

Ceftolozane/Tazobactam Activity When Tested Against Gram-negative Bacterial Isolates From Hospitalized Patients With Pneumonia in European Hospitals (2011-2012)

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

JMI Laboratories, North Liberty, IA, USA

David J. Farrell, PhD
JMI Laboratories
345 Beaver Creek Ctr, Ste A
North Liberty, Iowa, 52317, USA
Tel: +1 319-665-3370
E-mail: david-farrell@jmilabs.com

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INTRODUCTION

- 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, cefepime, and meropenem.
- Ceftolozane is able to evade resistance mechanisms employed by *P. aeruginosa*, such as efflux pumps and reduced uptake through porins, and it has also demonstrated a low propensity to select for resistance.
- Tazobactam is a potent inhibitor of most common class A and some class C β -lactamases that, by binding to the active site of these enzymes, protects ceftolozane from hydrolysis and broadens coverage to include most extended-spectrum β -lactamase (ESBL)-producing Enterobacteriaceae and some AmpC-derepressed Enterobacteriaceae.
- Gram-negative bacilli are the major cause of pneumonia in hospitalized patients and, with increasing antimicrobial resistance in these pathogens and empirical therapy for these infections becoming increasingly difficult, development of new therapeutic options is highly imperative.
- Ceftolozane/tazobactam is currently in Phase 3 trials for the treatment of complicated urinary tract infections, complicated intra-abdominal infection, and nosocomial pneumonia. We evaluated the in vitro activities of ceftolozane/tazobactam, piperacillin/tazobactam, ceftazidime, meropenem, and other comparator agents when tested against Gram-negative organisms isolated from patients hospitalized with pneumonia in European medical centres during 2011 and 2012.

MATERIALS AND METHODS

Organism Collection

- A total of 2992 Gram-negative isolates were consecutively collected from hospitalized patients with pneumonia during 2011 and 2012 from 31 medical centres located in 14 European countries (Belgium, France, Germany, Greece, Ireland, Italy, Poland, Portugal, Russia, Spain, Sweden, Turkey, United Kingdom, Ukraine), plus Israel.
- Only 1 strain per patient infectious episode was included in the surveillance collection. Of the 2992 patients, 1040 (34.8%) were from an intensive care unit, and 993 (33.5%) had ventilator-associated pneumonia recorded as the infection type.

Susceptibility Testing

- Both microdilution test methods conducted according to the Clinical and Laboratory Standards Institute (CLSI) were performed to determine antimicrobial susceptibility of ceftolozane/tazobactam, with tazobactam at a fixed concentration of 4 mg/L, and many comparator agents.
- Validated minimum inhibitory concentration (MIC) panels were manufactured by Thermo Fisher Scientific Inc. (Cleveland, OH, USA). Concurrent quality control (QC) testing was performed to ensure proper test conditions and procedures.
- Multidrug-resistant (MDR), extensively drug-resistant (XDR), and pandrug-resistant (PDR) *P. aeruginosa* and Enterobacteriaceae strains were classified according to recently recommended guidelines using nonsusceptibility (European Committee on Antimicrobial Susceptibility Testing [EUCAST] breakpoints) to ceftazidime, meropenem, piperacillin/tazobactam, levofloxacin, gentamicin, tigecycline, and colistin (for Enterobacteriaceae) and to ceftazidime, meropenem, piperacillin/tazobactam, levofloxacin, gentamicin, and colistin (for *P. aeruginosa*).
- Classifications were based on the following recommended parameters: MDR = nonsusceptible to ≥ 3 antimicrobial classes; XDR = susceptible to ≤ 2 antimicrobial classes; PDR = nonsusceptible to all antimicrobial classes.
- QC strains included: *Escherichia coli* ATCC 25922 and 35218 and *P. aeruginosa* ATCC 27853. QC ranges and interpretive criteria for comparator compounds used the CLSI M100-S24 guidelines and all QC results were within published ranges.

RESULTS

- P. aeruginosa* was the most common pathogen (32.5%) 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}], 1/>32 mg/L; 86.1% inhibited at ≤ 8 mg/L; **Tables 1 & 3**).
- The susceptibility of *P. aeruginosa* was moderate to ceftazidime (65.0%), cefepime (69.8%), meropenem (64.4%), piperacillin/tazobactam (61.1%), levofloxacin (62.4%) [CLSI], 52.3% [EUCAST], gentamicin (72.9%), and amikacin (85.0%) [CLSI], 80.0% [EUCAST]; **Table 3**). Colistin was the most active agent overall against *P. aeruginosa* (MIC_{50%/90} 1/>2 mg/L; 99.0% [CLSI], 99.8% [EUCAST]).
- Ceftolozane/tazobactam showed activity against ceftazidime-nonsusceptible (68.2% inhibited at ≤ 8 mg/L), cefepime-nonsusceptible (57.7% inhibited at ≤ 8 mg/L), meropenem-nonsusceptible *P. aeruginosa* (64.5% inhibited at ≤ 8 mg/L), and isolates nonsusceptible to other antimicrobial agents (**Tables 1 and 2**). Ceftolozane/tazobactam inhibited 59.1% of MDR (34.0% of all *P. aeruginosa* isolates) and 47.8% of XDR (25.8% of all *P. aeruginosa* isolates) *P. aeruginosa* isolates at MICs of ≤ 8 mg/L (**Table 1**). No PDR strains of *P. aeruginosa* were found.
- Ceftolozane/tazobactam was very active (MIC_{50%/90} 0.25/4 mg/L; 92.0/94.3% inhibited at $\leq 4/\leq 8$ mg/L) against 1675 Enterobacteriaceae and retained activity against many MDR (19.9% of all Enterobacteriaceae isolates) and XDR (2.5% of all Enterobacteriaceae isolates), inhibiting 75.7% of MDR isolates and 47.6% of XDR isolates at MIC values of ≤ 8 mg/L (**Table 1**).

RESULTS (Cont'd)

Table 1. Summary of Ceftolozane/Tazobactam Activity Tested Against Gram-negative Bacilli by Species and Resistance Phenotype Isolated From Patients Hospitalized With Pneumonia (Europe, 2011 to 2012)

Organism (No. Tested)/Resistance Phenotype	No. of Isolates (Cumulative %) Inhibited at Ceftolozane/Tazobactam MIC (mg/L) of:										MIC ₅₀	MIC ₉₀		
	≤ 0.06	0.12	0.25	0.5	1	2	4	8	16	32			>32	
<i>P. aeruginosa</i> (971)	0 (0.0)	1 (0.1)	30 (3.2)	372 (41.5)	253 (67.6)	98 (77.7)	64 (84.2)	18 (86.1)	10 (87.1)	10 (88.2)	115 (100.0)	1	>32	
CAZ NS (179)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	25 (14.5)	55 (45.3)	35 (64.8)	6 (68.2)	4 (70.4)	4 (72.6)	49 (100.0)	4	>32	
FEP NS (293)	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.4)	22 (8.9)	64 (30.7)	61 (51.5)	18 (57.7)	9 (60.8)	10 (64.2)	105 (100.0)	4	>32	
MEM NS (346)	0 (0.0)	0 (0.0)	0 (0.0)	43 (12.4)	77 (34.7)	58 (51.5)	37 (62.1)	8 (64.5)	10 (67.3)	9 (69.9)	104 (100.0)	2	>32	
P/T NS (378)	0 (0.0)	0 (0.0)	0 (0.0)	11 (2.9)	76 (23.0)	84 (45.2)	61 (61.4)	18 (66.1)	10 (68.8)	9 (71.2)	109 (100.0)	4	>32	
CAZ, MEM, and P/T NS (224)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	15 (7.6)	49 (28.6)	36 (44.6)	8 (56.3)	10 (52.7)	8 (56.3)	98 (100.0)	16	>32	
LXV NS (365)	0 (0.0)	0 (0.0)	0 (0.0)	6 (1.6)	47 (14.5)	89 (38.9)	62 (55.9)	36 (65.8)	7 (67.7)	9 (70.1)	102 (100.0)	2	>32	
GEN NS (263)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	20 (7.6)	52 (24.7)	46 (16.2)	1 (52.1)	3 (53.2)	7 (55.9)	107 (100.0)	4	>32	
MDR (330)	0 (0.0)	0 (0.0)	0 (0.0)	86 (24.6)	60 (20.6)	68 (41.2)	47 (55.5)	12 (59.1)	10 (62.1)	10 (65.2)	115 (100.0)	4	>32	
XDR (251)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	28 (11.6)	52 (32.3)	33 (45.4)	6 (47.8)	10 (51.8)	10 (55.8)	111 (100.0)	16	>32	
<i>Acinetobacter</i> spp. (346)	9 (2.6)	21 (3.2)	2 (3.8)	9 (6.4)	15 (10.7)	9 (13.3)	19 (18.8)	55 (34.7)	63 (52.9)	73 (74.0)	90 (100.0)	16	>32	
All Enterobacteriaceae (1675)	2 (0.1)	271 (16.2)	599 (52.1)	364 (73.8)	163 (83.5)	81 (88.4)	61 (92.0)	38 (94.3)	22 (95.6)	24 (97.0)	50 (100.0)	0.25	4	
MDR Enterobacteriaceae (333)	0 (0.0)	0 (0.0)	0 (0.0)	18 (5.4)	55 (21.9)	56 (38.7)	51 (54.1)	43 (67.0)	29 (75.7)	14 (79.9)	21 (86.2)	46 (100.0)	2	>32
XDR Enterobacteriaceae (42)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (9.5)	3 (16.7)	5 (28.6)	6 (47.6)	1 (50.0)	6 (64.3)	15 (100.0)	16	>32	
<i>E. coli</i> (521)	1 (0.2)	149 (28.8)	254 (77.5)	61 (89.2)	31 (95.2)	12 (97.5)	6 (98.7)	4 (99.4)	2 (99.8)	1 (100.0)	0.25	1	>32	
ESBL phenotype (114)	0 (0.0)	0 (0.0)	0 (0.0)	26 (22.8)	37 (55.3)	27 (79.0)	11 (86.6)	4 (97.4)	2 (99.1)	1 (100.0)	0.5	4	>32	
<i>Klebsiella</i> spp. (520)	0 (0.0)	88 (16.9)	149 (45.6)	79 (60.8)	50 (70.4)	36 (77.3)	30 (83.1)	16 (86.2)	9 (79.9)	18 (91.4)	45 (100.0)	4	>32	
ESBL phenotype (224)	0 (0.0)	1 (0.5)	9 (4.5)	27 (16.5)	38 (33.5)	33 (48.2)	29 (61.2)	15 (67.9)	9 (81.8)	18 (79.9)	45 (100.0)	4	>32	
ESBL phenotype and MEM S (76)	0 (0.0)	0 (0.0)	0 (0.0)	5 (6.7)	10 (19.7)	14 (38.2)	12 (54.0)	13 (71.1)	6 (79.0)	4 (84.2)	6 (100.0)	2	32	
<i>Enterobacter</i> spp. (239)	0 (0.0)	17 (7.1)	97 (47.7)	45 (66.5)	12 (71.6)	18 (79.1)	21 (87.9)	15 (94.1)	6 (96.7)	3 (100.0)	0.5	8	>32	
CAZ NS (82)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)	10 (13.4)	1 (19.5)	16 (39.0)	21 (64.6)	10 (51.8)	6 (90.2)	5 (96.3)	3 (100.0)	4	16
<i>Serratia</i> spp. (177)	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.3)	105 (61.6)	57 (93.8)	9 (98.9)	0 (98.9)	0 (99.4)	0 (99.4)	1 (100.0)	0.5	1	
<i>Proteus mirabilis</i> (85)	0 (0.0)	1 (1.2)	15 (18.8)	53 (81.2)	8 (90.6)	4 (95.3)	1 (96.5)	2 (98.8)	1 (100.0)	0	0.5	1	>32	
<i>Citrobacter</i> spp. (71)	0 (0.0)	9 (12.7)	46 (77.5)	4 (83.1)	2 (85.9)	2 (85.9)	4 (94.4)	1 (95.8)	3 (100.0)	0	0.25	4	>32	
Indole-positive <i>Proteus</i> spp. (62)	1 (1.6)	6 (11.3)	35 (67.7)	17 (95.2)	3 (100.0)						0.25	0.5	>32	

CAZ, ceftazidime; FEP, cefepime; GEN, gentamicin; MEM, meropenem; NS, nonsusceptible; P/T, piperacillin/tazobactam; LXV, levofloxacin.
 *Includes *Acinetobacter baumannii* (327 strains), *Acinetobacter baumannii* (2), *Acinetobacter junii* (1), *Acinetobacter pittii* (3), *Acinetobacter ursingii* (1), unspecified *Acinetobacter* (10).
 †Includes *Klebsiella pneumoniae* (386 strains), *Klebsiella oxytoca* (99), unspecified *Klebsiella* (35).
 ‡Includes *Enterobacter cloacae* (171 strains), *Enterobacter aerogenes* (65), *Enterobacter asburiae* (1), *Enterobacter amnigenus* (1), unspecified *Enterobacter* (1).
 §Includes *Serratia marcescens* (170 strains), *Serratia liquefaciens* (6), *Serratia rubidaea* (1).
 ¶Includes *Citrobacter koseri* (40 strains), *Citrobacter freundii* (27), *Citrobacter braakii* (2), unspecified *Citrobacter* (2).
 ††Includes *Morganella morganii* (47 strains), *Proteus vulgaris* (11), *Providencia rettgeri* (3), *Providencia stuartii* (1).

Table 3. Activity of Ceftolozane/Tazobactam and Comparator Antimicrobial Agents When Tested Against Gram-negative Bacilli From Patients Hospitalized With Pneumonia (Europe, 2011 - 2012)

Organism (No. Tested)/Antimicrobial Agent	MIC (mg/L)		%S/%I/%R		Organism (No. Tested)/Antimicrobial Agent	MIC (mg/L)		%S/%I/%R		Organism (No. Tested)/Antimicrobial Agent	MIC (mg/L)		%S/%I/%R	
	50%	90%	CLSI*	EUCAST†		50%	90%	CLSI*	EUCAST†		50%	90%	CLSI*	EUCAST†
<i>P. aeruginosa</i> (971)					<i>P. aeruginosa</i> (971)					<i>P. aeruginosa</i> (971)				
Ceftolozane/tazobactam	1	>32		(86.1)	Ceftolozane/tazobactam	32	>32		(34.7)*	Ceftolozane/tazobactam	0.5	1		(96.5)†
Ceftazidime	4	>32	65.0/77.2/73.3	65.0/0.0/35.0	Ceftazidime	>32	>32	15.0/41.8/0.9	-/-	Ceftazidime	0.06	2	94.3/0.0/5.9	89.4/4.7/5.9
Cefepime	4	>16	69.8/74.4/25.6	69.8/0.0/30.2	Cefepime	>16	>16	16.8/11.5/71.7	-/-	Cefepime	<0.5	4	89.4/2.4/8.2	88.2/3.6/8.2
Meropenem	1	>8	64.9/42/26.2	64.4/20/15.1	Meropenem	>8	>8	28.0/41.1/67.9	28.0/7.8/64.2	Ceftriaxone	<0.06	>8	83.5/0.0/16.5	83.5/0.0/16.5
Piperacillin/tazobactam	8	>64	61.1/16.6/22.3	61.1/0.0/38.9	Ampicillin/sulbactam	>32	>32	23.4/8.7/67.9	-/-	Piperacillin/tazobactam	<0.5	1	98.8/1.2/0.0	98.8/0.0/1.2
Levofloxacin	1	>4	62.6/6/31.0	52.3/10.1/37.6	Piperacillin/tazobactam	>64	>64	13.9/3.8/82.3	-/-	Meropenem	<0.06	0.12	100.0/0.0/0.0	100.0/0.0/0.0
Gentamicin	2	>8	72.9/3.7/23.4	72.9/0.0/27.1	Levofloxacin	>4	>4	13.6/11.3/75.1	12.1/1.5/86.4	Levofloxacin	<0.12	>4	89.4/0.0/10.6	82.3/7.1/10.6
Amikacin	4	16	85.0/3.2/11.8	80.0/5.0/15.0	Gentamicin	>8	>8	24.6/4.3/71.1	24.6/0.0/75.4	Gentamicin	<1	>8	80.0/2.4/17.6	77.6/2.4/20.0
Colistin	1	2	99.0/0.0/70.3	99.8/0.0/0.2	Tigecycline	1	2	-/-	-/-	Tigecycline ^a	2	4	73.5/23.5/1.2	37.7/37.6/24.7
<i>E. coli</i> (521)					Colistin	0.5	2	96.2/0.0/3.8	91.8/0.0/8.2	Colistin	>8	>8	-/-	0.0/0.0/100.0
Ceftolozane/tazobactam	0.25	1		(99.4)†	<i>Enterobacter</i> spp. (239)					<i>Enterobacter</i> spp. (239)				
Ceftazidime	0.25	16	85.4/25/12.1	79.3/6.1/14.6	Ceftolozane/tazobactam	0.5	8		(94.1)*	Ceftolozane/tazobactam	0.25	4		(95.8)†
Cefepime	<0.5	>16	82.0/4.0/14.0	80.6/2.5/16.9	Ceftazidime	0.5	>32	65.7/4.2/30.1	60.3/5.4/34.3	Ceftazidime	0.25	32	83.1/14.1/15.5	83.1/0.0/16.9
Ceftriaxone	<0.06	>8	79.0/4.0/19.9	79.7/0.4/19.9	Cefepime	<0.5	4	88.3/5.6/6.3	82.9/9.6/7.5	Cefepime	<0.5	<0.5	97.2/1.4/1.4	93.0/5.6/1.4
Piperacillin/tazobactam	2	32	88.1/6.3/5.6	82.0/6.1/11.9	Ceftriaxone	0.5	>8	59.8/3.8/36.4	59.8/3.8/36.4	Ceftriaxone	0.12	>8	83.1/14.1/15.5	83.1/1.4/15.5
Meropenem	<0.06	<0.06	100.0/0.0/0.0	100.0/0.0/0.0	Piperacillin/tazobactam	4	64	74.9/15.9/9.2	68.6/6.3/25.1	Piperacillin/tazobactam	2	32	87.3/9.9/2.8	78.9/8.1/2.6
Levofloxacin	<0.12	>4	64.7/2.3/33.0	64.5/0.2/25.3	Meropenem	<0.06	0.12	99.2/0.0/0.8	99.2/0.0/0.4	Meropenem	<0.06	<0.06	100.0/0.0/0.0	100.0/0.0/0.0
Gentamicin	4	>8	83.3/0.4/45.3	82.3/0.1/65.2	Levofloxacin	<0.12	2	93.2/1.7/71.1	88.3/2.0/8.8	Levofloxacin	<0.12	0.5	93.0/0.0/8.2	91.6/1.4/7.0
Tigecycline ^a	0.12	0.25	100.0/0.0/0.0	100.0/0.0/0.0	Gentamicin	<1	4	89.9/0.9/9.2	89.5/0.4/10.1	Gentamicin	<1	<1	97.2/0.2/2.8	95.8/1.4/2.8
Colistin	0.25	0.5	-/-	99.8/0.0/0.2	Tigecycline ^a	0.25	1	98.3/1.7/0.0	95.8/2.5/1.7	Tigecycline ^a	0.12	0.25	100.0/0.0/0.0	98.6/1.4/0.0
<i>K. pneumoniae</i> (386)					Colistin	0.5	2	-/-	-/-	Colistin	0.25	0.5	-/-	100.0/0.0/100.0
Ceftolozane/tazobactam	0.5	>32		(82.9)†	<i>Serratia</i> spp. (177)					Indole-positive <				