Ceftolozane/Tazobactam Activity Tested Against Contemporary (2013) Enterobacteriaceae Strains Causing Infections in United States (USA) Medical Centers

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D.J. Farrell, H.S. Sader, R.K. Flamm, R.N. Jones

JMI Laboratories, North Liberty, IA, USA

David J. Farrell
JMI Laboratories
345 Beaver Kreek Ctr, Ste A
North Liberty, IA, USA
Tel: 319-665-3370
E-mail: david-farrell@jmilabs.com

ABSTRACT

BACKGROUND: Ceftolozane/tazobactam (TOL/TAZ) is an antipseudomonal cephalosporin with a β-lactamase inhibitor currently under review by the FDA for treatment of cUTI and cIAI. TOL/TAZ provides coverage of most ESBL-producing Enterobacteriaceae (ENT).

METHODS: A total of 4051 ENT, consecutively collected from various infection sources from 30 USA medical centers in 2013, were tested for susceptibility (S) by CLSI broth microdilution methods (TOL/TAZ at a fixed 4 µg/mL of TAZ).

RESULTS: Overall, TOL/TAZ was active ($MIC_{50/90}$, 0.25/1 µg/mL) against ENT with 95.2% and 96.5% of strains inhibited at ≤4 and ≤8 µg/mL, respectively. ENT S to ceftazidime (CAZ), piperacillin/tazobactam, and gentamicin (GEN) was 88.9, 91.5, and 90.7%, respectively. ESBL-phenotype rates were 11.6% for *Escherichia coli* (EC) and 21.5% for *Klebsiella pneumoniae* (KPN). TOL/TAZ activity against non-ESBL-phenotype EC ($MIC_{50/90}$, 0.25/0.25 µg/mL) and KPN ($MIC_{50/90}$, 0.25/0.5 µg/mL) was similar to that of CAZ. In contrast, TOL/TAZ ($MIC_{50/90}$, 0.5/2 µg/mL) was ≥32-fold more active than CAZ ($MIC_{50/90}$, 16/>32 µg/mL) and ceftriaxone (CRO; $MIC_{50/90}$, >8/>8 µg/mL) against ESBL-phenotype EC. TOL/TAZ was active against EC strains non-S to levofloxacin (LVX; MIC_{50}, 1 µg/mL), GEN (MIC_{90}, 1 µg/mL) or both (MIC_{50} 2 µg/mL). ESBL-phenotype KPN strains had low S rates to meropenem (45.1%), GEN (52.1%), and LVX (26.8%). Against *Enterobacter* spp. (ESP) and *Citrobacter* spp., TOL/TAZ ($MIC_{50/90}$, 0.25/8 and 0.25/4 µg/mL, respectively) was slightly more active than CAZ ($MIC_{50/90}$, 0.25/>32 µg/mL for both). TOL/TAZ inhibited 78.1% of CAZ-non-S ESP at ≤8 µg/mL. *P. mirabilis* was highly S to TOL/TAZ (MIC_{90}, 0.5 µg/mL), including 11 ESBL-phenotype strains (MIC_{90}, 2 µg/mL). TOL/TAZ inhibited 57.6 and 64.8% of MDR ENT strains (n = 335, 8.3%) at ≤4 and ≤8 µg/mL, respectively. TOL/TAZ had similar activity to CAZ against indole (+) *Proteae* and *Serratia* spp.

CONCLUSIONS: TOL/TAZ demonstrated activity against ENT including ESBL- and MDR-phenotype strains from USA hospitals and may represent a valuable treatment option for Gram-negative infections.

Organism (No.)	Cumulative % Inhibited at TOL/TAZ MIC (µg/mL) of								$MIC_{50/90}$ (µg/mL)
	≤0.25	0.5	1	2	4	8	16	32	
Enterobacteriaceae (4051)	63.9	86.2	92.0	93.9	95.2	96.5	97.4	98.2	0.25/1
Escherichia coli (1683)	84.9	95.7	98.2	98.9	99.2	99.5	99.6	99.8	0.25/0.5
Klebsiella spp. (822)	64.1	81.1	86.0	88.0	88.2	89.4	90.8	93.4	0.25/16
Enterobacter spp. (508)	55.9	74.4	79.3	84.1	89.4	95.1	97.4	98.6	0.25/8
Serratia spp. (323)	2.5	65.0	92.0	96.0	97.5	97.8	97.8	98.5	0.5/1
Proteus mirabilis (256)	23.1	93.4	99.4	99.6	100.0	--	--	--	0.5/0.5
Indole (+) *Proteae* (252)	55.6	85.7	94.4	98.0	98.4	99.6	99.6	99.6	0.25/1
Citrobacter spp. (207)	71.0	83.1	85.5	86.0	90.3	93.2	98.1	98.1	0.25/4

BACKGROUND

- Ceftolozane/tazobactam is an antibacterial consisting of ceftolozane, a novel antipseudomonal cephalosporin, with tazobactam, a well-established β-lactamase inhibitor.
- Ceftolozane exerts its bactericidal activity by inhibiting essential penicillin-binding proteins, resulting in inhibition of cell-wall synthesis and subsequent cell death. Ceftolozane has demonstrated greater activity against *Pseudomonas aeruginosa* when directly compared with ceftazidime and cefepime.
- Tazobactam is a potent inhibitor of most common class A and some class C β-lactamases that protect ceftolozane from hydrolysis, by binding to the active site of these enzymes, and broadens coverage to include most extended-spectrum β-lactamase (ESBL)–producing Enterobacteriaceae and some AmpC-derepressed Enterobacteriaceae.
- In Phase 3 trials, ceftolozane/tazobactam demonstrated superior clinical efficacy to high-dose levofloxacin for the treatment of patients with complicated lower urinary tract infection/pyelonephritis. Ceftolozane/tazobactam plus metronidazole had noninferior clinical efficacy to meropenem in patients with complicated intra-abdominal infection. A Phase 3 clinical trial for ventilated nosocomial pneumonia (NP) is underway.
- In the present study, we evaluated the in vitro activity of ceftolozane/tazobactam against Enterobacteriaceae isolated from patients in 30 USA hospitals in 2013.

MATERIALS AND METHODS

Organism Collection

- A total of 4051 clinically significant, nonduplicate isolates, were consecutively collected in 30 USA medical centers (2013).

Susceptibility Testing

- Broth microdilution test methods conducted according to the Clinical and Laboratory Standards Institute (CLSI) guidelines 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 minimum inhibitory concentration (MIC) panels were manufactured by ThermoFisher Scientific Inc. (Cleveland, OH, 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-S24) and susceptibility breakpoints were used to determine susceptibility/resistance rates (CLSI and European Committee on Antimicrobial Susceptibility Testing [EUCAST], 2014). *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, 2014). No interpretive criteria for ceftolozane/tazobactam susceptibility have been established by CLSI, EUCAST, or the US Food and Drug Administration (FDA).
- Multidrug-resistant (MDR), extensively drug-resistant (XDR), and pandrug-resistant (PDR) bacteria were classified as such per recently recommended guidelines by Magiorakos et al (2012).

RESULTS

- Overall, ceftolozane/tazobactam ($MIC_{50/90}$, 0.25/1 µg/mL) inhibited 95.2% and 96.5% of 4051 Enterobacteriaceae at ≤4 and ≤8 µg/mL, respectively (**Table 1**). Ceftolozane/tazobactam retained activity ($MIC_{50/90}$, 2/>32 µg/mL) against many of the 335 (8.3%) MDR Enterobacteriaceae, inhibiting 57.6% and 64.8% of strains at ≤4 and ≤8 µg/mL, respectively (**Table 1**). Ceftolozane/tazobactam was not active ($MIC_{50/90}$, >32/>32 µg/mL) against most XDR (64/4051; 1.6%) Enterobacteriaceae and only 1 PDR isolate was found (a *Klebsiella pneumoniae* from New York, USA; ceftolozane/tazobactam MIC = 32 µg/mL).
- A total of 1683 *E. coli* strains were evaluated and 99.2% and 99.5% 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 ($MIC_{50/90}$, 0.25/2 µg/mL) were active against 89.1/89.1% and 92.2/89.8% of strains according to CLSI/EUCAST breakpoint criteria, respectively (**Table 2**). Ceftolozane/tazobactam activity against non-ESBL-phenotype *E. coli* ($MIC_{50/90}$, 0.25/0.25 µg/mL) was similar to that of ceftazidime ($MIC_{50/90}$, of 0.25/0.25 µg/mL). In contrast, ceftolozane/tazobactam was 16-fold more active than ceftazidime when tested against ESBL-phenotype *E. coli* ($MIC_{50/90}$, of 4/4 µg/mL).
- Ceftolozane/tazobactam inhibited 88.2% and 89.4% of *Klebsiella* spp. strains at ≤4 and ≤8 µg/mL, respectively ($MIC_{50/90}$, 0.25/16 µg/mL; **Table 1**). Ceftriaxone ($MIC_{50/90}$, ≤0.06/>8 µg/mL), ceftazidime ($MIC_{50/90}$, 0.12/>32 µg/mL) and cefepime ($MIC_{50/90}$, ≤0.5/16 µg/mL) inhibited 82.0/82.0%, 83.8/82.5% and 85.0/84.1% at the CLSI/EUCAST susceptible breakpoints, respectively (**Table 2**).
- Although ceftolozane/tazobactam was very active ($MIC_{50/90}$, of 0.25/0.5 µg/mL) against non-ESBL-phenotype *K. pneumoniae*, activity was low ($MIC_{50/90}$, of 32/>32 µg/mL) against ESBL-phenotype strains due to the higher rate of meropenem resistance in *Klebsiella* spp. (9.1%) compared with *E. coli* (0.1%; **Table 2**). However, activity was higher ($MIC_{50/90}$, of 1/>32 µg/mL) for most ESBL-phenotype strains that were meropenem susceptible (**Table 1**).
- Ceftolozane/tazobactam was very active against *Enterobacter* spp. (89.4% and 95.1% inhibited at ≤4 and ≤8 µg/mL, respectively), *Citrobacter* spp. (90.3% and 93.2% inhibited at ≤4 and ≤8 µg/mL, respectively), indole-positive *Proteus* spp. (98.4% and 99.6% inhibited at ≤4 and ≤8 µg/mL, respectively) and *Serratia* spp. (97.5% and 97.8% inhibited at ≤4 and ≤8 µg/mL, respectively; **Table 1**).
- Ceftolozane/tazobactam was very active against *Proteus mirabilis* ($MIC_{50/90}$, 0.5/0.5 µg/mL), including ESBL-producing strains ($MIC_{50/90}$, 1/2 µg/mL; **Table 1**).

Table 1. Cumulative MIC Distributions of Ceftolozane/Tazobactam Against 4051 Enterobacteriaceae Isolates, by Species and Resistance Phenotype

Antimicrobial Agent	No. of Isolates (Cumulative %) Inhibited at MIC (µg/mL)												MIC_{50}	MIC_{90}
	≤0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	>32		
All Enterobacteriaceae (4051)	2 (0.1)	18 (0.5)	825 (20.9)	1743 (63.9)	904 (86.2)	234 (92.0)	79 (93.9)	50 (95.2)	54 (96.5)	35 (97.4)	32 (98.2)	75 (100.0)	0.25	1
MDR (335)	0 (0.0)	0 (0.0)	1 (0.3)	25 (7.8)	77 (30.8)	43 (43.6)	28 (51.9)	19 (57.6)	24 (64.8)	20 (70.8)	26 (78.5)	72 (100.0)	2	>32
XDR (64)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (6.3)	2 (9.4)	4 (15.6)	3 (20.3)	4 (26.6)	13 (46.9)	34 (100.0)	>32	>32
E. coli (1683)	2 (0.1)	12 (0.8)	576 (35.1)	838 (84.8)	182 (95.7)	42 (98.2)	13 (98.9)	5 (99.2)	5 (99.5)	2 (99.6)	2 (99.8)	4 (100.0)	0.25	0.5
Non-ESBL-phenotype (1488)	2 (0.1)	12 (0.9)	570 (39.2)	786 (92.1)	107 (99.3)	9 (99.9)	2 (100.0)	--	--	--	--	--	0.25	0.25
ESBL-phenotype (195)	0 (0.0)	0 (0.0)	6 (3.1)	52 (29.7)	75 (68.2)	33 (85.1)	11 (90.8)	5 (93.3)	5 (95.9)	2 (96.9)	2 (97.9)	4 (100.0)	0.5	2
MEM-S (MIC, ≤1 µg/mL) (1681)	2 (0.1)	12 (0.8)	576 (35.1)	838 (84.9)	182 (95.8)	42 (98.3)	13 (99.0)	5 (99.3)	5 (99.6)	1 (99.7)	1 (99.8)	4 (100.0)	0.25	0.5
MEM-NS (MIC, ≥2 µg/mL) (2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (50.0)	1 (100.0)	--	16	--
Klebsiella spp. (822)	0 (0.0)	5 (0.6)	169 (21.2)	353 (64.1)	140 (81.1)	40 (86.0)	16 (88.0)	2 (88.2)	10 (89.4)	11 (90.8)	22 (93.4)	54 (100.0)	0.25	16
K. pneumoniae (659)	0 (0.0)	4 (0.6)	108 (17.0)	291 (61.2)	114 (78.5)	36 (83.9)	10 (85.4)	2 (85.7)	10 (87.3)	11 (88.9)	20 (92.0)	53 (100.0)	0.25	32
Non-ESBL-phenotype (517)	0 (0.0)	4 (0.8)	107 (21.5)	282 (76.0)	97 (94.8)	24 (99.4)	3 (100.0)	--	--	--	--	--	0.25	0.5
ESBL-phenotype (142)	0 (0.0)	0 (0.0)	1 (0.7)	9 (7.0)	17 (19.0)	12 (27.5)	7 (32.4)	2 (33.8)	10 (40.8)	11 (48.6)	20 (62.7)	53 (100.0)	32	> 32
ESBL and MEM-S (MIC, ≤1 µg/mL) (64)	0 (0.0)	0 (0.0)	1 (1.6)	9 (15.6)	17 (42.2)	12 (60.9)	6 (70.3)	2 (70.3)	4 (79.7)	4 (85.9)	2 (89.1)	7 (100.0)	1	>32
MEM-NS (MIC, ≥2 µg/mL) (78)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.3)	0 (1.3)	6 (9.0)	7 (17.9)	18 (41.0)	46 (100.0)	> 32	> 32
Klebsiella oxytoca (160)	0 (0.0)	1 (0.6)	60 (38.1)	62 (76.9)	24 (91.9)	4 (94.4)	6 (98.1)	0 (98.1)	0 (98.1)	0 (98.1)	2 (99.4)	1 (100.0)	0.25	0.5
Non-ESBL-phenotype (146)	0 (0.0)	1 (0.7)	60 (41.8)	61 (83.6)	21 (97.9)	3 (100.0)	--	--	--	--	--	--	0.25	0.5
ESBL-phenotype (14)	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.1)	3 (28.6)	1 (35.7)	6 (78.6)	0 (78.6)	0 (78.6)	0 (78.6)	2 (92.9)	1 (100.0)	2	32
Enterobacter spp. (508)	0 (0.0)	0 (0.0)	26 (5.1)	258 (55.9)	94 (74.4)	25 (79.3)	24 (84.1)	27 (89.4)	29 (95.1)	12 (97.4)	6 (98.6)	7 (100.0)	0.25	8
CAZ-S (MIC, ≤4 µg/mL) (394)	0 (0.0)	0 (0.0)	26 (6.6)	255 (71.3)	91 (94.4)	18 (99.0)	2 (99.5)	1 (99.7)	1 (100.0)	--	--	--	0.25	0.5
CAZ-NS (MIC, ≥8 µg/mL) (114)	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.6)	3 (5.3)	7 (11.4)	22 (30.7)	26 (53.5)	28 (78.1)	12 (88.6)	6 (93.9)	7 (100.0)	4	32
Enterobacter cloacae (367)	0 (0.0)	0 (0.0)	14 (3.8)	182 (53.4)	72 (73.0)	19 (78.2)	15 (82.3)	22 (88.3)	23 (94.6)	11 (97.5)	5 (98.9)	4 (100.0)	0.25	8
Enterobacter aerogenes (129)	0 (0.0)	0 (0.0)	10 (7.8)	69 (61.2)	21 (77.5)	6 (82.2)	9 (89.1)	4 (92.2)	5 (96.1)	1 (96.9)	1 (97.7)	3 (100.0)	0.25	4
Other *Enterobacter* spp. (12)	0 (0.0)	0 (0.0)	2 (16.7)	7 (75.0)	1 (83.3)	0 (83.3)	0 (83.3)	1 (91.7)	1 (100.0)	--	--	--	0.25	4
Citrobacter spp. (207)	0 (0.0)	0 (0.0)	29 (14.0)	118 (71.0)	25 (83.1)	5 (85.5)	1 (86.0)	9 (90.3)	6 (93.2)	10 (98.1)	0 (98.1)	4 (100.0)	0.25	4
Citrobacter koseri (73)	0 (0.0)	0 (0.0)	9 (12.3)	55 (87.7)	7 (97.3)	2 (100.0)	--	--	--	--	--	--	0.25	0.5
Citrobacter freundii (118)	0 (0.0)	0 (0.0)	20 (16.9)	51 (60.2)	16 (73.7)	3 (76.3)	1 (77.1)	8 (83.9)	5 (88.1)	10 (96.6)	0 (96.6)	4 (100.0)	0.25	16
Other *Citrobacter* spp. (16)	0 (0.0)	0 (0.0)	0 (0.0)	12 (75.0)	2 (87.5)	0 (87.5)	0 (87.5)	1 (93.8)	1 (100.0)	--	--	--	0.25	4
Proteus mirabilis (256)	0 (0.0)	0 (0.0)	1 (0.4)	58 (23.0)	180 (93.4)	13 (98.4)	3 (99.6)	1 (100.0)	--	--	--	--	0.5	0.5
Non-ESBL-phenotype (245)	0 (0.0)	0 (0.0)	1 (0.4)	58 (24.1)	175 (95.5)	9 (99.2)	2 (100.0)	--	--	--	--	--	0.5	0.5
ESBL-phenotype (11)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (45.5)	4 (81.8)	1 (90.9)	1 (100.0)	--	--	--	--	1	2
Indole-positive *proteus* spp. (252)	0 (0.0)	1 (0.4)	22 (9.1)	112 (53.6)	81 (85.7)	22 (94.4)	9 (98.0)	1 (98.4)	3 (99.6)	0 (99.6)	0 (99.6)	1 (100.0)	0.25	1
Serratia spp. (323)	0 (0.0)	0 (0.0)	2 (0.6)	6 (2.5)	202 (65.0)	87 (92.0)	13 (96.0)	5 (97.5)	1 (97.8)	0 (97.8)	2 (98.5)	5 (100.0)	0.5	1

CAZ-NS = ceftazidime-nonsusceptible; CAZ-R = ceftazidime-resistant; CAZ-S = ceftazidime-susceptible; MEM-NS = meropenem-nonsusceptible; MEM-S = meropenem-susceptible.

Table 2. Activity of Ceftolozane/Tazobactam and Comparator Antimicrobial Agents When Tested Against Enterobacteriaceae From USA Hospitals (2013)

Organism/Antimicrobial Agent (No. Tested)	MIC (µg/mL)		%S/%I/%R[a]	
	MIC_{50}	MIC_{90}	CLSI	EUCAST
E. coli (1683)				
Ceftolozane/tazobactam	0.25	0.5	-/-/-	-/-/-
Ceftriaxone	≤0.06	>8	89.1/0.2/10.7	89.1/0.2/10.7
Ceftazidime	0.25	2	92.2/1.5/6.3	89.8/2.4/7.8
Cefepime	≤0.5	1	91.4/1.8/6.8	90.4/1.8/7.7
Meropenem	≤0.06	≤0.06	99.9/0.0/0.1	99.9/0.1/0.0
Piperacillin/tazobactam	2	8	96.0/2.2/1.8	94.6/1.4/4.0
Levofloxacin	≤0.12	>4	70.3/0.9/28.8	69.9/0.3/29.7
Gentamicin	≤1	>8	88.3/0.3/11.4	87.7/0.6/11.7
Tigecycline[b]	0.12	0.12	100.0/0.0/0.0	100.0/0.0/0.0
Colistin	0.5	0.5	-/-/-	99.5/0.0/0.5
Klebsiella spp.[c] (822)				
Ceftolozane/tazobactam	0.25	16	-/-/-	-/-/-
Ceftriaxone	≤0.06	>8	82.0/1.0/17.0	82.0/1.0/17.0
Ceftazidime	0.12	>32	83.8/1.4/14.8	82.5/1.3/16.2
Cefepime	≤0.5	16	85.0/2.6/12.4	84.1/1.7/14.2
Meropenem	≤0.06	0.25	90.3/0.7/9.1	90.9/2.6/6.4
Piperacillin/tazobactam	4	>64	83.9/1.6/14.4	79.2/4.7/16.1
Levofloxacin	≤0.12	>4	86.6/0.7/12.7	85.4/1.2/13.4
Gentamicin	≤1	2	91.2/1.6/7.2	90.4/0.8/8.8
Tigecycline[b]	0.25	0.5	99.8/0.2/0.0	95.7/4.1/0.2
Colistin	0.5	1	-/-/-	97.5/0.0/2.5
Enterobacter spp.[d] (508)				
Ceftolozane/tazobactam	0.25	8	-/-	-/-
Ceftriaxone	0.25	>8	72.1/4.2/23.8	72.1/4.2/23.8
Ceftazidime	0.25	>32	77.6/1.5/20.9	74.0/3.6/22.4
Cefepime	≤0.5	2	92.7/4.0/3.3	88.6/7.7/3.7
Meropenem	≤0.06	≤0.06	99.2/0.3/0.4	99.6/0.4/0.0
Piperacillin/tazobactam	4	64	81.3/11.1/7.6	78.3/3.0/18.7
Levofloxacin	≤0.12	0.5	96.3/0.5/3.2	95.1/1.2/3.7
Gentamicin	≤1	≤1	96.9/0.1/3.0	96.5/0.3/3.2
Tigecycline[b]	0.25	0.5	99.4/0.6/0.0	96.6/2.9/0.6
Colistin	0.5	>8	-/-/-	82.2/0.0/17.8
P. mirabilis (256)				
Ceftolozane/tazobactam	0.5	0.5	-/-	-/-
Ceftriaxone	≤0.06	≤0.06	96.5/0.0/3.5	96.5/0.0/3.5
Ceftazidime	0.06	0.06	99.6/0.4/0.0	98.0/1.6/0.4
Cefepime	≤0.5	≤0.5	96.5/0.0/3.5	96.5/0.0/3.5
Meropenem	≤0.06	≤0.06	100.0/0.0	100.0/0.0
Piperacillin/tazobactam	≤0.5	1	100.0/0.0/0.0	100.0/0.0/0.0
Levofloxacin	≤0.12	>4	69.9/5.5/24.6	65.2/4.7/30.1
Gentamicin	≤1	8	88.6/4.3/7.1	85.0/3.6/11.4
Tigecycline[b]	1	4	86.7/12.9/0.4	53.9/32.8/13.3
Indole-positive *Proteus* spp.[e] (252)				
Ceftolozane/tazobactam	0.25	1	-/-	-/-
Ceftriaxone	≤0.06	1	90.0/4.4/5.6	90.0/4.4/5.6
Ceftazidime	0.12	2	92.4/3.1/4.4	85.7/6.7/7.6
Cefepime	≤0.5	≤0.5	98.8/0.4/0.8	98.4/0.3/1.2

Table 2 (cont'd)

Organism/Antimicrobial Agent (No. Tested)	MIC (µg/mL)		%S/%I/%R[a]	
	MIC_{50}	MIC_{90}	CLSI	EUCAST
Meropenem	≤0.06	0.12	100.0/0.0/0.0	100.0/0.0/0.0
Piperacillin/tazobactam	≤0.5	4	98.8/0.4/0.8	97.2/1.6/1.2
Levofloxacin	≤0.12	>4	78.2/5.1/16.7	73.0/5.2/21.8
Gentamicin	≤1	>8	84.9/2.8/12.3	77.8/7.2/15.1
Tigecycline[b]	0.5	1	96.4/3.1/0.4	90.9/5.5/3.6
Serratia spp.[f] (223)				
Ceftolozane/tazobactam	0.5	1	-/-	-/-
Ceftriaxone	0.25	4	87.1/2.5/10.4	87.1/2.5/10.4
Ceftazidime	0.25	0.5	96.3/0.7/3.1	95.4/0.8/3.7
Cefepime	≤0.5	≤0.5	96.9/2.1/0.9	96.6/0.9/2.5
Meropenem	≤0.06	≤0.06	98.5/0.0/1.5	98.5/0.3/1.2
Piperacillin/tazobactam	2	8	94.4/3.3/2.2	92.3/2.1/5.6
Levofloxacin	≤0.12	1	96.3/1.5/2.2	91.6/4.7/3.7
Gentamicin	≤1	≤1	97.8/0.9/1.3	97.5/0.3/2.2
Tigecycline[b]	0.5	1	99.1/0.7/0.3	96.6/2.5/0.9
Colistin	>8	>8	-/-/-	5.9/0.0/94.1
Citrobacter spp.[g] (207)				
Ceftolozane/tazobactam	0.25	4	-/-	-/-
Ceftriaxone	0.12	>8	80.6/0.5/18.9	80.6/0.5/18.9
Ceftazidime	0.25	>32	81.2/0.4/18.4	80.7/0.5/18.8
Cefepime	≤0.5	1	95.6/1.5/2.9	92.2/4.3/3.4
Meropenem	≤0.06	≤0.06	98.6/0.4/1.0	99.0/0.5/0.5
Piperacillin/tazobactam	4	64	85.4/6.3/8.3	81.6/3.8/14.6
Levofloxacin	≤0.12	1	92.8/4.3/2.9	90.3/2.5/7.2
Gentamicin	≤1	≤1	92.3/0.5/7.2	92.3/0.0/7.7
Tigecycline[b]	0.12	0.5	100.0/0.0/0.0	98.5/1.5/0.0
Colistin	0.5	1	-/-/-	98.5/0.0/1.5

[a]Criteria as published by the CLSI [2012] and EUCAST [2014]. [b]USA-FDA breakpoints were applied [Tygacil Product Insert, 2012]. [c]Includes: *K. oxytoca* (160 strains), *K. pneumoniae* subspecies *ozaenae* (3 strains), and *K. pneumoniae* (659 strains). [d]Includes: *E. aerogenes* (129 strains), *E. amnigenus* (1 strain), *E. asburiae* (6 strains), *E. cancerogenus* (1 strain), *E. cloacae* (367 strains), *E. gergoviae* (2 strains), *E. hormaechei* (1 strain), and *E. kobei* (1 strain). [e]Includes: *Morganella morganii* (146 strains), *Proteus vulgaris* (33 strains), *Providencia rettgeri* (34 strains), and *Providencia stuartii* (39 strains). [f]Includes: *S. fonticola* (2 strains), *S. liquefaciens* (2 strains), and *S. marcescens* (319 strains). [g]Includes: *C. amalonaticus* (2 strains), *C. braakii* (9 strains), *C. farmeri* (1 strain), *C. freundii* (118 strains), *C. koseri* (73 strains), and *C. youngae* (4 strains).

CONCLUSIONS

- Ceftolozane/tazobactam demonstrated greater potency than ceftriaxone and currently available anti-*P. aeruginosa* cephalosporins (ceftazidime and cefepime) and piperacillin/tazobactam when tested against Enterobacteriaceae strains, including ESBL (meropenem-susceptible) and MDR phenotypes, from USA hospitals during 2013.
- Ceftolozane/tazobactam may represent a valuable treatment option for Gram-negative infections, including those caused by various resistant organisms.

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