Antimicrobial Activity of Ceftolozane/Tazobactam Tested against Gram-negative Bacterial Isolates from Hospitalized Patients with Pneumonia in United States and European Hospitals (2012)

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Poster #C2-1633

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ABSTRACT

OBJECTIVE: Ceftolozane/tazobactam is a novel antibacterial with activity against *Pseudomonas aeruginosa* and other common Gram-negative pathogens. The *in vitro* activity of ceftolozane/tazobactam was tested against Gram-negative pathogen-causing pneumonia in the United States (US) and European (EU) hospitals.

METHODS: 2,968 isolates (1334/1634 from the US/EU) were consecutively collected in 28/31 hospitals in the US/EU (15 countries) from patients with pneumonia in 2012. Susceptibility (S) testing was performed by CLSI broth microdilution methods (ceftolozane/tazobactam at a fixed 4 μg/mL of tazobactam).

RESULTS: *P. aeruginosa* was the most common pathogen (34.3%) and ceftolozane/tazobactam was the most active β-lactam tested against *P. aeruginosa* (94.1% inhibited at ≤8 μg/mL). *P. aeruginosa* exhibited moderate S to meropenem (MER, 73.7%), ceftazidime (CAZ; 73.6%), cefepime (CPM, 76.5%), piperacillin/tazobactam (P/T; 69.5%), levofloxacin (LEV; 69.9%), and gentamicin (GEN; 80.7%). Ceftolozane/tazobactam exhibited activity against CAZ-non-S and MER-non-S *P. aeruginosa* isolates (Table 1). Against wild-type *Klebsiella pneumoniae* (KPN), ceftolozane/tazobactam (MIC_{90}, 0.5 μg/mL) activity was similar to that of CAZ (MIC_{90}, 0.5 μg/mL) while ESBL-phenotype KPN (35.7%) showed lower S to all β-lactams, including MER (71.2% S), as well as LEV (27.3% S) and GEN (40.2% S). Ceftolozane/tazobactam was active against *Escherichia coli* (MIC_{90}, 1 μg/mL), including ESBL-phenotype isolates (MIC_{90}, 4 μg/mL). Ceftolozane/tazobactam also showed greater activity than CAZ and P/T when tested against *Enterobacter* spp. (ESP) and *Serratia* spp., and demonstrated activity against CAZ-non-S ESP (81.5% inhibited at ≤8 μg/mL). Ceftolozane/tazobactam was active against *Proteus mirabilis* (MIC_{90}, 1 μg/mL), *Citrobacter* spp. (MIC_{90}, 2 μg/mL), and indole (+) *Proteae* (MIC_{90}, 1 μg/mL). All β-lactams had limited activity against *Acinetobacter* spp. and *Stenotrophomonas maltophilia.*

CONCLUSION: Ceftolozane/tazobactam demonstrated greater *in vitro* activity than currently available cephalosporins, carbapenems, and P/T when tested against *P. aeruginosa*. Additionally, ceftolozane/tazobactam demonstrated greater activity than currently available cephalosporins and P/T against Enterobacteriaceae.

INTRODUCTION

- Ceftolozane is a novel antipseudomonal cephalosporin with greater activity against *Pseudomonas aeruginosa* when compared with ceftazidime and cefepime.
- Ceftolozane has also demonstrated good activity against Enterobacteriaceae; but like 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 exerts its bactericidal activity by inhibiting essential penicillin-binding proteins (PBPs), resulting in inhibition of cell wall synthesis and subsequent cell death.
- Phase 3 trials of ceftolozane/tazobactam for the treatment of complicated urinary tract infections (cUTI) and complicated intra-abdominal infections (cIAI) are already being undertaken; and studies in nosocomial pneumonia are planned.
- We evaluated the *in vitro* activities of ceftolozane/tazobactam, ceftazidime, piperacillin/tazobactam, meropenem, and other comparator agents when tested against Gram-negative organisms isolated from hospitalized patients with pneumonia in the United States (US) and Europe (EU).

MATERIALS AND METHODS

Organism Collection: A total of 2,968 isolates (1,334 from the US and 1,634 from EU) were consecutively collected from 59 medical centers (28 in the US and 31 from 15 EU countries) in 2012 from patients with pneumonia. Only 1 strain per patient-infection episode was included in the surveillance collection.

Antimicrobial susceptibility testing: Minimum inhibitory concentration (MIC) values were determined using the reference Clinical and Laboratory Standards Institute (CLSI) broth microdilution method (M07-A9). Ceftolozane/tazobactam was tested at a fixed concentration of 4 μg/mL. *Escherichia coli* and *Klebsiella* spp. isolates were grouped as "ESBL-phenotype" based on the CLSI screening criteria for ESBL production, ie, MIC of ≥2 μg/mL for ceftazidime or ceftriaxone or aztreonam. Multidrug-resistant (MDR), extensively drug-resistant (XDR), and pandrug-resistant (PDR) Enterobacteriaceae and *P. aeruginosa* strains were classified according to recently recommended guidelines published by Magiorakos et al. (2012) and using the following antimicrobial class representative agents: ceftriaxone, meropenem, piperacillin/tazobactam, levofloxacin, gentamicin, tigecycline, and colistin for Enterobacteriaceae; and ceftazidime, meropenem, piperacillin/tazobactam, levofloxacin, gentamicin, and colistin for *P. aeruginosa*. CLSI susceptibility breakpoints were applied to classify strains from the US, whereas European Committee on Antimicrobial Susceptibility Testing (EUCAST) susceptibility breakpoints were applied to classify strains from the EU. Classifications were based on the following recommended parameters: MDR = acquired nonsusceptibility to at least 1 agent in ≥3 antimicrobial classes; XDR = nonsusceptible to at least 1 agent in all but ≤2 antimicrobial classes; PDR = nonsusceptible to all agents in all antimicrobial classes. Quality control ranges and interpretive criteria for comparator compounds used the CLSI M100-S23 guidelines.

RESULTS

- *P. aeruginosa* was the most common pathogen (34.3%) and ceftolozane/tazobactam was the most active β-lactam tested against *P. aeruginosa* (MIC required to inhibit the growth of 50%/90% of organisms [$MIC_{50/90}$], 0.5/4 μg/mL; 94.1% inhibited at ≤8 μg/mL; Tables 1 and 2). *P. aeruginosa* exhibited moderate susceptibility to meropenem (73.7%), ceftazidime (73.6%), cefepime (76.5%), piperacillin/tazobactam (69.5%), levofloxacin (69.9%), and gentamicin (80.7%).
- Ceftolozane/tazobactam showed activity against ceftazidime-nonsusceptible (77.7% inhibited at ≤8 μg/mL) and meropenem-nonsusceptible *P. aeruginosa* (78.0% inhibited at ≤8 μg/mL). Furthermore, 24.1% and 17.1% of *P. aeruginosa* strains were classified as MDR and XDR, respectively; and ceftolozane/tazobactam inhibited 75.6% of MDR and 66.1% of XDR strains at MICs of ≤8 μg/mL (Table 1).
- Ceftolozane/tazobactam was highly active against *P. aeruginosa* strains from US hospitals. Overall, 99.4% of strains were inhibited at ceftolozane/tazobactam MICs of ≤8 μg/mL. Among MDR and XDR strains, 96.3% and 93.2% of strains, respectively, exhibited a MIC ≤8 μg/mL for ceftolozane/tazobactam (Table 3).

RESULTS (CONT'D)

- Against *Klebsiella pneumoniae*, ceftolozane/tazobactam ($MIC_{50/90}$, 0.25/>32 μg/mL) inhibited 84.9% of strains at ≤8 μg/mL, whereas only 65.4% to 66.5% of strains were susceptible (based on CLSI breakpoints) to ceftazidime or ceftriaxone; 89.5% of strains were susceptible to meropenem. Among ESBL-phenotype *K. pneumoniae*, 57.6% were inhibited at ≤8 μg/mL of ceftolozane/tazobactam and 71.2% were susceptible to meropenem as per CLSI criteria (Tables 1 and 2).
- Ceftolozane/tazobactam was active against *E. coli* ($MIC_{50/90}$, 0.25/1 μg/mL; 98.6% inhibited at ≤8 μg/mL), including ESBL-phenotype isolates ($MIC_{50/90}$, 0.5/4 μg/mL; 93.4% inhibited at ≤8 μg/mL; Table 2).
- When tested against *Enterobacter* spp., ceftolozane/tazobactam ($MIC_{50/90}$, 0.25/8 μg/mL; 94.7% were inhibited at ≤8 μg/mL) showed greater activity than ceftazidime ($MIC_{50/90}$, 0.25/>32 μg/mL; 71.5% susceptibility) and piperacillin/tazobactam ($MIC_{50/90}$, 4/64 μg/mL; 78.9% susceptibility), based on CLSI breakpoints, and demonstrated activity against ceftazidime-nonsusceptible strains (81.5% inhibited at ≤8 μg/mL; Tables 1 and 2).
- Ceftolozane/tazobactam was active against *Serratia* spp. ($MIC_{50/90}$, 0.5/1 μg/mL; 99.5% inhibited at ≤8 μg/mL), *Proteus mirabilis* ($MIC_{50/90}$, 0.5/1 μg/mL; 98.8% inhibited at ≤8 μg/mL), *Citrobacter* spp. ($MIC_{50/90}$, 0.25/2 μg/mL; 94.9% inhibited at ≤8 μg/mL), *Klebsiella oxytoca* ($MIC_{50/90}$, 0.25/0.5 μg/mL; 100.0% inhibited at ≤8 μg/mL) and indole-positive *Proteae* ($MIC_{50/90}$, 0.25/1 μg/mL; 100.0% inhibited at ≤8 μg/mL; Table 2).
- Ceftolozane/tazobactam demonstrated greater activity against MDR and XDR Enterobacteriaceae from EU when compared with US strains. Ceftolozane/tazobactam inhibited 75.9% and 42.9% of MDR and XDR Enterobacteriaceae strains from EU at MICs of ≤8 μg/mL, respectively (Table 3).
- All β-lactams had limited activity against *Acinetobacter* spp. and *Stenotrophomonas maltophilia* (Table 2).

Table 1. Summary of Ceftolozane/Tazobactam Activity Tested against the Main Pathogen Groups Isolated from Hospitalized Patients with Pneumonia

Organism (No. Tested)	No. of Isolates (Cumulative %) Inhibited at Ceftolozane/Tazobactam MIC (μg/mL)[a] ≤0.5	1	2	4	8	16	32	>32	$MIC_{50/90}$
P. aeruginosa (1,019)	510 (50.0)[a]	256 (75.2)	109 (85.9)	69 (92.6)	15 (94.1)	5 (94.6)	4 (95.0)	51 (100.0)	0.5/4
Ceftazidime-non-S[b] (269)	2 (0.7)	42 (16.4)	83 (47.2)	67 (72.1)	15 (77.7)	5 (79.6)	4 (81.0)	51 (100.0)	4/>32
Meropenem-non-S[c] (268)	49 (18.3)	63 (41.8)	57 (63.1)	34 (75.7)	6 (78.0)	5 (79.9)	4 (81.3)	50 (100.0)	2/>32
MDR[d] (246)	9 (3.7)	52 (24.8)	69 (52.8)	48 (72.4)	8 (75.6)	5 (77.6)	4 (79.4)	51 (100.0)	2/>32
XDR[d] (174)	2 (1.1)	24 (13.8)	54 (46.0)	30 (63.2)	5 (66.1)	5 (69.0)	4 (71.3)	50 (100.0)	4/>32
K. pneumoniae (370)	244 (65.9)	29 (73.8)	17 (78.4)	15 (82.4)	9 (84.9)	6 (86.5)	12 (89.7)	38 (100.0)	0.25/>32
ESBL-phenotype[e] (132)	19 (14.4)	17 (27.3)	16 (39.4)	15 (50.8)	9 (57.6)	6 (62.1)	12 (71.2)	38 (100.0)	4/>32
E. coli (368)	331 (89.9)	23 (96.2)	5 (97.6)	2 (98.1)	2 (98.6)	2 (99.2)	0 (99.2)	3 (100.0)	0.25/1
ESBL-phenotype[e] (76)	40 (52.6)	22 (81.6)	5 (88.2)	2 (90.8)	2 (93.4)	2 (96.1)	0 (96.1)	3 (100.0)	0.5/4
Enterobacter spp. (284)	173 (71.5)	9 (74.6)	21 (82.0)	21 (89.4)	15 (94.7)	6 (96.8)	6 (98.9)	3 (100.0)	0.25/8
Ceftazidime-non-S[f] (81)	7 (8.6)	4 (13.6)	19 (37.0)	21 (63.0)	15 (81.5)	6 (88.9)	6 (96.3)	3 (100.0)	4/32
Serratia spp. (211)	134 (63.5)	63 (93.4)	11 (98.6)	1 (99.1)	1 (99.5)	0 (99.5)	0 (99.5)	1 (100.0)	0.5/1
MDR Enterobacteriaceae (238)[d]	53 (22.3)	29 (34.5)	39 (50.8)	26 (61.8)	21 (70.6)	10 (74.8)	16 (81.5)	44 (100.0)	2/>32
XDR Enterobacteriaceae (42)[d]	3 (7.1)	3 (14.3)	4 (23.8)	0 (23.8)	3 (31.0)	1 (33.3)	4 (42.9)	24 (100.0)	>32/>32

a. Underlined values indicate MIC_{50}.
b. According to criteria published by the CLSI [2013] and EUCAST [2013], ie, MIC, ≥16 μg/mL.
c. According to criteria published by the CLSI [2013] and EUCAST [2013], ie, MIC, ≥4 μg/mL.
d. MDR and XDR Enterobacteriaceae and *P. aeruginosa* strains were classified according to recently recommended guidelines published by Magiorakos et al. (2012) and using the following antimicrobial class representative agents: ceftriaxone, meropenem, piperacillin/tazobactam, levofloxacin, gentamicin, tigecycline, and colistin for Enterobacteriaceae; and ceftazidime, meropenem, piperacillin/tazobactam, levofloxacin, gentamicin, and colistin for *P. aeruginosa*. MDR = nonsusceptible to ≥1 agent in ≥3 antimicrobial classes and XDR = nonsusceptible to ≥1 agent in all but ≤2 antimicrobial classes. CLSI susceptibility breakpoints were applied to classify strains from the US, whereas EUCAST susceptibility breakpoints were applied to classify strains from Europe.
e. *E. coli* and *Klebsiella* spp. isolates were grouped as "ESBL-phenotype" based on the CLSI screening criteria for ESBL production, ie, MIC of ≥2 μg/mL for ceftazidime or ceftriaxone or aztreonam.
f. According to criteria published by the CLSI [2013], ie, MIC, ≥8 μg/mL.

Table 2. Activity of Ceftolozane/Tazobactam and Comparator Antimicrobial Agents when Tested against Bacterial Isolates from Hospitalized Patients with Pneumonia (US and EU, 2012)

Organisms (No. Tested)/ Antimicrobial Agent	MIC (μg/mL) MIC_{50}	MIC_{90}	%S / %I / %R CLSI[a]	EUCAST[a]
P. aeruginosa (1,019)				
Ceftolozane/tazobactam	0.5	4	(94.1)[b]	
Ceftazidime	2	>32	73.6 / 6.1 / 20.3	73.6 / 0.0 / 26.4
Cefepime	4	>16	76.5 / 12.8 / 10.7	76.5 / 0.0 / 23.5
Doripenem	0.5	8	75.7 / 11.6 / 12.7	68.4 / 18.9 / 12.7
Meropenem	0.5	>8	73.7 / 7.3 / 19.0	73.7 / 14.8 / 11.5
Piperacillin/tazobactam	8	>64	69.5 / 11.1 / 19.4	69.5 / 0.1 / 30.6
Levofloxacin	0.5	>4	69.9 / 6.6 / 23.5	61.0 / 8.9 / 30.1
Gentamicin	2	>8	80.7 / 4.2 / 15.1	80.7 / 0.0 / 19.3
Amikacin	4	16	92.9 / 2.1 / 5.0	87.3 / 5.6 / 7.1
Colistin	1	2	98.5 / 1.1 / 0.4	98.5 / 0.0 / 1.5
Ceftazidime-non-S (MIC, ≥16 μg/mL; 269)[a]				
Ceftolozane/tazobactam	4	>32	(77.7)[b]	
Ceftazidime	32	>32	0.0 / 23.0 / 77.0	0.0 / 0.0 / 100.0
Cefepime	16	>16	20.8 / 40.9 / 38.3	20.8 / 0.0 / 79.2
Doripenem	4	>8	40.5 / 19.7 / 39.8	33.8 / 26.4 / 39.8
Meropenem	8	>8	39.0 / 9.0 / 52.0	39.0 / 27.5 / 33.5
Piperacillin/tazobactam	>64	>64	3.7 / 24.6 / 71.7	3.7 / 0.0 / 96.3
Levofloxacin	>4	>4	35.7 / 8.2 / 56.1	27.5 / 8.2 / 64.3
Gentamicin	4	>8	53.2 / 7.0 / 39.8	53.2 / 0.0 / 46.8
Amikacin	8	>32	80.3 / 4.5 / 15.2	68.4 / 11.9 / 19.7
Colistin	1	2	97.4 / 1.9 / 0.7	97.4 / 0.0 / 2.6
Meropenem-non-S (MIC, ≥4 μg/mL; 268)[a]				
Ceftolozane/tazobactam	2	>32	(78.0)[b]	
Ceftazidime	16	>32	38.8 / 14.2 / 47.0	38.8 / 0.0 / 61.2
Cefepime	16	>16	42.5 / 31.0 / 26.5	42.5 / 0.0 / 57.5
Doripenem	4	>8	11.2 / 40.7 / 48.1	0.7 / 51.2 / 48.1
Meropenem	8	>8	0.0 / 27.6 / 72.4	0.0 / 56.3 / 43.7
Piperacillin/tazobactam	64	>64	30.2 / 26.5 / 43.3	30.2 / 0.0 / 69.8
Levofloxacin	>4	>4	33.2 / 6.7 / 60.1	20.1 / 13.1 / 66.8
Gentamicin	8	>8	49.3 / 8.9 / 41.8	49.3 / 0.0 / 50.7
Amikacin	8	>32	78.0 / 5.6 / 16.4	64.6 / 13.4 / 22.0
Colistin	1	2	97.0 / 2.3 / 0.7	97.0 / 0.0 / 3.0
K. pneumoniae (370)				
Ceftolozane/tazobactam	0.25	>32	(84.9)[b]	
Ceftazidime	0.25	>32	66.5 / 2.7 / 30.8	64.9 / 1.6 / 33.5
Ceftriaxone	≤0.06	>8	65.4 / 0.5 / 34.1	65.4 / 0.5 / 34.1
Piperacillin/tazobactam	4	>64	74.0 / 8.2 / 17.8	66.7 / 7.3 / 26.0
Meropenem	≤0.06	2	89.5 / 1.6 / 8.9	91.1 / 2.7 / 6.2
Levofloxacin	≤0.12	>4	71.8 / 4.4 / 23.8	69.9 / 1.9 / 28.2
Gentamicin	≤1	>8	77.6 / 1.6 / 20.8	74.6 / 3.0 / 22.4
Tigecycline[c]	0.25	1	98.9 / 1.1 / 0.0	94.6 / 4.3 / 1.1
Colistin	0.5	1	- / - / -	92.7 / 0.0 / 7.3
ESBL-phenotype (132)				
Ceftolozane/tazobactam	4	>32	(57.6)[b]	
Ceftazidime	>32	>32	6.1 / 7.5 / 86.4	1.5 / 4.6 / 93.9
Ceftriaxone	>8	>8	3.0 / 1.5 / 95.5	3.0 / 1.5 / 95.5
Piperacillin/tazobactam	64	>64	33.8 / 20.8 / 45.4	20.8 / 13.0 / 66.2
Meropenem	≤0.06	>8	71.2 / 3.8 / 25.0	75.0 / 7.6 / 17.4
Levofloxacin	>4	>4	27.3 / 11.3 / 61.4	23.5 / 3.8 / 72.7
Gentamicin	>8	>8	40.2 / 4.5 / 55.3	31.8 / 8.4 / 59.8
Tigecycline[c]	0.5	1	97.7 / 2.3 / 0.0	91.6 / 6.1 / 2.3
Colistin	0.5	>8	- / - / -	84.1 / 0.0 / 15.9
E. coli (368)				
Ceftolozane/tazobactam	0.25	1	(98.6)[b]	
Ceftazidime	0.25	8	87.5 / 2.7 / 9.8	81.0 / 6.5 / 12.5
Ceftriaxone	≤0.06	>8	81.0 / 0.5 / 18.5	81.0 / 0.5 / 18.5
Piperacillin/tazobactam	2	32	89.7 / 4.9 / 5.4	84.5 / 5.2 / 10.3
Meropenem	≤0.06	≤0.06	99.7 / 0.0 / 0.3	99.7 / 0.3 / 0.0
Levofloxacin	≤0.12	>4	64.4 / 1.1 / 34.5	64.1 / 0.3 / 35.6
Gentamicin	≤1	>8	83.2 / 0.8 / 16.0	81.5 / 1.7 / 16.8
Tigecycline[c]	0.12	0.25	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Colistin	0.25	0.5	- / - / -	100.0 / 0.0 / 0.0
ESBL-phenotype (76)				
Ceftolozane/tazobactam	0.5	4	(93.4)[b]	
Ceftazidime	8	>32	39.5 / 13.1 / 47.4	7.9 / 31.6 / 60.5
Ceftriaxone	>8	>8	7.9 / 2.6 / 89.5	7.9 / 2.6 / 89.5
Piperacillin/tazobactam	16	>64	67.1 / 14.5 / 18.4	48.7 / 18.4 / 32.9
Meropenem	≤0.06	≤0.06	98.7 / 0.0 / 1.3	98.7 / 1.3 / 0.0
Levofloxacin	>4	>4	19.7 / 2.7 / 77.6	18.4 / 1.3 / 80.3
Gentamicin	2	>8	71.1 / 0.0 / 28.9	69.7 / 1.4 / 28.9
Tigecycline[c]	0.12	0.25	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Colistin	0.25	0.5	- / - / -	100.0 / 0.0 / 0.0
Enterobacter spp.[d] (284)				
Ceftolozane/tazobactam	0.25	8	(94.7)[b]	
Ceftazidime	0.25	>32	71.5 / 2.4 / 26.1	66.2 / 5.3 / 28.5
Ceftriaxone	0.25	>8	65.4 / 2.8 / 31.8	65.4 / 2.8 / 31.8
Piperacillin/tazobactam	4	64	78.9 / 13.7 / 7.4	71.8 / 7.1 / 21.1
Meropenem	≤0.06	0.12	99.6 / 0.0 / 0.4	99.6 / 0.0 / 0.4
Levofloxacin	≤0.12	1	93.0 / 2.1 / 4.9	91.2 / 1.8 / 7.0
Gentamicin	≤1	≤1	93.0 / 1.4 / 5.6	92.3 / 0.7 / 7.0
Tigecycline[c]	0.25	0.5	99.6 / 0.4 / 0.0	96.5 / 3.1 / 0.4
Colistin	0.5	>8	- / - / -	86.3 / 0.0 / 13.7
Acinetobacter spp.[e] (233)				
Ceftolozane/tazobactam	32	>32	(32.2)[b]	
Ceftazidime	>32	>32	22.7 / 3.5 / 73.8	- / - / -
Cefepime	>16	>16	21.5 / 9.0 / 69.5	- / - / -
Doripenem	>8	>8	26.6 / 25.3 / 48.1	26.6 / 5.2 / 68.2
Meropenem	>8	>8	31.3 / 3.0 / 65.7	29.6 / 4.7 / 65.7
Ampicillin/sulbactam	32	>32	26.6 / 15.0 / 58.4	- / - / -
Piperacillin/tazobactam	>64	>64	23.2 / 0.0 / 76.8	- / - / -
Levofloxacin	>4	>4	18.0 / 8.6 / 73.4	18.0 / 0.0 / 82.0
Gentamicin	>8	>8	27.0 / 2.6 / 70.4	27.0 / 0.0 / 73.0
Tigecycline	1	2	- / - / -	- / - / -
Colistin	1	2	91.8 / 0.0 / 8.2	91.8 / 0.0 / 8.2
Serratia spp.[f] (211)				
Ceftolozane/tazobactam	0.5	1	(99.5)[b]	
Ceftazidime	0.25	0.5	99.1 / 0.0 / 0.9	96.7 / 2.4 / 0.9
Ceftriaxone	0.25	8	85.7 / 2.4 / 11.9	85.7 / 2.4 / 11.9
Piperacillin/tazobactam	2	8	93.4 / 4.2 / 2.4	90.0 / 3.4 / 6.6
Meropenem	≤0.06	≤0.06	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Levofloxacin	≤0.12	1	96.7 / 2.8 / 0.5	93.4 / 3.3 / 3.3
Gentamicin	≤1	≤1	97.6 / 0.0 / 2.4	96.7 / 0.9 / 2.4
Tigecycline[c]	0.5	1	100.0 / 0.0 / 0.0	97.2 / 2.8 / 0.0
Colistin	>8	>8	- / - / -	2.4 / 0.0 / 97.6
S. maltophilia (186)				
Ceftolozane/tazobactam	16	>32	(39.8)[b]	
Ceftazidime	32	>32	31.0 / 15.7 / 53.3	- / - / -
Levofloxacin	1	4	81.7 / 9.7 / 8.6	- / - / -
TMP/SMX[g]	≤0.5	4	93.5 / 0.0 / 6.5	95.7 / 0.0 / 4.3
Tigecycline	0.5	2	- / - / -	- / - / -
P. mirabilis (82)				
Ceftolozane/tazobactam	0.5	1	(98.8)[b]	
Ceftazidime	0.06	2	96.3 / 0.0 / 3.7	89.0 / 7.3 / 3.7
Ceftriaxone	≤0.06	8	84.1 / 1.3 / 14.6	84.1 / 1.3 / 14.6
Piperacillin/tazobactam	≤0.5	1	98.8 / 1.2 / 0.0	98.8 / 0.0 / 1.2
Meropenem	≤0.06	0.12	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Levofloxacin	≤0.12	>4	75.6 / 8.5 / 15.9	68.3 / 7.3 / 24.4
Gentamicin	≤1	>8	81.7 / 3.7 / 14.6	78.0 / 3.7 / 18.3
Tigecycline[c]	2	4	78.0 / 22.0 / 0.0	43.9 / 34.1 / 22.0
Colistin	>8	>8	- / - / -	0.0 / 0.0 / 100.0
Citrobacter spp.[h] (79)				
Ceftolozane/tazobactam	0.25	2	(94.9)[b]	
Ceftazidime	0.25	>32	84.8 / 1.3 / 13.9	84.8 / 0.0 / 15.2
Ceftriaxone	0.12	>8	84.8 / 1.3 / 13.9	84.8 / 1.3 / 13.9
Piperacillin/tazobactam	2	64	88.5 / 6.4 / 5.1	78.2 / 10.3 / 11.5
Meropenem	≤0.06	≤0.06	98.7 / 1.3 / 0.0	100.0 / 0.0 / 0.0
Levofloxacin	≤0.12	4	89.9 / 6.3 / 3.8	86.1 / 3.8 / 10.1
Gentamicin	≤1	≤1	96.2 / 0.0 / 3.8	94.9 / 1.3 / 3.8
Tigecycline[c]	0.12	0.5	100.0 / 0.0 / 0.0	93.7 / 6.3 / 0.0
Colistin	0.5	1	- / - / -	100.0 / 0.0 / 0.0
K. oxytoca (74)				
Ceftolozane/tazobactam	0.25	0.5	(100.0)[b]	
Ceftazidime	0.12	0.5	97.3 / 0.0 / 2.7	94.6 / 2.7 / 2.7
Ceftriaxone	≤0.06	8	83.8 / 2.7 / 13.5	83.8 / 2.7 / 13.5
Piperacillin/tazobactam	2	>64	85.1 / 1.4 / 13.5	83.8 / 1.3 / 14.9
Meropenem	≤0.06	≤0.06	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Levofloxacin	≤0.12	≤0.12	97.3 / 0.0 / 2.7	97.3 / 0.0 / 2.7
Gentamicin	≤1	≤1	97.3 / 1.3 / 1.4	97.3 / 0.0 / 2.7
Tigecycline[c]	0.25	0.5	100.0 / 0.0 / 0.0	98.6 / 1.4 / 0.0
Colistin	0.25	0.5	- / - / -	100.0 / 0.0 / 0.0
Indole-positive *Proteae*[i] (62)				
Ceftolozane/tazobactam	0.25	1	(100.0)[b]	
Ceftazidime	0.12	4	91.8 / 4.9 / 3.3	85.2 / 6.6 / 8.2
Ceftriaxone	≤0.06	4	85.5 / 0.0 / 14.5	85.5 / 0.0 / 14.5
Piperacillin/tazobactam	≤0.5	2	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Meropenem	≤0.06	0.12	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Levofloxacin	≤0.12	>4	82.3 / 3.2 / 14.5	80.6 / 1.7 / 17.7
Gentamicin	≤1	4	90.3 / 3.2 / 6.5	83.9 / 6.4 / 9.7
Tigecycline[c]	0.5	1	100.0 / 0.0 / 0.0	91.9 / 8.1 / 0.0
Colistin	>8	>8	- / - / -	0.0 / 0.0 / 100.0

a. Criteria as published by the CLSI [2013] and EUCAST [2013].
b. Percentage inhibited at ceftolozane/tazobactam MICs of ≤8 μg/mL; for comparison purpose only.
c. In the absence of CLSI breakpoint data, US Food and Drug Administration (FDA) breakpoints were applied when available [Tygacil Product Insert, 2012].
d. Includes: *Enterobacter aerogenes* (97 strains), *E. asburiae* (3 strains), *E. cloacae* (181 strains), *E. cloacae* complex (1 strain), and *E. sakazakii* (2 strains).
e. Includes: *Acinetobacter baumannii* (219 strains), *A. berezinae* (two strains), *A. haemolyticus* (one strain), *A. junii* (1 strain), *A. lwoffii* (1 strain), *A. pittii* (6 strains), *A. ursingii* (2 strains), and unspeciated *Acinetobacter* (1 strain)
f. Includes: *Serratia liquefaciens* (5 strains), *S. marcescens* (203 strains), *S. rubidaea* (2 strains), and unspeciated *Serratia* (1 strain).
g. TMP/SMX=trimethoprim/sulfamethoxazole.
h. Includes: *Citrobacter braakii* (5 strains), *C. freundii* (31 strains), *C. koseri* (39 strains), *C. sedlakii* (2 strains), and unspeciated *Citrobacter* (2 strains).
i. Includes: *Morganella morganii* (43 strains), *Proteus vulgaris* (11 strains), *Providencia rettgeri* (4 strains), and *P. stuartii* (4 strains).

Table 3. Antimicrobial Susceptibility Patterns of Isolates from Hospitalized Patients with Pneumonia, Stratified by Geographic Region

Organism/Antimicrobial	% Susceptible (No. Tested) US (CLSI)[a]	EUROPE (EUCAST)[a]
P. aeruginosa	(500)	(519)
Ceftolozane/tazobactam[b]	99.4	89.0
Ceftazidime	82.0	65.5
Ceftriaxone	82.6	70.7
Piperacillin/tazobactam	76.2	63.0
Meropenem	80.6	67.1
Levofloxacin	76.6	54.7
Gentamicin	87.0	74.6
Amikacin	97.4[c]	82.3
MDR *P. aeruginosa*[c]	(82)	(164)
Ceftolozane/tazobactam[b]	96.3	62.4
Ceftazidime	25.6	11.6
Ceftriaxone	29.3	25.0
Piperacillin/tazobactam	9.8	6.7
Meropenem	23.2	18.3
Levofloxacin	20.7	4.9
Gentamicin	50.0	30.5
Amikacin	90.2[c]	51.2
XDR *P. aeruginosa*[c]	(44)	(130)
Ceftolozane/tazobactam[b]	93.2	56.9
Ceftazidime	9.1	3.8
Ceftriaxone	13.6	16.9
Piperacillin/tazobactam	2.3	1.5
Meropenem	11.4	8.5
Levofloxacin	9.1	8.5
Gentamicin	34.1	20.0
Amikacin	88.6[c]	61.5
Klebsiella spp.	(191)	(253)
Ceftolozane/tazobactam[b]	88.5	86.6
Ceftazidime	81.2	62.5
Ceftriaxone	79.6	60.1
Piperacillin/tazobactam	82.7	63.5
Meropenem	90.6	93.3
Levofloxacin	83.2	68.3
Gentamicin	92.1	70.8
Tigecycline[d]	99.5[c]	95.2
E. coli	(130)	(238)
Ceftolozane/tazobactam[b]	98.5	98.7
Ceftazidime	86.9	79.8
Ceftriaxone	83.8	79.4
Piperacillin/tazobactam	90.0	83.6
Meropenem	99.2	100.0
Levofloxacin	63.1	64.7
Gentamicin	83.8	81.5
Tigecycline[d]	100.0[c]	100.0
Enterobacter spp.	(150)	(134)
Ceftolozane/tazobactam[b]	92.9	95.5
Ceftazidime	78.0	58.1
Ceftriaxone	71.8	58.2
Piperacillin/tazobactam	83.3	66.4
Meropenem	100.0	99.3
Levofloxacin	96.0	86.6
Gentamicin	96.7	88.1
Tigecycline[d]	100.0[c]	97.0
Serratia spp.	(107)	(104)
Ceftolozane/tazobactam[b]	100.0	99.0
Ceftazidime	100.0	94.2
Ceftriaxone	87.7	83.7
Piperacillin/tazobactam	95.3	88.5
Meropenem	100.0	100.0
Levofloxacin	95.3	94.2
Gentamicin	99.1	94.2
Tigecycline[d]	100.0[c]	97.1
MDR Enterobacteriaceae[c]	(68)[e]	(170)[f]
Ceftolozane/tazobactam[b]	57.4	75.9
Ceftazidime	25.0	15.3
Ceftriaxone	8.8	5.9
Piperacillin/tazobactam	27.9	20.1
Meropenem	70.6	89.4
Levofloxacin	14.7	16.5
Gentamicin	54.4	34.1
Tigecycline[d]	94.1[c]	85.8
XDR Enterobacteriaceae[c]	(14)[g]	(28)[h]
Ceftolozane/tazobactam[b]	7.1	42.9
Ceftazidime	7.1	14.3
Ceftriaxone	0.0	0.0
Piperacillin/tazobactam	7.1	14.3
Meropenem	14.3	42.9
Levofloxacin	0.0	0.0
Gentamicin	28.6	21.4
Tigecycline[d]	92.9[c]	50.0

a. CLSI [2013] criteria were applied to US strains, whereas EUCAST [2013] criteria were applied for EU strains.
b. Percentage inhibited at ceftolozane/tazobactam MICs of ≤8 μg/mL; for comparison purposes only.
c. MDR, XDR Enterobacteriaceae and *P. aeruginosa* strains were classified according to recently recommended guidelines published by Magiorakos et al (2012).
d. In the absence of CLSI breakpoint, US FDA breakpoints were applied when available [Tygacil Product Insert, 2012].
e. Includes: *Citrobacter freundii* (3 strains), *E. cloacae* (11 strains), *E. coli* (10 strains), *K. oxytoca* (1 strain), *K. pneumoniae* (27 strains), *M. morganii* (2 strains), *P. mirabilis* (6 strains), *P. rettgeri* (1 strain), *P. stuartii* (1 strain), and *Serratia marcescens* (6 strains).
f. Includes: *C. freundii* (3 strains), *Citrobacter koseri* (1 strain), *E. aerogenes* (6 strains), *E. cloacae* (16 strains), *E. coli* (32 strains), *K. pneumoniae* (77 strains), *M. morganii* (3 strains), *P. mirabilis* (16 strains), and *S. marcescens* (16 strains).
g. Includes: *C. freundii* (1 strain), *E. coli* (1 strain), *K. pneumoniae* (11 strains), and *P. mirabilis* (1 strain).
h. Includes: *E. cloacae* (2 strains), *K. pneumoniae* (18 strains), *P. mirabilis* (5 strains), and *S. marcescens* (3 strains).

CONCLUSIONS

- Ceftolozane/tazobactam generally demonstrated greater *in vitro* activity than the currently available agents: cephalosporins, carbapenems, and piperacillin/tazobactam, when tested against *P. aeruginosa.*
- Ceftolozane/tazobactam exhibited remarkable activity against MDR and XDR *P. aeruginosa*.
- Against Enterobacteriaceae, ceftolozane/tazobactam activity was greater than that of several currently available cephalosporins that were tested, as well as piperacillin/tazobactam.
- Ceftolozane/tazobactam may represent a valuable treatment option for Gram-negative infections, including pneumonia caused by MDR and XDR *P. aeruginosa.*
- Currently, ceftolozane/tazobactam is NOT approved by the FDA or EMEA, however a Phase III clinical trial to evaluate ceftolozane/tazobactam in ventilator-associated pneumonia at a dose of 3 g every 8 hours is underway. [NCT01853982].

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ACKNOWLEDGMENT

We wish to express our appreciation to Dr. David J. Farrell for scientific assistance in performing these analyses.

This study was funded by Cubist Pharmaceuticals