of 8 $\mu\text{g/ml}$ could be too high when lower-dose regimens are used and preserves the use of cefepime against pathogens with higher MIC values (4 and 8 $\mu\text{g/ml}$), as long as the cefepime dosage is adequate (7, 11, 12).

Cefepime-tazobactam (WCK 4282) consists of cefepime combined with a high proportion of tazobactam, a penicillanic acid-sulfone which is a well-established β -lactamase inhibitor. Unlike clavulanate and sulbactam, tazobactam is a moderate inhibitor of inducible and constitutively expressed AmpC enzymes, although this activity is strain dependent and it is less potent against strains with totally derepressed AmpC β -lactamases (13). When it is combined with cefepime, which is not well hydrolyzed by AmpC β -lactamases, tazobactam restores the activity of cefepime against strains expressing derepressed AmpC β -lactamases (14). Cefepime-tazobactam is under clinical development for use at dosing regimens of 2 g of cefepime combined with 2 g of tazobactam administered every 8 h as a prolonged 90-min infusion. Therefore, since the current susceptibility breakpoint for cefepime alone when these cefepime dosing regimens are used is $\leq 8 \mu\text{g/ml}$ (1, 7), a tentative susceptibility breakpoint of $\leq 8 \mu\text{g/ml}$ for cefepime-tazobactam was utilized in the present investigation for comparison purposes. Additionally, the results of *in vivo* PK-PD studies, population PK studies, and Monte Carlo simulation indicated that the high-proportion cefepime-tazobactam combination generates a concentration-time profile adequate to cover strains with a cefepime-tazobactam MIC of 16 $\mu\text{g/ml}$. Thus, a PK-PD breakpoint of 16 $\mu\text{g/ml}$ has been proposed for this combination (8, 9).

When it was tested against the *Enterobacteriaceae*, the antimicrobial spectrum of cefepime-tazobactam was very similar to that of meropenem. The high-proportion combination with tazobactam extended the activity of cefepime against most *E. coli*

and *K. pneumoniae* isolates with an ESBL-screening-positive phenotype and increased its coverage of *Enterobacteriaceae* isolates approximately 13% overall. For instance, 98.7 and 71.3% of *E. coli* and *K. pneumoniae* isolates with an ESBL-screening-positive phenotype, respectively, were inhibited by cefepime-tazobactam at $\leq 8/8$ $\mu\text{g/ml}$ (99.4 and 77.2%, respectively, were inhibited by cefepime-tazobactam at $\leq 16/8$ $\mu\text{g/ml}$). In summary, roughly 97% of *Enterobacteriaceae* isolates overall and 70% of *K. pneumoniae* isolates showing an ESBL-screening-positive phenotype were susceptible to meropenem and inhibited by cefepime-tazobactam at 8/8 $\mu\text{g/ml}$ or less. Furthermore, the activity of cefepime-tazobactam against *P. aeruginosa* was comparable to the activities of other antipseudomonal β -lactams tested (meropenem, piperacillin-tazobactam, and ceftazidime). In conclusion, cefepime-tazobactam was the β -lactam with the widest spectrum of activity against all sampled organism groups, excluding *Acinetobacter baumannii*. The *in vitro* results presented here, coupled with the vast clinical and safety experience recorded for both cefepime and tazobactam (15–18), support the further clinical development of cefepime-tazobactam as a treatment for serious infections caused by Gram-negative bacilli, including multidrug-resistant pathogens.

MATERIALS AND METHODS

Organism collection. A total of 7,981 Gram-negative isolates were collected as part of the SENTRY Antimicrobial Surveillance Program (19) from 146 medical institutions worldwide (the United States [69 medical centers], Europe [44 medical centers], Latin America [8 medical centers], Asia-West Pacific region excluding China [APAC; 15 medical centers], and China [10 medical centers]). Each participant center was requested to collect consecutive bacterial isolates (one per patient) from patients with various infection types, including pneumonia, bloodstream infections, urinary tract infections, acute bacterial skin and skin structure infections, intra-abdominal infections, and others. Only bacterial isolates determined by local criteria to be significant as the reported probable cause of infection were included in the program. The isolates were collected in 2014, except for those from China (417 isolates), which were collected during 2013.

Antimicrobial susceptibility testing. The MIC values for cefepime-tazobactam and the comparator agents were determined using the CLSI broth microdilution method described in CLSI document M07-A10 (20). Cefepime was combined with tazobactam at fixed concentrations of 4 and 8 $\mu\text{g/ml}$. The cefepime susceptibility breakpoints published in CLSI document M100-S26 (7) for a low dosage (≤ 2 $\mu\text{g/ml}$; 1 g every 12 h) and a high dosage (≤ 8 $\mu\text{g/ml}$; 2 g every 8 h) were applied to cefepime-tazobactam for comparison purposes only. Moreover, the percentages of isolates inhibited at the proposed PK-PD breakpoint of 16 $\mu\text{g/ml}$ were also determined (8, 9). Susceptibility interpretations published in CLSI document M100-S26 (7) and by EUCAST (21) were used for comparator agents, when available. Quality control (QC) was performed using *E. coli* ATCC 25922, ATCC 35218, and NCTC 13353; *K. 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 those for cefepime-tazobactam (22).

Resistant subsets. *Escherichia coli*, *Klebsiella pneumoniae*, *K. oxytoca*, and *Proteus mirabilis* isolates were grouped as isolates with an extended-spectrum β -lactamase (ESBL)-screening-positive phenotype on the basis of the CLSI screening criteria for ESBL production, i.e., an MIC of ≥ 2 $\mu\text{g/ml}$ for ceftazidime, ceftriaxone, and/or aztreonam (7), for the purpose of the analysis of the susceptibility testing results. Although other β -lactamases, such as AmpC and KPC, may also produce an ESBL-screening-positive phenotype, these strains were grouped together because they usually demonstrate resistance to various broad-spectrum β -lactam compounds.

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