Poster # 846

Activity of the Novel Antimicrobial Combination Ceftolozane/Tazobactam, Tested Against Bacterial Isolates in USA Hospitals from Patients with Pneumonia (2011)

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ABSTRACT

Background: Ceftolozane (formerly CXA-101) is a novel oxyimino-aminothiazolyl cephalosporin. Ceftolozane combined with tazobactam (formerly CXA-201) is currently under clinical development for treatment of ventilator associated bacterial pneumonia (VABP), as well as intra-abdominal and urinary tract infections (fixed 4 µg/ml of tazobactam).

Methods: 1089 strains were consecutively collected in 26 USA hospitals from patients with pneumonia and tested for susceptibility by CLSI broth microdilution methods.

Results: *P. aeruginosa* (PSA) exhibited low susceptibility to ceftazidime (CAZ; 79.5%), cefepime (CPM, 79.5%), piperacillin/tazobactam (P/T; 72.6%) and meropenem (MER, 74.0%). Ceftolozane/tazobactam was the most active β-lactam tested against PSA and inhibited 97.6 and 94.2% of strains at ≤8 and ≤4 µg/ml, respectively. Ceftolozane/tazobactam exhibited activity against PSA strains non-susceptible to CAZ, to MER, and to both CAZ and MER (57 strains; $MIC_{50/90}$ 4/>32 µg/ml; 78.9% inhibited at ≤8 µg/ml). Ceftolozane/tazobactam ($MIC_{50/90}$, 0.25/0.5 µg/ml) activity was similar to that of CAZ ($MIC_{50/90}$, of 0.12/0.5 µg/ml) against non-ESBL-phenotype *Klebsiella* spp., while ESBL-phenotype strains exhibited lower susceptibility to all β-lactams, including MER (66.0% S), as well as ciprofloxacin (27.7% S) and gentamicin (48.9% S). Against *Enterobacter* spp., ceftolozane/tazobactam was slightly more active than CAZ and P/T (Table).

Conclusion: Ceftolozane/tazobactam demonstrated greater in vitro activity than currently available anti-PSA cephalosporins (CAZ and CPM) and P/T, when tested against PSA and Enterobacteriaceae strains causing pneumonia in USA hospitals (2011).

Organism (no. tested)	MIC_{50}/MIC_{90}/%S			
	TOL/TAZ	CAZ	PIP/TAZ	MER
P. aeruginosa (503)	1/4/97.6[a]	2/32/79.5	8/>64/72.6	0.5/8/74.0
CAZ-non-S (103)	4/16/88.4[a]	32/>32/0.0	>64/>64/3.9	4/>8/44.7
MER-non-S (131)	1/8/90.8[a]	8/>32/56.5	32/>64/45.0	8/>8/0.0
Klebsiella spp. (239)	0.25/32/89.5[a]	0.25/>32/83.3	4/>64/83.7	≤0.06/0.12/93.3
Enterobacter spp. (131)	0.5/8/90.8[a]	0.25/>32/73.3	4/64/80.2	≤0.06/≤0.06/97.7
CAZ-non-S (35)	4/32/65.7[a]	>32/>32/0.0	32/>64/31.4	≤0.06/0.5/91.4
E.coli (123)	0.25/1/99.2[a]	0.25/8/89.4	2/16/90.2	≤0.06/≤0.06/100.0
Serratia spp. (85)	0.5/1/98.8[a]	0.12/0.5/96.5	2/4/96.5	≤0.06/0.12/98.8

a. % inhibited at ≤8 µg/ml of TOL/TAZ.
Abbreviations: TOL/TAZ = ceftolozane/tazobactam; CAZ = ceftazidime; PIP/TAZ = piperacillin/tazobactam; and MER = meropenem.

INTRODUCTION

Ceftolozane/tazobactam is currently under clinical development for treatment of ventilator associated bacterial pneumonia (VABP), complicated intraabdominal infections (cIAI) and urinary tract infections (cUTI). Preliminary studies on the pharmacokinetics of ceftolozane/tazobactam have shown that the dose of 1000/500mg q8h infused over 60 minutes is predicted to achieve >90% target attainment rate (40% time above MIC) for Enterobacteriaceae and *Pseudomonas aeruginosa* isolates with MIC of 8 µg/ml.

Ceftolozane (formerly CXA-101 and FR264205) is a novel oxyimino-aminothiazolyl cephalosporin with very potent activity against *P. aeruginosa*. Ceftolozane has also demonstrated good activity against Enterobacteriaceae; however, 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. In order to increase its activity against β-lactamase producing strains, ceftolozane was combined with tazobactam, a β-lactamase inhibitor which has been extensively used in combination with piperacillin. In the present study, we evaluated the *in vitro* activity of ceftolozane/tazobactam against Gram-negative organisms isolated from patients in 32 United States (USA) hospitals.

MATERIALS & METHODS

Organism collection: A total of 1,089 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 503 *P. aeruginosa* (20.5% ceftazidime-non-susceptible, and 26.0% meropenem-non-susceptible), 239 *Klebsiella* spp. (19.7% ESBL-phenotype and 6.7% meropenem-non-susceptible), 131 *Enterobacter* spp. (26.7% ceftazidime-non-susceptible), 123 *E. coli*, 85 *Serratia* spp. and eight *Citrobacter* spp.

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 alone and 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.

RESULTS

- Ceftolozane/tazobactam was the most active β-lactam tested against *P. aeruginosa* and inhibited 97.6 and 94.2% of strains at ≤8 and ≤4 µg/ml, respectively. Ceftolozane/tazobactam ($MIC_{50/90}$, 1/4 µg/ml) was 2- to ≥8-fold more active than ceftazidime ($MIC_{50/90}$, 2/32 µg/ml) or cefepime ($MIC_{50/90}$, 4/>16 µg/ml) when tested against *P. aeruginosa* (Tables 1 and 2 and Figure 1).
- *P. aeruginosa* exhibited low susceptibility to ceftazidime (79.5%), cefepime (79.5%), piperacillin/tazobactam (72.6%), meropenem (74.0%) and doripenem (78.9%; Table 2).
- Ceftolozane/tazobactam showed activity against *P. aeruginosa* strains non-susceptible to ceftazidime ($MIC_{50/90}$, 4/16 µg/ml; 88.3% inhibited at ≤8 µg/ml), to meropenem ($MIC_{50/90}$, 1/8 µg/ml; 90.8% inhibited at ≤8 µg/ml), and to both ceftazidime and meropenem (57 strains; $MIC_{50/90}$, 4/32 µg/ml; 78.9% inhibited at ≤8 µg/ml; Table 1).
- *E. coli* strains were very susceptible to ceftolozane/tazobactam ($MIC_{50/90}$, 0.25/0.5 µg/ml; 99.2% inhibited at ≤8 µg/ml), including strains with an ESBL phenotype ($MIC_{50/90}$, 1/8 µg/ml; 94.7% inhibited at ≤8 µg/ml; Table 1). *E. coli* susceptibility rates to ceftriaxone and ceftazidime were only 85.4 and 89.4%, respectively (Table 2).
- Ceftolozane/tazobactam ($MIC_{50/90}$, 0.25/0.5 µg/ml) activity was similar to that of ceftazidime ($MIC_{50/90}$, 0.12/0.5 µg/ml) against non-ESBL-phenotype *Klebsiella* spp. (data not shown), while ESBL-phenotype strains exhibited lower susceptibility to all β-lactams, including meropenem (MIC_{90}, >8 µg/ml; 66.0% susceptible), as well as ciprofloxacin (MIC_{90}, >4 µg/ml; 27.7% susceptible) and gentamicin (MIC_{90}, >8 µg/ml; 48.9% susceptible; Table 2).
- Against *Enterobacter* spp., ceftolozane/tazobactam ($MIC_{50/90}$, 0.5/8 µg/ml; 90.8% inhibited at ≤8 µg/ml) was slightly more potent than ceftazidime ($MIC_{50/90}$, 0.25/>32 µg/ml; 73.3% susceptible), ceftriaxone ($MIC_{50/90}$, 0.25/>8 µg/ml; 69.5% susceptible) and piperacillin/tazobactam ($MIC_{50/90}$, 4/64 µg/ml; 80.2% susceptible; Table 2). Ceftolozane/tazobactam showed some activity against ceftazidime-non-susceptible *Enterobacter* spp. ($MIC_{50/90}$, 4/32 µg/ml; 65.7% inhibited at ≤8 µg/ml), but was less active than cefepime ($MIC_{50/90}$, 1/16 µg/ml; 82.9% susceptible at ≤8 µg/ml) against these organisms (Table 1 and 2).
- Ceftolozane/tazobactam was also active against *Serratia* spp ($MIC_{50/90}$, 0.5/1 µg/ml; 98.8% inhibited at ≤8 µg/ml) and *Citrobacter* spp. (MIC_{50}, 0.12 µg/ml; highest MIC, 4 µg/ml [eight strains tested]; Tables 1 and 2).

RESULTS

Table 1. Summary of ceftolozane/tazobactam activity tested against organisms from patients with pneumonia (USA, 2011)

Organism (no. tested)	No. of isolates (cumulative %) inhibited at MIC (µg/ml):									MIC_{50}	MIC_{90}
	≤0.12	0.25	0.5	1	2	4	8	16	32	>32		
Pseudomonas aeruginosa (503)	1 (0.2)	23 (4.8)	167 (38.0)	209 (79.5)	44 (88.3)	30 (94.2)	17 (97.6)	5 (98.6)	2 (99.0)	5 (100.0)	1	4
ceftazidime-susceptible (400)	1 (0.3)	23 (6.0)	167 (47.8)	192 (95.8)	16 (99.8)	1 (100.0)	-	-	-	-	1	1
ceftazidime-non-susceptible (103)	-	-	-	17 (16.5)	28 (43.7)	29 (71.8)	17 (88.3)	5 (93.2)	2 (95.1)	5 (100.0)	4	16
meropenem-susceptible (372)	1 (0.3)	21 (5.9)	153 (47.0)	148 (86.8)	26 (93.8)	15 (97.8)	8 (100.0)	-	-	-	1	2
meropenem-non-susceptible (131)	-	2 (1.5)	14 (12.2)	61 (58.8)	18 (72.5)	15 (84.0)	9 (90.8)	5 (94.7)	2 (96.2)	5 (100.0)	1	8
ceftazidime and meropenem-non-susceptible (57)	-	-	-	8 (14.0)	14 (38.6)	14 (63.2)	9 (78.9)	5 (87.7)	2 (91.2)	5 (100.0)	4	32
Escherichia coli (123)	46 (37.4)	49 (77.2)	17 (91.1)	4 (94.3)	3 (96.7)	2 (98.4)	1 (99.2)	0 (99.2)	1 (100.0)	-	0.25	0.5
ESBL-phenotype (19)	-	3 (15.8)	6 (47.4)	3 (63.2)	3 (78.9)	2 (89.5)	1 (94.7)	0 (94.7)	1 (100.0)	-	1	8
non ESBL (104)	46 (44.2)	46 (88.5)	11 (99.0)	1 (100.0)	-	-	-	-	-	-	0.25	0.5
Klebsiella spp. (239)	47 (19.7)	89 (56.9)	44 (75.3)	20 (83.7)	6 (86.2)	5 (88.3)	3 (89.5)	0 (89.5)	7 (92.5)	18 (100.0)	0.25	32
ESBL-phenotype (47)	-	1 (2.1)	6 (14.9)	2 (19.1)	5 (29.8)	5 (40.4)	3 (46.8)	0 (46.8)	7 (61.7)	18 (100.0)	32	> 32
non ESBL (192)	47 (24.5)	88 (70.3)	38 (90.1)	18 (99.5)	1 (100.0)	-	-	-	-	-	0.25	0.5
Enterobacter spp. (131)	15 (11.5)	45 (45.8)	28 (67.2)	16 (79.4)	5 (83.2)	5 (87.0)	5 (90.8)	6 (95.4)	4 (98.5)	2 (100.0)	0.5	8
ceftazidime-susceptible (96)	15 (15.6)	45 (62.5)	26 (89.6)	9 (99.0)	1 (100.0)	-	-	-	-	-	0.25	1
ceftazidime-non-susceptible (35)	-	-	2 (5.7)	7 (25.7)	4 (37.1)	5 (51.4)	5 (65.7)	6 (82.9)	4 (94.3)	2 (100.0)	4	32
Serratia spp. (85)	1 (1.2)	5 (7.1)	50 (65.9)	24 (94.1)	1 (95.3)	2 (97.6)	1 (98.8)	0 (98.8)	1 (100.0)	-	0.5	1
Citrobacter spp. (8)	4 (50.0)	2 (75.0)	1 (87.5)	0 (87.5)	0 (87.5)	1 (100.0)	-	-	-	-	0.12	1

Table 2. Activity of ceftolozane/tazobactam and comparator antimicrobial agents when tested against *Pseudomonas aeruginosa* from patients with pneumonia (USA, 2011).

Organism/antimicrobial agent (no. tested)	MIC (µg/ml)		%S / %R	
	MIC_{50}	MIC_{90}	CLSI[a]	EUCAST[a]
Pseudomonas aeruginosa (503)				
Ceftolozane/tazobactam	1	4	- / -	- / -
Ceftolozane	1	4	- / -	- / -
Cefepime	4	>16	79.5 / 11.3	79.5 / 20.5
Doripenem	0.5	8	78.9 / 10.3	68.8 / 10.3
Meropenem	0.5	8	74.0 / 16.7	74.0 / 9.1
Aztreonam	8	>16	63.0 / 23.1	8.5 / 23.1
Piperacillin/tazobactam	8	>64	72.6 / 17.1	72.6 / 27.4
Ciprofloxacin	0.25	>4	73.4 / 21.1	64.4 / 26.6
Gentamicin	2	>8	86.1 / 10.7	86.1 / 13.9
Amikacin	4	8	96.6 / 1.8	92.8 / 3.4
Colistin	1	2	99.8 / 0.2	99.8 / 0.2
ceftazidime-non-susceptible (103)				
Ceftolozane/tazobactam	4	16	- / -	- / -
Ceftolozane	4	16	- / -	- / -
Ceftazidime	32	>32	0.0 / 82.5	0.0 / 100.0
Cefepime	16	>16	17.5 / 49.5	17.5 / 82.5
Doripenem	4	>8	45.6 / 38.8	32.0 / 38.8
Aztreonam	>16	>16	6.8 / 73.8	0.0 / 73.8
Piperacillin/tazobactam	>64	>64	3.9 / 79.6	3.9 / 96.1
Ciprofloxacin	2	>4	41.7 / 45.6	34.0 / 58.3
Gentamicin	2	>8	66.0 / 30.1	66.0 / 34.0
Amikacin	4	32	89.3 / 5.8	80.6 / 10.7
Colistin	1	2	100.0 / 0.0	100.0 / 0.0
meropenem-non-susceptible (131)				
Ceftolozane/tazobactam	1	8	- / -	- / -
Ceftolozane	1	8	- / -	- / -
Ceftazidime	8	>32	56.5 / 38.9	56.5 / 43.5
Cefepime	8	>16	51.9 / 28.2	51.9 / 48.1
Doripenem	4	>8	20.6 / 39.7	3.1 / 39.7
Meropenem	8	>8	0.0 / 64.1	0.0 / 35.1
Aztreonam	>16	>16	24.4 / 52.7	0.0 / 52.7
Piperacillin/tazobactam	32	>64	45.0 / 38.2	45.0 / 55.0
Ciprofloxacin	1	>4	51.1 / 45.0	35.1 / 48.9
Gentamicin	2	>8	65.6 / 26.7	65.6 / 34.4
Amikacin	4	16	91.6 / 4.6	84.7 / 8.4
Colistin	1	2	100.0 / 0.0	100.0 / 0.0

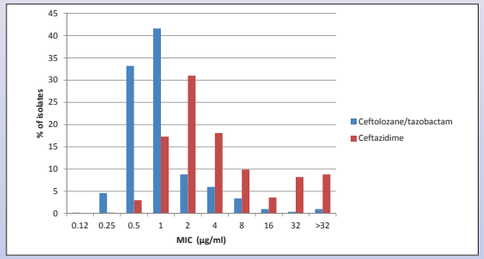
a. Criteria as published by the CLSI [2012] and EUCAST [2012].

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

Organism/antimicrobial agent (no. tested)	MIC (µg/ml)		%S / %R	
	MIC_{50}	MIC_{90}	CLSI[a]	EUCAST[a]
Escherichia coli (123)				
Ceftolozane/tazobactam	0.25	0.5	- / -	- / -
Ceftolozane	0.25	8	- / -	- / -
Ceftriaxone	≤0.06	>8	85.4 / 14.6	85.4 / 14.6
Ceftazidime	0.25	8	89.4 / 8.1	86.2 / 10.6
Cefepime	≤0.5	4	91.9 / 7.3	87.8 / 9.8
Meropenem	≤0.06	≤0.06	100.0 / 0.0	100.0 / 0.0
Piperacillin/tazobactam	2	16	90.2 / 7.3	87.8 / 9.8
Ciprofloxacin	≤0.03	>4	63.4 / 36.6	61.8 / 36.6
Gentamicin	≤1	>8	85.4 / 13.8	82.9 / 14.6
Tigecycline[b]	0.12	0.12	100.0 / 0.0	100.0 / 0.0
Colistin	≤0.25	0.5	- / -	100.0 / 0.0
Klebsiella spp. (239)				
Ceftolozane/tazobactam	0.25	32	- / -	- / -
Ceftolozane	0.25	>32	- / -	- / -
Ceftriaxone	≤0.06	>8	81.2 / 18.0	81.2 / 18.0
Ceftazidime	0.12	>32	83.3 / 15.9	81.2 / 16.7
Cefepime	≤0.5	>16	88.3 / 10.5	83.7 / 12.6
Meropenem	≤0.06	0.12	93.3 / 6.7	93.3 / 6.3
Piperacillin/tazobactam	4	>64	83.7 / 13.8	76.6 / 16.3
Ciprofloxacin	≤0.03	>4	84.1 / 15.1	82.4 / 15.9
Gentamicin	≤1	8	89.1 / 9.6	88.7 / 10.9
Tigecycline[b]	0.25	1	97.1 / 0.4	92.1 / 2.9
Colistin	≤0.25	1	- / -	97.1 / 2.9
ESBL-phenotype (47)				
Ceftolozane/tazobactam	32	>32	- / -	- / -
Ceftolozane	>32	>32	- / -	- / -
Ceftriaxone	>8	>8	4.3 / 91.5	4.3 / 91.5
Ceftazidime	>32	>32	14.9 / 80.9	4.3 / 85.1
Cefepime	>16	>16	40.4 / 53.2	19.1 / 63.8
Meropenem	≤0.06	>8	66.0 / 34.0	66.0 / 31.9
Piperacillin/tazobactam	>64	>64	23.4 / 70.2	23.4 / 76.6
Ciprofloxacin	>4	>4	27.7 / 68.1	23.4 / 72.3
Gentamicin	8	>8	48.9 / 44.7	46.8 / 51.1
Tigecycline[b]	0.5	2	93.6 / 0.0	87.2 / 6.4
Colistin	0.5	4	- / -	87.2 / 12.8
Enterobacter spp. (131)				
Ceftolozane/tazobactam	0.5	8	- / -	- / -
Ceftolozane	0.5	16	- / -	- / -
Ceftriaxone	0.25	>8	69.5 / 29.0	69.5 / 29.0
Ceftazidime	0.25	>32	73.3 / 21.4	70.2 / 26.7
Cefepime	≤0.5	2	95.4 / 2.3	89.3 / 5.3
Meropenem	≤0.06	≤0.06	97.7 / 1.5	98.5 / 0.0
Piperacillin/tazobactam	4	64	80.2 / 8.4	74.0 / 19.8
Ciprofloxacin	≤0.03	0.25	95.4 / 4.6	93.1 / 4.6
Gentamicin	≤1	≤1	93.1 / 5.4	92.3 / 6.9
Tigecycline[b]	0.25	0.5	98.5 / 0.0	96.9 / 1.5
Colistin	≤0.25	>4	- / -	87.8 / 12.2
ceftazidime-non-susceptible (35)				
Ceftolozane/tazobactam	4	32	- / -	- / -
Ceftolozane	16	>32	- / -	- / -
Ceftriaxone	>8	>8	0.0 / 100.0	0.0 / 100.0
Ceftazidime	1	16	82.9 / 8.6	60.0 / 20.0
Meropenem	≤0.06	0.5	91.4 / 5.7	94.3 / 0.0
Piperacillin/tazobactam	32	>64	31.4 / 31.4	14.3 / 68.6
Ciprofloxacin	≤0.03	>4	82.9 / 17.1	77.1 / 17.1
Gentamicin	≤1	>8	77.1 / 17.1	74.3 / 22.9
Tigecycline[b]	0.25	1	94.3 / 0.0	94.3 / 5.7
Colistin	≤0.25	>4	- / -	85.7 / 14.3
Serratia spp. (85)				
Ceftolozane/tazobactam	0.5	1	- / -	- / -
Ceftolozane	0.5	1	- / -	- / -
Ceftriaxone	0.25	1	91.8 / 8.2	91.8 / 8.2
Ceftazidime	0.12	0.5	96.5 / 2.4	94.1 / 3.5
Cefepime	≤0.5	≤0.5	98.8 / 0.0	96.5 / 2.4
Meropenem	≤0.06	0.12	97.6 / 1.2	98.8 / 1.2
Piperacillin/tazobactam	2	4	96.5 / 1.2	95.3 / 3.5
Ciprofloxacin	≤0.03	0.25	96.5 / 3.5	94.1 / 3.5
Gentamicin	≤1	≤1	98.8 / 1.2	98.8 / 1.2
Tigecycline[b]	0.5	1	97.6 / 0.0	97.6 / 2.4
Colistin	>4	>4	- / -	4.7 / 95.3

a. Criteria as published by the CLSI [2012] and EUCAST [2012].
b. US-FDA breakpoints were applied [Tygacil Product Insert, 2010].

Figure 1. Ceftolozane/tazobactam and ceftazidime MIC distributions for *P. aeruginosa* strains (n=503) from patients hospitalized with pneumonia in USA medical centers (2011).



CONCLUSIONS

- Ceftolozane/tazobactam was the most active β-lactam tested against *P. aeruginosa* strains.
- Ceftolozane/tazobactam demonstrated greater *in vitro* activity than currently available anti-pseudomonal cephalosporins (ceftazidime and cefepime) and piperacillin/tazobactam, when tested against *P. aeruginosa* and Enterobacteriaceae strains causing pneumonia in USA hospitals (2011); only 51 strains (4.7%) had ceftalozane/tazobactam MICs at >8 µg/ml.
- Ceftolozane/tazobactam could represent a valuable treatment option for pneumonia and other infections caused by Gram-negative organisms, including multidrug-resistant strains.

REFERENCES

1. 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.
2. 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.
3. Clinical and Laboratory Standards Institute (2012). M100-S22. Performance standards for antimicrobial susceptibility testing: 22nd informational supplement. Wayne, PA: CLSI.
4. 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.
5. 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.
6. 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.
7. 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.
8. Moya B, Zamorano L, Juan C, Ge Y, Oliver A (2010). Affinity of the new cephalosporin CXA-101 to penicillin-binding proteins of *Pseudomonas aeruginosa*. *Antimicrob Agents Chemother* 54: 3933-3937.
9. 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.
10. 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 Microbiol Infect Dis* 70: 137-141.

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