Antimicrobial Activity of Ceftolozane/Tazobactam and Comparator Agents Tested Against Enterobacteriaceae Isolates From 14 European Countries and Israel (2012)

D.J. Farrell, H.S. Sader, M. Castanheira, R.N. Jones

JMI Laboratories, North Liberty, IA, USA

Poster # ePA442

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

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 (PBPs), 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, 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.
- Ceftolozane/tazobactam is currently in Phase 3 trials for the treatment of complicated urinary tract infections (cUTI), complicated intra-abdominal infections, and nosocomial ventilated pneumonia. We evaluated the in vitro activities of ceftolozane/tazobactam, ceftazidime, meropenem, and other comparator agents when tested against clinical Enterobacteriaceae isolates collected from hospitals in Europe (EU) and Israel.

MATERIALS AND METHODS

Organism Collection

- A total of 4518 Enterobacteriaceae isolates were consecutively collected in 2012 from 31 medical centres located in 14 EU countries, including Russia, Turkey, and Ukraine, plus Israel. The number of isolates per country varied from 36 in Israel to 669 in France.

Susceptibility Testing

- Broth microdilution test methods conducted according to the Clinical and Laboratory Standards Institute (CLSI) were performed to determine antimicrobial susceptibility of ceftolozane, 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 assure proper test conditions and procedures.
- Multidrug-resistant (MDR), extensively drug-resistant (XDR), and pandrug-resistant (PDR) Enterobacteriaceae strains were classified according to recently recommended guidelines using nonsusceptibility (European Committee on Antimicrobial Susceptibility Testing [EUCAST] breakpoints) to ceftriaxone, meropenem, piperacillin/tazobactam, levofloxacin, gentamicin, tigecycline, and colistin.
- Classifications were based on the following recommended parameters: MDR = non-susceptible to ≥3 antimicrobial classes; XDR = susceptible to ≤2 antimicrobial classes; PDR = nonsuscceptible 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

- Overall, ceftolozane/tazobactam (MIC required to inhibit the growth of 50%/90% of organisms [$MIC_{50/90}$], 0.25/2 mg/L) inhibited 93.9% and 95.3% of 4518 Enterobacteriaceae at ≤4 and ≤8 mg/L, respectively (**Table 1**). Meropenem was the most active agent ($MIC_{50/90}$, ≤0.06/≤0.06 mg/L; 97.5% [CLSI]/97.8% [EUCAST] susceptible) followed by tigecycline (98.5% [CLSI]/93.6% [EUCAST]). Susceptibility rates for other agents (CLSI/EUCAST) were lower; ceftazidime (81.9%/77.5%), cefepime (83.3%/80.8%), ceftriaxone (76.1%), piperacillin/tazobactam (87.1%/82.2%), levofloxacin (77.1%/75.6%), and gentamicin (85.5%/83.8%). Colistin resistance (EUCAST criteria) was 19.2% (**Table 2**).
- Ceftolozane/tazobactam retained activity ($MIC_{50/90}$, 1/>32 mg/L) against many of the 765 (16.9%) MDR Enterobacteriaceae, inhibiting 70.1% and 75.3% of 765 MDR strains at ≤4 and ≤8 mg/L, respectively (**Table 1**). Against these MDR strains, ceftolozane/tazobactam was up to 32-fold more potent than ceftazidime ($MIC_{50/90}$, 32/>32 mg/L) and piperacillin/tazobactam ($MIC_{50/90}$, 32/>64 mg/L) and at least 8- and 16-fold more potent than ceftriaxone and cefepime, respectively (**Table 2**). Meropenem was the most potent ($MIC_{50/90}$, ≤0.06/8 mg/L; 87.0% susceptible by EUCAST) agent against the MDR subset followed by tigecycline ($MIC_{50/90}$, 0.5/2 mg/L; 83.1% susceptible by EUCAST). Colistin resistance was 29.8% against the MDR subset (**Table 2**).
- Overall, 114 (2.5%) Enterobacteriaceae were classified as XDR and 4 strains were found to be PDR. Ceftolozane/tazobactam exhibited limited activity against XDR Enterobacteriaceae strains (**Table 1**). Resistance rates (EUCAST) for other agents ranged from 16.7% (tigecycline) to 94.6% (ceftriaxone) against XDR strains (**Table 2**).
- Ceftolozane/tazobactam demonstrated potent activity against 2064 *E. coli* ($MIC_{50/90}$, 0.25/0.5 mg/L; 98.7 and 99.2% inhibited at ≤4 and ≤8 mg/L, respectively), including ESBL screen-positive phenotype strains ($MIC_{50/90}$, 0.5/2 mg/L; 93.1% and 95.5% inhibited at ≤4 and ≤8 mg/L, respectively). All non-ESBL-phenotype strains were inhibited at a ceftolozane/tazobactam MIC of ≤2 mg/L (**Table 1**).
- Ceftolozane/tazobactam showed potent activity against non-ESBL-phenotype strains of *Klebsiella pneumoniae* ($MIC_{50/90}$, 0.25/0.5 mg/L; highest MIC, 2 mg/L), and retained activity against many ESBL screen-positive strains ($MIC_{50/90}$, 4/>32 mg/L; 58.5% and 61.7% inhibited at ≤4 and ≤8 mg/L, respectively); however, it was inactive against meropenem-nonsuscepible *K. pneumoniae* ($MIC_{50/90}$ >32/>32 mg/L; **Table 1**). Tigecycline ($MIC_{50/90}$ 0.5/1 mg/L; 93.1% susceptible [EUCAST]) and colistin ($MIC_{50/90}$ 0.5/8 mg/L; 87.1% susceptible [EUCAST]) exhibited the highest in vitro activity against ESBL-phenotype *K. pneumoniae* (**Table 2**).

RESULTS (cont'd)

Table 1. Cumulative MIC Distributions of Ceftolozane/Tazobactam Tested Against Enterobacteriaceae, Including Various Resistance Subsets

Organism/Resistant Subset (No. Tested)	No. of Isolates (Cumulative %) Inhibited at Ceftolozane/Tazobactam MIC (mg/L) of:											
	≤0.12	0.25	0.5	1	2	4	8	16	32	>32	MIC_{50}	MIC_{90}
All Enterobacteriaceae (4518)	712 (15.8)	2017 (60.4)	1007 (82.7)	281 (88.9)	128 (91.7)	96 (93.9)	65 (95.3)	46 (96.3)	30 (97.0)	136 (100.0)	0.25	2
MDR (765)	2 (0.3)	87 (11.6)	198 (37.5)	98 (50.3)	81 (60.9)	70 (70.1)	40 (75.3)	32 (79.5)	25 (82.8)	132 (100.0)	1	>32
XDR (114)	0 (0.0)	2 (1.8)	10 (10.5)	5 (14.9)	9 (22.8)	7 (29.0)	7 (35.1)	6 (40.4)	4 (43.9)	64 (>100.0)	>32	>32
PDR (4)	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)	4 (100.0)	>32	>32
CAZ S (3502)	705 (20.1)	1889 (74.1)	742 (95.3)	137 (99.2)	25 (99.9)	3 (>99.9)	1 (100.0)	-	-	-	0.25	0.5
CAZ NS (1016)	7 (0.7)	128 (13.3)	265 (39.4)	144 (53.4)	103 (63.7)	93 (72.8)	64 (79.1)	46 (83.7)	30 (86.6)	136 (100.0)	1	>32
E. coli (2064)	499 (24.2)	1201 (82.4)	249 (94.4)	61 (97.4)	20 (98.4)	8 (98.7)	9 (99.2)	8 (99.6)	4 (99.8)	5(100.0)	0.25	0.5
Non-ESBL-phenotype (1685)	491 (29.1)	1096 (94.2)	93 (99.7)	3 (99.9)	2 (100.0)	-	-	-	-	-	0.25	0.25
ESBL-phenotype (379)	8 (2.1)	105 (29.8)	156 (71.0)	58 (86.3)	18 (91.0)	8 (93.1)	9 (95.5)	8 (97.6)	4 (98.7)	5 (100.0)	0.5	2
K. pneumoniae (794)	96 (12.4)	261 (45.0)	145 (63.2)	66 (71.5)	42 (76.8)	38 (81.6)	11 (83.0)	12 (84.5)	16 (86.5)	107 (100.0)	0.5	>32
Non-ESBL-phenotype (442)	94 (21.7)	234 (74.2)	90 (95.6)	22 (99.6)	2 (100.0)	-	-	-	-	-	0.25	0.5
ESBL-phenotype (352)	2 (0.6)	27 (8.2)	55 (23.9)	44 (36.4)	40 (47.7)	38 (58.5)	11 (61.7)	12 (65.1)	16 (69.6)	107 (100.0)	4	>32
ESBL-phenotype MEM S (268)	2 (0.8)	27 (10.8)	55 (31.3)	44 (47.8)	39 (62.3)	38 (76.5)	11 (80.6)	8 (83.6)	11 (87.7)	33 (100.0)	2	>32
MEM S (710)	96 (13.5)	261 (50.3)	145 (70.7)	66 (80.0)	41 (85.8)	38 (91.1)	11 (92.7)	8 (93.8)	11 (95.4)	33 (100.0)	0.25	4
MEM NS (84)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)	0 (1.2)	0 (1.2)	4 (6.0)	5 (11.9)	74 (100.0)	>32	>32
Klebsiella oxytoca (160)	53 (33.1)	69 (76.3)	21 (89.4)	5 (92.5)	5 (95.6)	4 (98.1)	1 (98.8)	1 (99.4)	0 (99.4)	1 (100.0)	0.25	1
Enterobacter spp. (473)	31 (6.6)	183 (45.2)	108 (68.1)	33 (75.1)	31 (81.6)	28 (87.5)	32 (94.3)	7 (95.8)	7 (97.3)	13 (100.0)	0.5	8
Citrobacter spp. (224)	18 (8.0)	136 (68.8)	28 (81.3)	8 (84.8)	5 (87.1)	6 (89.7)	6 (92.4)	12 (97.8)	1 (98.2)	4 (100.0)	0.25	8
Proteus mirabilis (278)	0 (0.0)	39 (14.0)	203 (87.1)	17 (93.2)	8 (96.0)	3 (97.1)	3 (98.2)	4 (99.6)	1 (100.0)	-	0.5	1
Indole-positive *Proteae* (270)	14 (5.2)	115 (47.8)	103 (85.9)	22 (94.1)	5 (95.9)	3 (97.0)	1 (97.4)	2 (98.2)	1 (98.5)	4 (100.0)	0.5	1
Serratia spp. (255)	1 (0.4)	13 (5.5)	150 (64.3)	69 (91.4)	12 (96.1)	6 (98.4)	2 (99.2)	0 (99.2)	0 (99.2)	2 (100.0)	0.5	1

CAZ S, ceftazidime susceptible; CAZ NS, ceftazidime nonsuscceptible; MEM S, meropenem susceptible; MEM NS, meropenem nonsusceptible.

Table 2. Activity of Ceftolozane/Tazobactam and Comparator Antimicrobial Agents When Tested Against Enterobacteriaceae From European and Israeli Hospitals (2012)

Organism (No. Tested)/ Antimicrobial Agent	MIC (mg/L)		%S/%I/%R	
	50%	90%	CLSI[a]	EUCAST[a]
Enterobacteriaceae (4518)				
Ceftolozane/tazobactam	0.25	2	-/-/-	-/-/-
Ceftazidime	0.25	32	81.9/3.0/15.1	77.5/4.4/18.1
Cefepime	≤0.5	>16	83.3/3.7/13.0	80.8/4.5/14.7
Ceftriaxone	≤0.06	>8	76.1/0.9/23.0	76.1/0.9/23.0
Meropenem	≤0.06	≤0.06	97.5/0.3/2.2	97.8/0.5/1.7
Piperacillin/tazobactam	2	64	87.1/5.1/7.8	82.2/4.9/12.9
Levofloxacin	≤0.12	>4	77.1/2.8/20.1	75.6/1.6/22.8
Gentamicin	≤1	>8	85.5/0.8/13.7	83.8/1.7/14.5
Tigecycline[b]	0.12	1	98.5/1.5/<0.1	93.6/4.9/1.5
Colistin	0.5	>8	-/-/-	79.8/0.0/19.2
MDR (765)				
Ceftolozane/tazobactam	1	>32	-/-/-	-/-/-
Ceftazidime	32	>32	28.8/7.4/63.8	17.0/11.8/71.2
Cefepime	>16	>16	29.9/10.1/60.0	21.1/13.9/65.0
Ceftriaxone	>8	>8	11.9/2.1/86.0	11.9/2.1/86.0
Meropenem	≤0.06	8	85.6/1.4/13.0	87.0/3.0/10.0
Piperacillin/tazobactam	32	>64	48.7/18.8/32.5	29.1/19.6/51.3
Levofloxacin	>4	>4	20.8/9.7/69.5	14.3/6.5/79.2
Gentamicin	>8	>8	41.8/3.5/54.7	35.3/6.5/58.2
Tigecycline[b]	0.5	2	95.4/4.5/0.1	83.1/12.3/4.6
Colistin	0.5	>8	-/-/-	70.2/0.0/29.8
XDR (114)				
Ceftolozane/tazobactam	>32	>32	-/-/-	-/-/-
Ceftazidime	>32	>32	16.7/5.2/78.1	6.1/10.5/83.3
Cefepime	>16	>16	16.7/12.3/71.0	7.9/17.5/74.6
Ceftriaxone	>8	>8	1.8/1.8/96.4	1.8/1.8/96.4
Meropenem	8	>8	43.0/0.0/57.0	43.0/12.3/44.7
Piperacillin/tazobactam	>64	>64	22.8/9.7/67.5	19.3/3.5/77.2
Levofloxacin	>4	>4	10.5/7.0/82.5	4.4/6.1/89.5
Gentamicin	8	>8	45.6/7.0/47.4	26.3/19.3/54.4
Tigecycline[b]	1	4	83.3/15.8/0.9	50.9/32.4/16.7
Colistin	>8	>8	-/-/-	30.7/0.0/69.3
E. coli (2064)				
Ceftolozane/tazobactam	0.25	0.5	-/-/-	-/-/-
Ceftazidime	0.25	8	88.5/2.8/8.7	83.8/4.7/11.5
Cefepime	≤0.5	16	85.4/3.1/11.5	83.0/3.8/13.2
Ceftriaxone	≤0.06	>8	82.2/0.2/17.6	82.2/0.2/17.6
Meropenem	≤0.06	≤0.06	>99.9/0.0/<0.1	>99.9/0.0/0.0
Piperacillin/tazobactam	2	16	92.0/3.7/4.3	87.1/4.9/8.0
Levofloxacin	≤0.12	>4	70.9/1.8/27.3	70.7/0.2/29.1
Gentamicin	≤1	>8	86.1/0.4/13.5	84.9/1.2/13.9
Tigecycline[b]	0.12	0.25	100.0/0.0/0.0	100.0/0.0/0.0
Colistin	0.25	0.5	-/-/-	99.3/0.0/0.7
ESBL-phenotype (379)				
Ceftolozane/tazobactam	0.5	2	-/-/-	-/-/-
Ceftazidime	8	32	37.5/15.0/47.5	11.6/25.9/62.5
Cefepime	>16	>16	21.2/16.1/62.7	10.1/18.2/71.7
Ceftriaxone	>8	>8	3.2/1.0/95.8	3.2/1.0/95.8
Meropenem	≤0.06	≤0.06	99.7/0.0/0.3	99.7/0.3/0.0
Piperacillin/tazobactam	8	>64	74.0/13.5/12.5	54.4/19.6/26.0
Levofloxacin	>4	>4	23.0/1.8/75.2	22.7/0.3/77.0
Gentamicin	2	>8	62.2/0.2/37.6	60.1/2.1/37.8
Tigecycline[b]	0.12	0.25	100.0/0.0/0.0	100.0/0.0/0.0
Colistin	0.25	0.5	-/-/-	99.4/0.0/0.6

Organism (No. Tested)/ Antimicrobial Agent	MIC (mg/L)		%S/%I/%R	
	50%	90%	CLSI[a]	EUCAST[a]
K. pneumoniae (794)				
Ceftolozane/tazobactam	0.5	>32	-/-/-	-/-/-
Ceftazidime	0.5	>32	61.0/4.6/34.4	56.5/4.5/39.0
Cefepime	≤0.5	>16	59.4/6.1/34.5	58.8/3.5/37.7
Ceftriaxone	0.25	>8	57.8/0.9/41.3	57.8/0.9/41.3
Meropenem	≤0.06	8	88.3/1.1/10.6	89.4/1.9/8.7
Piperacillin/tazobactam	8	>64	70.3/7.5/22.2	62.5/7.8/29.7
Levofloxacin	0.25	>4	64.6/6.6/28.8	62.5/2.1/35.4
Gentamicin	≤1	>8	73.4/1.4/25.2	71.9/1.5/26.6
Tigecycline[b]	0.25	1	99.0/1.0/0.0	94.9/4.1/1.0
Colistin	0.5	1	-/-/-	93.0/0/7.0
ESBL-phenotype (352)				
Ceftolozane/tazobactam	4	>32	-/-/-	-/-/-
Ceftazidime	32	>32	11.9/10.5/77.6	2.0/9.9/88.1
Cefepime	>16	>16	8.5/13.7/77.8	7.1/8.0/84.9
Ceftriaxone	>8	>8	4.8/2.0/93.2	4.8/2.0/93.2
Meropenem	≤0.06	>8	74.1/2.0/23.9	76.1/4.3/19.6
Piperacillin/tazobactam	64	>64	38.6/15.0/46.4	27.4/11.2/61.4
Levofloxacin	>4	>4	32.2/11.7/56.1	27.9/4.3/67.8
Gentamicin	>8	>8	43.2/2.5/54.3	39.8/3.4/56.8
Tigecycline[b]	0.5	1	98.3/1.7/0.0	93.1/5.2/1.7
Colistin	0.5	8	-/-/-	87.1/0/12.9
K. oxytoca (160)				
Ceftolozane/tazobactam	0.25	1	-/-/-	-/-/-
Ceftazidime	0.12	0.5	97.5/0.6/1.9	93.8/3.7/2.5
Cefepime	≤0.5	1	95.0/3.7/1.3	91.3/6.2/2.5
Ceftriaxone	≤0.06	8	85.6/0.6/13.8	85.6/0.6/13.8
Meropenem	≤0.06	≤0.06	99.4/0.6/0.0	100.0/0/0.0
Piperacillin/tazobactam	2	>64	85.5/1.3/13.2	84.3/1.2/14.5
Levofloxacin	≤0.12	0.5	96.9/0/3.1	94.4/2.5/3.1
Gentamicin	≤1	≤1	97.5/0/2.5	97.5/0/2.5
Tigecycline[b]	0.12	0.25	99.4/0.6/0.0	98.8/0.6/0.6
Colistin	0.25	0.5	-/-/-	99.4/0/0.6
Enterobacter spp.[c] (473)				
Ceftolozane/tazobactam	0.5	8	-/-/-	-/-/-
Ceftazidime	0.5	>32	67.0/3.8/29.2	63.6/3.4/33.0
Cefepime	≤0.5	4	86.0/5.3/8.7	80.9/9.1/10.0
Ceftriaxone	0.5	>8	63.1/2.3/34.6	63.1/2.3/34.6
Meropenem	≤0.06	0.12	97.3/0.4/2.3	97.7/1.2/1.1
Piperacillin/tazobactam	4	64	79.0/12.5/8.5	72.2/6.8/21.0
Levofloxacin	≤0.12	1	91.3/2.1/6.6	90.0/1.3/8.7
Gentamicin	≤1	>8	88.8/1.0/10.2	87.5/1.3/11.2
Tigecycline[b]	0.25	0.5	98.9/1.1/0.0	96.6/2.3/1.1
Colistin	0.5	4	-/-/-	89.4/0/10.6

Organism (No. Tested)/ Antimicrobial Agent	MIC (mg/L)		%S/%I/%R	
	50%	90%	CLSI[a]	EUCAST[a]
Citrobacter spp.[d] (224)				
Ceftolozane/tazobactam	0.25	8	-/-/-	-/-/-
Ceftazidime	0.25	>32	80.8/1.8/17.4	77.7/3.1/19.2
Cefepime	≤0.5	1	96.0/1.3/2.7	92.0/4.9/3.1
Ceftriaxone	0.12	>8	79.8/0.5/19.7	79.8/0.5/19.7
Meropenem	≤0.06	≤0.06	99.6/0/0.4	99.6/0/0.4
Piperacillin/tazobactam	2	64	86.2/5.8/8.0	79.9/6.3/13.8
Levofloxacin	≤0.12	0.5	92.0/3.1/4.9	91.5/0.5/8.0
Gentamicin	≤1	≤1	94.6/0.5/4.9	94.2/0.4/5.4
Tigecycline[b]	0.12	0.25	100.0/0.0/0.0	99.6/0.4/0.0
Colistin	0.25	1	-/-/-	99.6/0/0.4
P. mirabilis (278)				
Ceftolozane/tazobactam	0.5	1	-/-/-	-/-/-
Ceftazidime	0.06	4	92.8/1.4/5.8	87.8/5.0/7.2
Cefepime	≤0.5	2	92.1/3.9/4.0	88.5/6.8/4.7
Ceftriaxone	≤0.06	8	86.0/1.8/12.2	86.0/1.8/12.2
Meropenem	≤0.06	0.12	100.0/0.0/0.0	100.0/0.0/0.0
Piperacillin/tazobactam	≤0.5	2	98.9/1.1/0.0	98.2/0.7/1.1
Levofloxacin	≤0.12	>4	84.2/2.1/13.7	77.3/6.9/15.8
Gentamicin	≤1	>8	81.9/1.5/16.6	78.0/3.9/18.1
Tigecycline[b]	2	4	82.4/17.6/0.0	34.9/47.5/17.6
Colistin	>8	>8	-/-/-	0.0/0.0/100.0
Indole-positive *Proteae*[e] (270)				
Ceftolozane/tazobactam	0.5	1	-/-/-	-/-/-
Ceftazidime	0.06	8	87.1/4.2/8.7	83.3/3.8/12.9
Cefepime	≤0.5	≤0.5	95.9/1.5/2.6	94.8/1.5/3.7
Ceftriaxone	≤0.06	4	81.0/3.0/16.0	81.0/3.0/16.0
Meropenem	≤0.06	0.12	100.0/0/0.0	100.0/0.0/0.0
Piperacillin/tazobactam	≤0.5	2	97.0/2.3/0.7	96.7/0.3/3.0
Levofloxacin	≤0.12	4	87.8/4.4/7.8	82.6/5.2/12.2
Gentamicin	≤1	8	89.2/1.9/8.9	83.6/5.6/10.8
Tigecycline[b]	0.5	2	98.1/1.5/0.4	87.8/10.3/1.9
Colistin	>8	>8	-/-/-	0.0/0.0/100.0
Serratia spp.[f] (255)				
Ceftolozane/tazobactam	0.5	1	-/-/-	-/-/-
Ceftazidime	0.12	1	97.2/0.4/2.4	92.5/4.7/2.8
Cefepime	≤0.5	1	94.5/1.9/3.6	92.1/3.9/4.0
Ceftriaxone	0.25	>8	83.1/1.2/15.7	83.1/1.2/15.7
Meropenem	≤0.06	≤0.06	99.2/0/0.8	99.2/0.4/0.4
Piperacillin/tazobactam	2	16	92.5/4.0/3.5	89.8/2.7/7.5
Levofloxacin	≤0.12	1	95.7/0.7/3.6	93.7/2.0/4.3
Gentamicin	≤1	2	95.7/0.4/3.9	93.3/2.4/4.3
Tigecycline[b]	0.5	1	100.0/0/0.0	94.5/5.5/0.0
Colistin	>8	>8	-/-/-	6.3/0.0/93.7

[a]Criteria as published by the CLSI (2014) and EUCAST (2014).

[b]In the absence of CLSI breakpoint, US Food and Drug Administration breakpoints were applied when available (Tygacil [product insert]. Pfizer Inc, 2012).

[c]Includes: *Enterobacter aerogenes* (122 strains), *Enterobacter asburiae* (1 strain), *Enterobacter cloacae* (350 strains).

[d]Includes: *Citrobacter braakii* (10 strains), unspeciated *Citrobacter* (9 strains), *Citrobacter freundii* (112 strains), *Citrobacter farmeri* (2 strains), *Citrobacter koseri* (90 strains), *Citrobacter youngae* (1 strain).

[e]Includes: *Morganella morganii* (169 strains), *Proteus vulgaris* (69 strains), *Providencia rettgeri* (11 strains), *Providencia stuartii* (21 strains).

[f]Includes: *Serratia liquefaciens* (11 strains), *Serratia marcescens* (244 strains).

- Ceftolozane/tazobactam showed good activity against *Enterobacter* spp. ($MIC_{50/90}$, 0.5/8 mg/L; inhibited 87.5% and 94.3% of strains at MIC of ≤4 and ≤8 mg/L, respectively). Ceftolozane/tazobactam also demonstrated good activity against *K. oxytoca* ($MIC_{50/90}$, 0.25/1 mg/L), *Citrobacter* spp. ($MIC_{50/90}$, 0.25/8 mg/L), *P. mirabilis* ($MIC_{50/90}$, 0.5/1 mg/L), indole-positive *Proteae* ($MIC_{50/90}$, 0.5/1 mg/L), and *Serratia* spp. ($MIC_{50/90}$, 0.5/1 mg/L; **Table 1**).
- Ceftolozane/tazobactam ($MIC_{50/90}$, 0.25/1 mg/L) demonstrated the same potency as ceftazidime against ceftazidime-susceptible isolates but remained active against most ceftazidime-nonsuscceptible strains and inhibited 95.3% of all isolates, and >90% of isolates in 10 countries, at MIC of ≤8 mg/L (**Tables 1** and **3**).
- Resistance (by EUCAST criteria) to ceftazidime was extremely high (>60% nonsuscceptible isolates) in Poland, Russia, and Ukraine, and ceftolozane/tazobactam showed lower activity against Enterobacteriaceae from these countries as well (**Table 3**).
- Susceptibility to meropenem was high overall (97.8%) and >95% in most countries, but lower in Poland (74.7%), Italy (90.4%), and Israel (91.7%; **Table 3**).
- The overall MDR rate was 16.9% and varied widely, ranging from 3.0% in Sweden to 59.6% in Ukraine. The overall XDR rate was 2.4% and also varied widely ranging from 0.0% in the UK, Sweden and Belgium to 18.4% in Poland. Four PDR isolates were found (all *K. pneumoniae* from 2 medical centres in Italy).

Table 3. Antimicrobial Activity of Ceftolozane/Tazobactam, Ceftazidime, and Meropenem Against Enterobacteriaceae Strains Stratified by Country and MDR Status (2012)

Country (No. Tested)	Ceftolozane/ Tazobactam $MIC_{50/90}$ (% at ≤8 mg/L)	Ceftazidime $MIC_{50/90}$ (% at ≤1 mg/L)[a]	Meropenem $MIC_{50/90}$ (% at ≤2 mg/L)[a]	%MDR/%XDR/ %PDR[b]
Belgium (151)	0.25/1 (98.0)	0.25/16 (70.9)	≤0.06/≤0.06 (100.0)	20.5/0.0/0.0
France (669)	0.25/1 (98.5)	0.12/16 (83.9)	≤0.06/≤0.06 (99.9)	11.2/1.1/0.0
Germany (499)	0.25/1 (98.2)	0.12/8 (85.4)	≤0.06/≤0.06 (100.0)	10.2/0.6/0.0
Greece (208)	0.25/4 (92.3)	0.12/16 (78.9)	≤0.06/0.12 (95.7)	15.4/4.3/0.0
Ireland (415)	0.25/1 (99.0)	0.25/8 (76.9)	≤0.06/≤0.06 (100.0)	14.5/0.5/0.0
Israel (36)	0.5/>32 (86.1)	0.25/>32 (66.7)	≤0.06/1 (91.7)	25.0/8.3/0.0
Italy (550)	0.25/>32 (87.6)	0.25/>32 (70.2)	≤0.06/0.5 (90.4)	27.3/7.8/0.7
Poland (87)	1/>32 (64.4)	16/>32 (39.1)	≤0.06/>8 (74.7)	50.6/18.4/0.0
Portugal (177)	0.25/2 (96.1)	0.25/32 (71.8)	≤0.06/≤0.06 (100.0)	22.6/1.7/0.0
Russia (139)	1/>32 (82.7)	8/>32 (33.1)	≤0.06/0.25 (99.3)	56.1/6.5/0.0
Spain (517)	0.25/0.5 (99.0)	0.25/2 (89.4)	≤0.06/≤0.06 (100.0)	7.9/0.6/0.0
Sweden (300)	0.25/0.5 (100.0)	0.12/0.5 (94.0)	≤0.06/≤0.06 (100.0)	3.0/0.0/0.0
Turkey (332)	0.25/4 (94.0)	0.25/32 (67.5)	≤0.06/0.12 (97.0)	24.7/1.5/0.0
UK (386)	0.25/0.5 (99.2)	0.12/8 (84.5)	≤0.06/≤0.06 (100.0)	8.3/0.0/0.0
Ukraine (52)	1/32 (86.5)	16/>32 (26.9)	≤0.06/0.12 (98.1)	59.6/13.5/0.0
Overall (4518)	0.25/1 (95.3)	0.25/32 (77.5)	≤0.06/≤0.06 (97.8)	16.9/2.4/0.1

[a]Susceptible breakpoint established by EUCAST (2014).

[b]MDR, XDR, and PDR bacteria were classified according to Magiorakos AP, et al. *Clin Microbiol Infect.* 2012;18: 268-281.

CONCLUSIONS

- Antimicrobial susceptibility, MDR, and XDR of Enterobacteriaceae varied widely among EU countries. MDR, XDR, and resistance rates to ceftazidime were generally elevated and particularly high in some Eastern EU nations.
- At an MIC of ≤8 mg/L, ceftolozane/tazobactam provides greater coverage than β-lactams (except for carbapenems) currently available for treatment of Enterobacteriaceae infections and could represent a valuable addition to treatment options for this pathogen.

SELECTED REFERENCES

Clinical and Laboratory Standards Institute. 2012. *Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; Approved standard, 9th ed.* CLSI document M7-A9. CLSI, Wayne, PA.

Clinical and Laboratory Standards Institute. 2014. *Performance standards for antimicrobial susceptibility testing: 24th informational supplement.* CLSI document M100-S24. CLSI, Wayne, PA.

European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters. Version 4.0, January 2014. Available at: http://www.eucast.org/clinical_breakpoints/. Accessed January 1, 2014.

Farrell DJ, et al. *Antimicrob Agents Chemother* 2013;57:6305-6310.

Giske CG, et al. *J Antimicrob Chemother* 2009;64:430-431.

Livermore DM, et al. *J Antimicrob Chemother* 2010;65:1972-1974.

Livermore DM, et al. *Int J Antimicrob Agents* 2009;34:402-406.

Magiorakos AP, et al. *Clin Microbiol Infect* 2012;18:268-281.

Sader HS, et al. *Antimicrob Agents Chemother* 2011;55:2390-2394.

This study was funded in part by educational/research grants from Cubist.

Presented at the 24th European Congress of Clinical Microbiology and Infectious Diseases

May 10-13, 2014, Barcelona, Spain