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ACTIVITY OF THE NOVEL ANTIMICROBIAL CEFTOLOZANE/TAZOBACTAM TESTED AGAINST CONTEMPORARY CLINICAL STRAINS FROM USA HOSPITALS (2011)

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ABSTRACT

Background: Ceftolozane (formerly CXA-101) is a novel oxyimino-aminothiazolyl cephalosporin. Ceftolozane combined with tazobactam is currently under Phase 3 clinical development. We evaluated the activity of ceftolozane/tazobactam (formerly CXA-201) against Gram-negative organisms isolated from patients in 32 USA hospitals in 2011.

Methods: Susceptibility testing of ceftolozane/tazobactam (tazobactam at fixed 4 µg/ml) and comparators was performed by CLSI broth microdilution methods against 5076 clinical strains, including 973 *P. aeruginosa* (PSA; 19.1% ceftazidime [CAZ]-non-susceptible [S]) and 21.7% meropenem [MER]-non-S), 1244 *E. coli* (13.5% ESBL-phenotype), 840 *Klebsiella* spp. (16.8% ESBL-phenotype and 3.3% MER-non-S), and 525 *Enterobacter* spp. (ESP; 22.3% CAZ-non-S), among others.

Results: Against PSA, ceftolozane/tazobactam ($MIC_{50/90}$, 1/4 µg/ml) was 2- to 8-fold more active than CAZ ($MIC_{50/90}$, 2/32 µg/ml) or cefepime (CPM; $MIC_{50/90}$, 4/16 µg/ml) and inhibited 89.6% of MER-non-S strains at MIC of ≤8 µg/ml. Ceftolozane/tazobactam exhibited activity against PSA strains non-S to CAZ ($MIC_{50/90}$, 4/16 µg/ml), to MER ($MIC_{50/90}$, 1/16 µg/ml) and to both CAZ and MER ($MIC_{50/90}$, 4/>32 µg/ml). Piperacillin/tazobactam (P/T; $MIC_{50/90}$, 8/>64 µg/ml) was active against 74.6% of PSA at S breakpoint of ≤16 µg/ml. Ceftolozane/tazobactam activity against non-ESBL-phenotype *E. coli* ($MIC_{50/90}$, 0.12/0.25 µg/ml) and *K. pneumoniae* ($MIC_{50/90}$, 0.25/0.5 µg/ml) was similar to that of CAZ ($MIC_{50/90}$, of 0.12/0.25 and 0.12/0.5 µg/ml, respectively). In contrast, ceftolozane/tazobactam was 16- to 32-fold more active than CAZ when tested against ESBL-phenotype *E. coli*. Against ESP and *Citrobacter* spp., ceftolozane/tazobactam ($MIC_{50/90}$, 0.25/8 µg/ml for both) was slightly more active than CAZ ($MIC_{50/90}$, 0.25/>32 µg/ml for both).

Conclusions: Ceftolozane/tazobactam demonstrated greater potency than currently available anti-PSA cephalosporins (CAZ and CPM) and P/T when tested against PSA and Enterobacteriaceae strains from USA hospitals. ceftolozane/tazobactam may represent a valuable treatment option for Gram-negative infections, including those caused by resistance organisms.

INTRODUCTION

Ceftolozane (formerly CXA-101 and FR264205) is an oxyimino-aminothiazolyl cephalosporin with greater activity against *Pseudomonas aeruginosa* when compared to ceftazidime and cefepime. Ceftolozane has also demonstrated good activity against Enterobacteriaceae; but similar to other structurally similar cephalosporins, ceftolozane activity can be adversely affected by bacterial production of extended spectrum β-lactamases (ESBL) and stably-derepressed AmpC β-lactamases. To decrease this vulnerability, ceftolozane was combined with tazobactam, a β-lactamase inhibitor with established safety and efficacy when in combination with piperacillin.

Ceftolozane/tazobactam (CXA-201) is currently under clinical development for treatment of complicated intraabominal infections (cIAI) and urinary tract infections (cUTI). Population pharmacokinetic analysis have shown that the proposed clinical dose of 1000/500mg q8h infused over 60 minutes is predicted to achieve >90% target attainment rate (40% time above MIC) for Enterobacteriaceae and *P. aeruginosa* with a MIC of 8 µg/ml. In the present study, we evaluated the in vitro activity of ceftolozane/tazobactam against Gram-negative organisms isolated from patients in 32 USA hospitals.

MATERIALS & METHODS

Organism collection: A total of 5,076 clinically significant, consecutively collected, non-duplicate isolates of Gram-negative bacilli from patients hospitalized in 32 USA medical centers (2011) were utilized for this study. The organism collection included 973 *P. aeruginosa* (19.1% ceftazidime-non-susceptible, and 21.7% meropenem-non-susceptible), 1,244 *E. coli* (13.5% ESBL-phenotype), 840 *Klebsiella* spp. (16.8% ESBL-phenotype and 3.3% meropenem-non-susceptible), and 525 *Enterobacter* spp. (22.3% ceftazidime-non-susceptible), among others.

MATERIALS & METHODS

Susceptibility testing: Broth microdilution test methods conducted according to the Clinical and Laboratory Standards Institute (CLSI) were performed to determine the antimicrobial susceptibility of ceftolozane combined with tazobactam at a fixed concentration of 4 µg/ml in addition to other comparator agents. Validated MIC panels were manufactured by ThermoFisher Scientific Inc., formerly TREK Diagnostics (Cleveland, Ohio, USA). Concurrent quality control (QC) testing was performed to assure proper test conditions and procedures. QC strains included: *Escherichia coli* ATCC 25922 and 35218 and *P. aeruginosa* ATCC 27853. All QC results were within published ranges.

Susceptibility percentages and validation of QC results were based on the CLSI guidelines (M100-S22) and susceptibility breakpoints were used to determine susceptibility/resistance rates (CLSI and EUCAST, 2012). *E. coli* and *Klebsiella* spp. isolates for which ceftriaxone or ceftazidime MIC were ≥2 µg/ml were considered to be phenotype-positive for ESBL production (CLSI, 2012). No interpretive criteria for ceftolozane/tazobactam susceptibility have been established by CLSI EUCAST or the USA Food and Drug Administration.

RESULTS

- Against *P. aeruginosa*, ceftolozane/tazobactam ($MIC_{50/90}$, 1/4 µg/ml) was two- to eight-fold more active than ceftazidime ($MIC_{50/90}$, 2/32 µg/ml) or cefepime ($MIC_{50/90}$, 4/16 µg/ml), and inhibited 94.7 and 97.7% of strains at MIC of ≤4 and ≤8 µg/ml, respectively (Tables 1 and 2 and Figure 1).

  Among clinically available β-lactam compounds, the best anti-*P. aeruginosa* coverage was provided by doripenem ($MIC_{50/90}$, 0.5/4 µg/ml; 82.3% susceptible by CLSI criteria) and ceftazidime (80.9% susceptible; Table 2).

- Ceftolozane/tazobactam exhibited activity against *P. aeruginosa* strains non-susceptible to ceftazidime ($MIC_{50/90}$, 4/16 µg/ml), to meropenem ($MIC_{50/90}$, 1/16 µg/ml) and to both ceftazidime and meropenem ($MIC_{50/90}$, 4/>32 µg/ml). Ceftolozane/tazobactam inhibited 80.6 and 89.6% of meropenem-non-susceptible strains at MIC of ≤4 and ≤8 µg/ml, respectively (Table 1).

- A total of 1,244 *E. coli* strains were evaluated and 98.8 and 99.3% of strains were inhibited at ≤4 and ≤8 µg/ml of ceftolozane/tazobactam, respectively ($MIC_{50/90}$, 0.25/0.5 µg/ml; Table 1). Ceftriaxone ($MIC_{50/90}$, ≤0.06/>8 µg/ml) and ceftazidime ($MIC_{50/90}$, 0.12/2 µg/ml) were active against 87.7/87.7% and 91.5/88.3% of strains according to CLSI/EUCAST breakpoint criteria, respectively (Table 3).

  Ceftolozane/tazobactam activity against non-ESBL-phenotype *E. coli* ($MIC_{50/90}$, 0.12/0.25 µg/ml) was similar to that of ceftazidime ($MIC_{50/90}$, of 0.12/0.25 µg/ml). In contrast, ceftolozane/tazobactam was 16- to 32-fold more active than ceftazidime when tested against ESBL-phenotype *E. coli* (data not shown).

- Ceftolozane/tazobactam inhibited 91.4 and 92.1% of *Klebsiella* spp. strains at ≤4 and ≤8 µg/ml, respectively ($MIC_{50/90}$, 0.25/2 µg/ml; Table 1). Ceftriaxone ($MIC_{50/90}$, ≤0.06/>8 µg/ml), ceftazidime ($MIC_{50/90}$, 0.12/32 µg/ml) and cefepime ($MIC_{50/90}$, ≤0.5/8 µg/ml) inhibited 84.4/84.4%, 86.2/84.9% and 90.0/86.3% at the CLSI/EUCAST susceptible breakpoints, respectively (Table 3).

- Ceftolozane/tazobactam was very active against *P. mirabilis* ($MIC_{50/90}$, 0.5/0.5 µg/ml), including ESBL-producing strains (highest MIC, 1 µg/ml; Table 1). Against *Enterobacter* spp. (87.6 and 93.1% inhibited at ≤4 and ≤8 µg/ml, respectively) and *Citrobacter* spp. (87.9 and 90.8% inhibited at ≤4 and ≤8 µg/ml, respectively), ceftolozane/tazobactam ($MIC_{50/90}$, 0.25/8 µg/ml for both) was slightly more active than ceftazidime ($MIC_{50/90}$, 0.25/>32 µg/ml for both; Table 3).

RESULTS

- Ceftolozane/tazobactam was also active against *H. influenzae* (MIC_{50} and MIC_{90}, 0.12 µg/ml) and β-haemolytic streptococci ($MIC_{50/90}$, 0.25/0.5 µg/ml; Table 1). Ceftolozane/tazobactam in vitro activity against *S. pneumoniae*, as with other β-lactams, varied according to the susceptibility to penicillin. The highest ceftolozane/tazobactam MIC value observed among penicillin-susceptible strains was only 0.25 µg/ml, while penicillin-resistant strains exhibited higher ceftolozane/tazobactam MIC values (MIC_{50}, 4 µg/ml; data not shown).

- *Acinetobacter* spp. and *S. maltophilia* strains exhibited limited susceptibility to ceftolozane/tazobactam (MIC_{90}, >32 µg/ml) and all β-lactam compounds tested (Table 2).

Table 1. Summary of ceftolozane/tazobactam activity tested against the main pathogen groups included in the 2011 report (USA)

Organism (no. tested)	no. of isolates (cumulative %) inhibited at ceftolozane/tazobactam MIC (µg/ml) of: ≤0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	≥32
Pseudomonas aeruginosa (973)	-	-	1 (0.1)	33 (3.5)	412 (45.8)	338 (80.6)	79 (88.7)	58 (94.7)	30 (97.7)	7 (98.5)	15 (100.0)
ceftazidime-S (787)	-	-	1 (0.1)	33 (4.3)	412 (56.7)	311 (96.2)	27 (99.6)	3 (100.0)	-	-	-
ceftazidime-non-S (186)	-	-	-	-	-	27 (14.5)	52 (42.5)	55 (72.0)	30 (88.2)	7 (91.9)	15 (100.0)
meropenem-S (726)	-	-	1 (0.1)	31 (4.2)	390 (55.4)	254 (89.7)	44 (94.5)	31 (98.8)	11 (100.0)	-	-
meropenem-non-S (211)	-	-	-	2 (1.0)	22 (11.4)	84 (51.2)	35 (67.8)	27 (80.6)	19 (89.6)	7 (92.9)	15 (100.0)
ceftazidime- and meropenem-non-S (104)	-	-	-	-	-	12 (11.5)	25 (35.6)	26 (60.6)	19 (78.8)	7 (85.6)	15 (100.0)
Acinetobacter spp. (208)	25 (12.0)	1 (12.5)	2 (13.5)	7 (16.8)	10 (21.6)	19 (30.6)	22 (41.3)	12 (47.1)	17 (55.3)	26 (68.4)	65 (100.0)
Stenotrophomonas maltophilia (171)	-	-	-	-	5 (2.9)	15 (11.7)	18 (22.2)	19 (33.3)	28 (49.7)	22 (62.6)	64 (100.0)
Escherichia coli (1244)	1 (0.1)	3 (0.3)	547 (44.3)	513 (85.5)	112 (94.5)	35 (97.3)	12 (98.3)	6 (98.8)	6 (99.3)	4 (99.6)	5 (100.0)
non-ESBL-phenotype (1076)	1 (0.1)	3 (0.4)	540 (50.6)	465 (93.8)	62 (99.5)	5 (100.0)	-	-	-	-	-
ESBL-phenotype (168)	-	-	7 (4.2)	48 (32.7)	50 (62.5)	30 (80.4)	12 (87.5)	6 (91.1)	6 (94.6)	4 (97.0)	5 (100.0)
Klebsiella spp. (840)	1 (0.1)	3 (0.5)	204 (24.8)	335 (64.6)	130 (80.1)	65 (87.9)	16 (90.0)	12 (91.4)	6 (92.1)	4 (92.6)	62 (100.0)
Klebsiella pneumoniae (668)	-	3 (0.4)	131 (20.1)	270 (60.5)	112 (77.2)	60 (86.2)	15 (88.5)	7 (89.5)	6 (90.4)	4 (91.0)	60 (100.0)
non-ESBL-phenotype (551)	-	3 (0.5)	129 (24.0)	267 (72.4)	104 (91.3)	46 (99.6)	2 (100.0)	-	-	-	-
ESBL-phenotype, meropenem-S (78)	-	-	2 (2.6)	3 (6.4)	8 (16.7)	14 (34.6)	13 (51.3)	7 (60.3)	6 (68.0)	3 (71.8)	22 (100.0)
ESBL-phenotype, meropenem-non-S (36)	-	-	-	-	-	-	1 (2.8)	-	-	1 (5.6)	34 (100.0)
Klebsiella oxytoca (164)	1 (0.6)	0 (0.6)	72 (44.5)	61 (81.7)	16 (91.5)	4 (93.9)	3 (95.7)	5 (98.8)	0 (98.8)	0 (98.8)	2 (100.0)
Other Klebsiella spp. (8)	-	-	1 (12.5)	4 (62.5)	2 (87.5)	1 (100.0)	-	-	-	-	-
Enterobacter spp. (525)	1 (0.2)	2 (0.6)	63 (12.6)	212 (53.0)	110 (73.9)	36 (80.8)	17 (84.0)	19 (87.6)	29 (93.1)	15 (96.0)	21 (100.0)
ceftazidime-S (408)	1 (0.2)	2 (0.7)	63 (16.2)	210 (67.6)	106 (93.6)	24 (99.5)	2 (100.0)	-	-	-	-
ceftazidime-non-S (117)	-	-	-	2 (1.7)	4 (5.1)	12 (15.4)	15 (28.2)	19 (44.4)	29 (69.2)	15 (82.1)	21 (100.0)
Serratia spp. (287)	-	-	2 (0.7)	12 (4.9)	184 (69.0)	73 (94.4)	7 (96.9)	4 (98.3)	3 (99.3)	0 (99.3)	2 (100.0)
Proteus mirabilis (203)	-	-	3 (1.5)	71 (36.5)	118 (94.6)	11 (100.0)	-	-	-	-	-
ESBL-phenotype (7)	-	-	-	-	5 (71.4)	2 (100.0)	-	-	-	-	-
non-ESBL-phenotype (196)	-	-	3 (1.5)	71 (37.8)	113 (95.4)	9 (100.0)	-	-	-	-	-
Citrobacter spp. (174)	-	1 (0.6)	37 (21.8)	85 (70.7)	21 (82.8)	2 (83.9)	1 (84.5)	6 (87.9)	5 (90.8)	8 (95.4)	8 (100.0)
Indole-positive Proteae (139)	-	-	14 (10.1)	65 (57.6)	40 (86.3)	10 (93.5)	3 (95.7)	3 (97.8)	0 (97.8)	1 (98.6)	2 (100.0)
Salmonella spp. (12)	-	-	-	3 (25.0)	9 (100.0)	-	-	-	-	-	-
Haemophilus influenzae (51)	3 (5.9)	13 (31.4)	32 (94.1)	2 (98.0)	1 (100.0)	-	-	-	-	-	-
Streptococcus pneumoniae (56)	-	7 (12.5)	24 (55.4)	3 (60.7)	3 (66.1)	2 (69.6)	4 (76.8)	9 (92.9)	4 (100.0)	-	-
β-haemolytic streptococci (113)	-	-	35 (32.1)	45 (72.3)	23 (92.9)	7 (99.1)	1 (100.0)	-	-	-	-

Abbreviations: ESBL, extended spectrum β-lactamases; S, susceptible.

Table 2. Activity of ceftolozane/tazobactam and comparator antimicrobial agents when tested against non-fermentative Gram-negative bacilli from USA hospitals (2011)

Organism/antimicrobial agent (no. tested)	MIC (µg/ml) MIC_{50}	MIC (µg/ml) MIC_{90}	%S / %R[a] CLSI	%S / %R[a] EUCAST
P. aeruginosa (973)				
Ceftolozane/tazobactam	1	4	-/-	-/-
Ceftazidime	2	32	80.9 / 15.5	80.9 / 19.1
Cefepime	4	16	80.7 / 9.5	80.7 / 19.3
Doripenem	0.5	4	82.3 / 9.2	74.2 / 9.2
Meropenem	0.5	8	78.3 / 14.9	78.3 / 8.0
Piperacillin/tazobactam	8	>64	74.6 / 15.2	74.6 / 25.4
Levofloxacin	0.5	>4	72.3 / 21.3	60.4 / 27.7
Gentamicin	≤1	8	88.1 / 8.9	88.1 / 11.9
Amikacin	2	8	96.8 / 1.4	93.6 / 3.2
Colistin	1	2	99.8 / 0.1	99.8 / 0.2
Acinetobacter spp. (208)				
Ceftolozane/tazobactam	8	>32	-/-	-/-
Ceftazidime	32	>32	42.3 / 52.4	-/-
Cefepime	16	>16	42.3 / 49.0	-/-
Doripenem	8	>8	44.7 / -	44.7 / 50.5
Meropenem	8	>8	49.0 / 48.6	48.6 / 48.6
Ampicillin/sulbactam	16	>32	49.0 / 33.2	-/-
Piperacillin/tazobactam	>64	>64	44.7 / 55.3	-/-
Levofloxacin	>4	>4	45.7 / 50.5	45.7 / 54.3
Gentamicin	8	>8	47.1 / 50.0	47.1 / 52.9
Colistin	0.5	2	97.6 / 2.4	97.6 / 2.4
S. maltophilia (171)				
Ceftolozane/tazobactam	16	>32	-/-	-/-
Ceftazidime	16	>32	42.7 / 45.0	-/-
Cefepime	>16	>16	-/-	-/-
Levofloxacin	1	>4	71.8 / 15.9	-/-

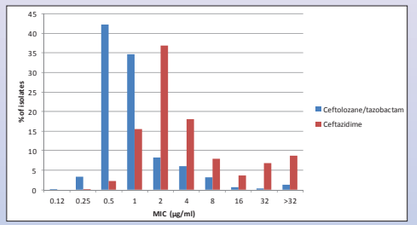
a. Criteria as published by the CLSI [2012] and EUCAST [2012].

Table 3. Activity of ceftolozane/tazobactam and comparator antimicrobial agents when tested against Enterobacteriaceae from USA hospitals (2011)

Organism/antimicrobial agent (no. tested)	MIC (µg/ml) MIC_{50}	MIC (µg/ml) MIC_{90}	%S / %R[a] CLSI	%S / %R[a] EUCAST
E. coli (1,244)				
Ceftolozane/tazobactam	0.25	0.5	-/-	-/-
Ceftriaxone	≤0.06	>8	87.7 / 12.1	87.7 / 12.1
Ceftazidime	0.12	2	91.5 / 7.0	88.3 / 8.5
Cefepime	≤0.5	4	93.1 / 5.9	89.0 / 8.7
Meropenem	≤0.06	≤0.06	99.8 / 0.2	99.8 / 0.1
Piperacillin/tazobactam	2	8	94.5 / 3.9	92.2 / 5.5
Levofloxacin	≤0.12	>4	70.1 / 29.2	69.6 / 29.9
Gentamicin	≤1	>8	87.6 / 12.1	86.7 / 12.4
Tigecycline[e]	0.06	0.12	100.0 / 0.0	100.0 / 0.0
Colistin	≤0.25	0.5	-/-	100.0 / 0.0
Klebsiella spp.[f] (840)				
Ceftolozane/tazobactam	0.25	2	-/-	-/-
Ceftriaxone	≤0.06	>8	84.4 / 14.6	84.4 / 14.6
Ceftazidime	0.12	32	86.2 / 13.1	84.9 / 13.8
Cefepime	≤0.5	8	90.0 / 8.7	86.3 / 11.1
Meropenem	≤0.06	≤0.06	95.1 / 4.6	95.4 / 4.3
Piperacillin/tazobactam	4	>64	86.8 / 11.2	81.2 / 13.2
Levofloxacin	≤0.12	>4	86.5 / 12.3	85.6 / 13.5
Gentamicin	≤1	2	92.3 / 6.5	91.3 / 7.7
Tigecycline[e]	0.25	1	98.1 / 0.4	94.2 / 1.9
Colistin	≤0.25	0.5	-/-	98.8 / 1.2
Enterobacter spp.[g] (525)				
Ceftolozane/tazobactam	0.25	8	-/-	-/-
Ceftriaxone	0.25	>8	74.3 / 23.4	74.3 / 23.4
Ceftazidime	0.25	>32	77.7 / 20.2	75.4 / 22.3
Cefepime	≤0.5	2	96.2 / 2.9	88.0 / 5.3
Meropenem	≤0.06	≤0.06	97.5 / 1.9	96.1 / 0.4
Piperacillin/tazobactam	2	64	81.9 / 8.0	75.6 / 18.1
Levofloxacin	≤0.12	0.5	94.1 / 4.8	93.5 / 5.9
Gentamicin	≤1	≤1	94.5 / 4.8	93.7 / 5.5
Tigecycline[e]	0.25	0.5	98.9 / 0.0	95.0 / 1.1
Colistin	≤0.25	>4	-/-	83.6 / 16.4
Serratia spp.[h] (287)				
Ceftolozane/tazobactam	0.5	1	-/-	-/-
Ceftriaxone	0.25	1	92.7 / 6.3	92.7 / 6.3
Ceftazidime	0.12	0.5	96.9 / 2.4	95.8 / 3.1
Cefepime	≤0.5	≤0.5	98.6 / 0.3	97.6 / 1.7
Meropenem	≤0.06	≤0.06	99.0 / 0.3	99.7 / 0.3
Piperacillin/tazobactam	2	4	97.6 / 1.0	96.9 / 2.4
Levofloxacin	≤0.12	0.5	96.5 / 1.0	94.8 / 3.5
Gentamicin	≤1	≤1	98.3 / 1.7	97.9 / 1.7
Tigecycline[e]	0.5	1	97.9 / 0.7	95.8 / 2.1
Colistin	>4	>4	-/-	4.5 / 95.5
P. mirabilis (203)				
Ceftolozane/tazobactam	0.5	0.5	-/-	-/-
Ceftriaxone	≤0.06	≤0.06	97.0 / 2.5	97.0 / 2.5
Ceftazidime	0.06	0.06	99.5 / 0.0	97.0 / 0.5
Cefepime	≤0.5	≤0.5	98.5 / 1.5	97.5 / 1.5
Meropenem	≤0.06	≤0.06	100.0 / 0.0	100.0 / 0.0
Piperacillin/tazobactam	≤0.5	1	99.0 / 0.5	99.0 / 1.0
Levofloxacin	≤0.12	>4	77.2 / 18.3	75.2 / 22.8
Gentamicin	≤1	8	89.2 / 6.9	86.2 / 10.8
Tigecycline[e]	2	4	83.7 / 1.0	42.6 / 16.3
Citrobacter spp.[i] (174)				
Ceftolozane/tazobactam	0.25	8	-/-	-/-
Ceftriaxone	0.12	>8	83.3 / 16.1	83.3 / 16.1
Ceftazidime	0.25	>32	83.3 / 16.7	83.3 / 16.7
Cefepime	≤0.5	1	97.7 / 1.1	90.2 / 2.3
Meropenem	≤0.06	≤0.06	98.3 / 1.7	98.3 / 0.6
Piperacillin/tazobactam	2	64	85.1 / 8.6	82.2 / 14.9
Levofloxacin	≤0.12	1	94.8 / 4.0	91.4 / 5.2
Gentamicin	≤1	≤1	95.4 / 4.0	93.7 / 4.6
Tigecycline[e]	0.12	0.5	100.0 / 0.0	99.4 / 0.0
Colistin	≤0.25	0.5	-/-	100.0 / 0.0
Indole-positive Proteus spp.[j] (139)				
Ceftolozane/tazobactam	0.25	1	-/-	-/-
Ceftriaxone	≤0.06	4	82.0 / 14.4	82.0 / 14.4
Ceftazidime	0.12	16	84.9 / 11.5	79.1 / 15.1
Cefepime	≤0.5	≤0.5	100.0 / 0.0	100.0 / 0.0
Meropenem	≤0.06	0.12	100.0 / 0.0	100.0 / 0.0
Piperacillin/tazobactam	≤0.5	4	96.4 / 2.2	96.4 / 3.6
Levofloxacin	≤0.12	>4	80.6 / 12.9	75.5 / 19.4
Gentamicin	≤1	8	87.8 / 8.6	84.9 / 12.2
Tigecycline[e]	0.5	2	95.0 / 1.4	87.1 / 5.0

a. Criteria as published by the CLSI [2012] and EUCAST [2012].
b. USA-FDA breakpoints were applied [Tygacil Product Insert, 2010].
c. Includes: *K. oxytoca* (164 strains), *K. ozaenae* (3 strains), *K. planticola* (1 strain), *K. pneumoniae* (668 strains), and unspecified *Klebsiella* (4 strains).
d. Includes: *E. aerogenes* (120 strains), *E. amnigenus* (1 strain), *E. asburiae* (6 strains), *E. cloacae* (385 strains), *E. sakazakii* (1 strain), and unspecified *Enterobacter* (12 strains).
e. Includes: *S. liquefaciens* (9 strains), *S. marcescens* (274 strains), *S. odorifera* (1 strain), *S. rubidaea* (1 strain), and unspecified *Serratia* (2 strains).
f. Includes: *M. morganii* (115 strains), *P. vulgaris* (7 strains), *P. rettgeri* (6 strains), *P. stuartii* (8 strains), and unspecified *Proteus* (3 strains).
g. Includes: *C. amalonaticus* (5 strains), *C. braakii* (2 strains), *C. freundii* (88 strains), *C. koseri* (61 strains), *C. youngae* (1 strain), and unspecified *Citrobacter* (17 strains).

Figure 1. Ceftolozane/tazobactam and ceftazidime MIC distributions for *P. aeruginosa* strains (n=973) from USA medical centers (2011).



CONCLUSIONS

- Ceftolozane/tazobactam demonstrated greater potency than currently available anti-*P. aeruginosa* cephalosporins (ceftazidime and cefepime) and piperacillin/tazobactam when tested against *P. aeruginosa* and Enterobacteriaceae strains from USA hospitals during 2011.

- Ceftolozane/tazobactam may represent a valuable treatment option for Gram-negative infections, including those caused by various resistant organisms.

REFERENCES

Bulik CC, Tessier PR, Keel RA, Sutherland CA, Nicolau DP (2012). In vivo comparison of CXA-101 (FR264205) with and without tazobactam versus piperacillin-tazobactam using human simulated exposures against phenotypically diverse gram-negative organisms. *Antimicrob Agents Chemother* 56: 544-549.

Clinical and Laboratory Standards Institute (2012). *M07-A9. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard: ninth edition.* Wayne, PA: CLSI.

Clinical and Laboratory Standards Institute (2012). *M100-S22. Performance standards for antimicrobial susceptibility testing: 22nd informational supplement.* Wayne, PA: CLSI.

European Committee on Antimicrobial Susceptibility Testing (2012). Breakpoint tables for interpretation of MICs and zone diameters. Version 2.0, January 2012. Available at: http://www.eucast.org/clinical_breakpoints/. Accessed January 1, 2012.

Ge Y, Whitehouse MJ, Friedland I, Talbot GH (2010). Pharmacokinetics and safety of CXA-101, a new antipseudomonal cephalosporin, in healthy adult male and female subjects receiving single- and multiple- dose intravenous infusions. *Antimicrob Agents Chemother* 54: 3427-3431.

Hershberger E, Mouksassi MS, Steenbergen J, Benziger D, Fenneteau F, Marier JF, Friedland I (2011). CXA-101/tazobactam (CXA/TAZ) probability of target attainment using population pharmacokinetic analysis. Abstr. P1520. 21st ECCMID, May 7-10, 2011, Milan, Italy.

Juan C, Zamorano L, Perez JL, Ge Y, Oliver A (2010). Activity of a new antipseudomonal cephalosporin, CXA-101 (FR264205), against carbapenem-resistant and multidrug-resistant *Pseudomonas aeruginosa* clinical strains. *Antimicrob Agents Chemother* 54: 846-851.

Sader HS, Rhomberg PR, Farrell DJ, Jones RN (2011). Antimicrobial activity of CXA-101, a novel cephalosporin tested in combination with tazobactam against Enterobacteriaceae, *Pseudomonas aeruginosa*, and *Bacteroides fragilis* strains having various resistance phenotypes. *Antimicrob Agents Chemother* 55: 2390-2394.

Titelman E, Karlsson IM, Ge Y, Giske CG (2011). In vitro activity of CXA-101 plus tazobactam (CXA-201) against CTX-M-14- and CTX-M-15-producing *Escherichia coli* and *Klebsiella pneumoniae*. *Diagn*

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