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Antimicrobial Activity of Ceftolozane/Tazobactam and Comparator Agents Tested Against Enterobacteriaceae Isolates From 15 European Countries and Israel (2013)

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AMENDED ABSTRACT

OBJECTIVE: To evaluate the activity of ceftolozane/tazobactam, ceftazidime, meropenem, and other comparator agents against Enterobacteriaceae isolates from 15 European (EU) countries and Israel. Ceftolozane is a novel oxyimino-aminothiazolyl cephalosporin with potent anti-pseudomonal activity. The addition of tazobactam broadens coverage to include most extended-spectrum β-lactamase-producing Enterobacteriaceae. Ceftolozane/tazobactam is currently in clinical development in patients with ventilator-associated bacterial pneumonia, and recently approved for complicated intra-abdominal infections (in combination with metronidazole) and complicated urinary tract infections in the USA.

METHODS: A total of 4875 Enterobacteriaceae isolates were consecutively collected in 2013 from 34 medical centers located in 15 EU countries, including Russia, Turkey, and Ukraine, plus Israel. Susceptibility testing was performed by CLSI broth microdilution methods and MIC interpretations for comparator agents were as published by EUCAST and CLSI. Ceftolozane/tazobactam was tested at a fixed 4 mg/L concentration of tazobactam.

RESULTS: The number of isolates per country varied from 41 in Ukraine to 838 in Germany. Ceftolozane/tazobactam ($MIC_{50/90}$ 0.25/2 mg/L) demonstrated similar potency as ceftazidime ($MIC_{50/90}$ 0.25/32 mg/L) against ceftazidime-susceptible isolates but remained active against most ceftazidime-nonsusceptible strains and inhibited 91.7% of all isolates, and >90% of isolates in 12 countries, at MIC of ≤2 mg/L. In contrast, ceftazidime susceptibility was 78.0% overall and >90% only in Sweden (94.8%). Nonsusceptibility (by EUCAST criteria) to ceftazidime was very high (>50%) in Poland and Russia, and ceftolozane/tazobactam also showed lower activity against Enterobacteriaceae from these countries. Susceptibility to meropenem was high overall (97.4%) and >95% in 13/16 countries, but lower in Poland (75.3%), Italy (90.8%), and Greece (93.1%). Overall susceptibility rates (by EUCAST criteria) to piperacillin/tazobactam, cefepime, ciprofloxacin, and gentamicin were 81.8, 81.7, 71.8, and 86.1%, respectively, below ceftolozane/tazobactam at ≤2/≤4 mg/L (91.7/93.4%). The overall MDR rate was 15.7% and varied widely ranging from 3.0% in Sweden to 50.0% in Poland. The overall XDR rate was 2.8% and also varied widely ranging from 0.0% in Sweden to 31.3% in Poland. Two PDR isolates were found (both *Klebsiella pneumoniae* from Italy and Turkey).

CONCLUSION: In 2013, antimicrobial susceptibility of MDR and XDR Enterobacteriaceae varied widely among EU countries. MDR, XDR resistance rates to ceftazidime were generally elevated and particularly high in some Eastern EU nations. At MIC values of ≤2 and ≤4 mg/L, ceftolozane/tazobactam had higher susceptibility rates than β-lactams (except for carbapenems) currently available for treatment of infections caused by Enterobacteriaceae and could represent a valuable treatment addition for these pathogens.

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 ESBL-producing Enterobacteriaceae and some AmpC-derepressed Enterobacteriaceae.
- Ceftolozane/tazobactam has recently been approved by the United States Food and Drug Administration (FDA) for the treatment of complicated urinary tract infections (cUTI), and in combination with metronidazole for the treatment of complicated intra-abdominal infections (cIAI). A Phase 3 trial for the treatment of nosocomial pneumonia (NP) is underway.
- We evaluated the in vitro activities of ceftolozane/tazobactam, ceftazidime, piperacillin/tazobactam, meropenem, and other comparator agents when tested against clinical Enterobacteriaceae isolates collected from hospitals in Europe (EU) and Israel during 2013.

MATERIALS AND METHODS

Organism Collection

- A total of 4875 clinically significant, consecutively collected, nonduplicate isolates of Enterobacteriaceae were evaluated from the following infection types: pneumonia in hospitalized patients, bloodstream infections, acute bacterial skin and skin structure infections, intra-abdominal infections among hospitalized patients, and patients with urinary tract infections. The isolates were collected in 2013 from 34 medical centers located in 15 EU countries, including Turkey, Russia, and Ukraine, plus Israel.

Susceptibility Testing

- Broth microdilution was conducted according to the methodology of the Clinical and Laboratory Standards Institute (CLSI) to determine antimicrobial susceptibility of ceftolozane with tazobactam at a fixed concentration of 4 mg/L and several 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 = 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-S25 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 91.7% and 93.4% of 4875 Enterobacteriaceae at ≤2 and ≤4 mg/L, respectively (**Table 1**). Meropenem was the most active agent ($MIC_{50/90}$ ≤0.06/≤0.06 mg/L; 97.3%[CLSI]/97.4%[EUCAST] susceptible) followed by tigecycline (98.6% [FDA breakpoint], 94.9% [EUCAST]). Susceptibility rates for other agents (CLSI/EUCAST) were lower; ceftazidime (82.2%/78.0%), cefepime (83.7%/81.7%), ceftriaxone (76.6%), piperacillin/tazobactam (86.2%/81.8%), levofloxacin (77.8%/75.8%), and gentamicin (87.5%/86.1%). Colistin susceptibility (EUCAST criteria) was 80.4% (**Table 2**).
- 767 (15.7%) of the Enterobacteriaceae were MDR. Ceftolozane/tazobactam retained activity ($MIC_{50/90}$ 1/>32 mg/L) against 60.4% and 66.0% of strains at ≤2 and ≤4 mg/L, respectively (**Table 1**).
- 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, against the MDR strains (**Table 2**). Meropenem was the most potent ($MIC_{50/90}$ ≤0.06/8 mg/L; 83.5% susceptible by EUCAST) agent against the MDR subset followed by tigecycline ($MIC_{50/90}$ 0.5/2 mg/L; 82.9% susceptible by EUCAST). Colistin susceptibility was 69.8% against the MDR subset (**Table 2**).
- Overall, 136 (2.8%) of Enterobacteriaceae were classified as XDR and 2 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 10.3% (tigecycline) to 97.8% (ceftriaxone) against XDR strains (**Table 2**).
- Ceftolozane/tazobactam demonstrated potent activity against 2184 *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; 98.5 and 99.0% inhibited at ≤2 and ≤4 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; 44.9 and 51.1% inhibited at ≤2 and ≤4 mg/L, respectively); however, in general, it was inactive against meropenem-nonsusceptible *K. pneumoniae* ($MIC_{50/90}$ >32/>32 mg/L; **Table 1**). Tigecycline ($MIC_{50/90}$ 0.5/1 mg/L; 93.8% susceptible [EUCAST]) and colistin ($MIC_{50/90}$ 0.5/>8 mg/L; 83.3% susceptible [EUCAST]) exhibited the highest in vitro activity against ESBL-phenotype *K. pneumoniae* (**Table 2**).
- Ceftolozane/tazobactam showed good activity against *Enterobacter* spp. ($MIC_{50/90}$, 0.5/8 mg/L; inhibited 81.8 and 86.7% of strains at MIC of ≤2 and ≤4 mg/L, respectively). Ceftolozane/tazobactam also demonstrated good activity against *Klebsiella oxytoca* ($MIC_{50/90}$, 0.25/1 mg/L), *Citrobacter* spp. ($MIC_{50/90}$, 0.25/8 mg/L), *Proteus mirabilis* ($MIC_{50/90}$, 0.5/1 mg/L), indole-positive *Proteae* ($MIC_{50/90}$, 0.5/1 mg/L) and *Serratia* spp. ($MIC_{50/90}$, 0.5/2 mg/L; **Table 1**).
- Resistance (by EUCAST criteria) to ceftazidime was very high (>50% nonsusceptible isolates) in Poland and Russia, and ceftolozane/tazobactam showed lower activity against Enterobacteriaceae from these countries as well (**Table 3**).
- Susceptibility to meropenem was high overall (97.4%) and >95% in most countries, but lower in Poland (75.3%), Italy (90.8%), and Greece (93.1%; **Table 3**).
- The overall MDR rate was 15.7% and varied widely, ranging from 3.0% in Sweden to 50.0% in Poland. The overall XDR rate was 2.8% and also varied widely, ranging from 0.0% in Sweden to 31.3% in Poland. Two PDR isolates were found (both *K. pneumoniae* from Italy and Turkey).

RESULTS (cont'd)

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

Organism/Resistant Subset (No. Tested)	Number of Isolates (Cumulative %) Inhibited at Ceftolozane/Tazobactam MIC (mg/L) of:										MIC_{50}	MIC_{90}
	≤0.12	0.25	0.5	1	2	4	8	16	32	>32		
All Enterobacteriaceae (4875)	877 (18.0)	2079 (60.6)	1030 (81.8)	339 (88.7)	147 (91.7)	82 (93.4)	74 (94.9)	50 (96.0)	44 (96.9)	153 (100.0)	0.25	2
MDR (767)	3 (0.4)	77 (10.4)	189 (35.1)	115 (50.1)	79 (60.4)	43 (66.0)	46 (72.0)	30 (75.9)	37 (80.7)	148 (100.0)	1	>32
XDR (136)	0 (0.0)	0 (0.0)	3 (2.2)	12 (11.0)	10 (18.4)	8 (24.3)	9 (30.9)	4 (33.8)	10 (41.2)	80 (100.0)	>32	>32
PDR (2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (50.0)	0 (50.0)	0 (50.0)	0 (50.0)	0 (50.0)	2 (100.0)	>32	
CAZ-S (4005)	876 (21.9)	1999 (71.8)	855 (93.1)	209 (98.4)	52 (99.7)	9 (99.9)	4 (>99.9)	0 (>99.9)	1 (100.0)		0.25	0.5
CAZ-NS (870)	1 (0.1)	80 (9.3)	175 (29.4)	130 (44.4)	95 (55.3)	73 (63.7)	70 (71.7)	50 (77.5)	43 (82.4)	153 (100.0)	2	>32
E. coli (2184)	658 (30.1)	1120 (81.4)	259 (93.3)	85 (97.2)	30 (98.5)	11 (99.0)	7 (99.4)	3 (99.5)	4 (99.7)	7 (100.0)	0.25	0.5
non-ESBL-phenotype (1778)	654 (36.8)	1009 (93.5)	112 (99.8)	2 (99.9)	1 (100.0)						0.25	0.25
ESBL-phenotype (406)	4 (1.0)	111 (28.3)	147 (64.5)	83 (85.0)	29 (92.1)	11 (94.8)	7 (96.6)	3 (97.3)	4 (98.3)	7 (100.0)	0.5	2
K. pneumoniae (874)	91 (10.4)	317 (46.7)	155 (64.4)	73 (72.8)	33 (76.5)	23 (79.2)	12 (80.6)	13 (82.0)	29 (85.4)	128 (100.0)	0.5	>32
non-ESBL-phenotype (502)	89 (17.7)	294 (76.3)	97 (95.6)	20 (99.6)	2 (100.0)						0.25	0.5
ESBL-phenotype (372)	2 (0.5)	23 (6.7)	58 (22.3)	53 (36.6)	31 (44.9)	23 (51.1)	12 (54.3)	13 (57.8)	29 (65.6)	128 (100.0)	4	>32
ESBL-phenotype-MEM-S (245)	2 (0.8)	23 (10.2)	58 (33.9)	53 (55.5)	31 (68.2)	22 (77.1)	11 (81.6)	10 (85.7)	12 (90.6)	23 (100.0)	1	32
MEM-S (747)	91 (12.2)	317 (54.6)	155 (75.4)	73 (85.1)	33 (89.6)	22 (92.5)	11 (94.0)	10 (95.3)	12 (96.9)	23 (100.0)	0.25	4
MEM-NS (122)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	1 (1.6)	0 (1.6)	17 (15.6)	103 (100.0)	>32	>32
K. oxytoca (188)	69 (36.7)	67 (72.3)	26 (86.2)	9 (91.0)	8 (95.2)	4 (97.3)	2 (98.4)	2 (99.5)	0 (99.5)	1 (100.0)	0.25	1
Enterobacter spp. (565)	22 (3.9)	230 (44.6)	118 (65.5)	52 (74.7)	40 (81.8)	28 (86.7)	34 (92.7)	25 (97.2)	8 (98.6)	8 (100.0)	0.5	8
Citrobacter spp. (219)	22 (10.0)	131 (69.9)	28 (82.7)	7 (85.8)	3 (87.2)	6 (90.0)	12 (95.4)	6 (98.2)	1 (98.6)	3 (100.0)	0.25	8
Proteus mirabilis (309)	0 (0.0)	72 (23.3)	203 (89.0)	14 (93.5)	7 (95.8)	7 (98.1)	5 (99.7)	0 (99.7)	0 (99.7)	1 (100.0)	0.5	1
Indole-positive *Proteae* (287)	14 (4.9)	130 (50.2)	98 (84.3)	32 (95.5)	4 (96.9)	2 (97.6)	0 (97.6)	1 (97.9)	2 (98.6)	4 (100.0)	0.25	1
Serratia spp. (242)	0 (0.0)	9 (3.7)	141 (62.0)	66 (89.3)	22 (98.4)	1 (98.8)	2 (99.6)	0 (99.6)	0 (99.6)	1 (100.0)	0.5	2

Abbreviations: MDR, multidrug-resistant; XDR, extensively drug-resistant; PDR, pandrug-resistant; CAZ-S, ceftazidime-susceptible; CAZ-NS, ceftazidime-nonsusceptible; CAZ-R, ceftazidime-resistant; MEM-S, meropenem-susceptible; MEM-NS, meropenem-nonsusceptible.

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

Organism (No. Tested)/ Antimicrobial Agent	MIC (mg/L)		%S/%I/%R	
	50%	90%	CLSI[a]	EUCAST[a]
Enterobacteriaceae (4875)				
Ceftolozane/tazobactam	0.25	2	91.7/1.7/6.6[b]	-/-/-
Ceftazidime	0.25	32	82.2/2.4/15.4	78.0/4.2/17.8
Cefepime	≤0.5	>16	83.7/3.9/12.4	81.7/3.8/14.5
Ceftriaxone	≤0.06	>8	76.6/1.1/22.3	76.6/1.1/22.3
Meropenem	≤0.06	≤0.06	97.3/0.1/2.6	97.4/0.6/2.0
Piperacillin/tazobactam	2	64	86.2/5.2/8.6	81.8/4.4/13.8
Levofloxacin	≤0.12	>4	77.8/2.3/19.9	75.8/2.0/22.2
Gentamicin	≤1	>8	87.5/0.6/11.9	86.1/1.4/12.5
Tigecycline[b]	0.25	1	98.6/1.3/0.1	94.9/3.7/1.4
Colistin	0.5	>8	-/-/-	80.4/0.0/19.6
MDR (767)				
Ceftolozane/tazobactam	1	>32	60.4/5.6/34.0[b]	-/-/-
Ceftazidime	32	>32	28.8/6.7/64.5	18.0/10.8/71.2
Cefepime	>16	>16	29.9/11.2/58.9	23.6/11.0/65.4
Ceftriaxone	>8	>8	13.1/2.6/84.3	13.1/2.6/84.3
Meropenem	≤0.06	8	83.1/0.4/16.5	83.5/3.8/12.7
Piperacillin/tazobactam	32	>64	46.3/17.6/36.1	29.2/17.1/53.7
Levofloxacin	>4	>4	21.7/7.8/70.5	14.2/7.4/78.3
Gentamicin	>8	>8	44.4/2.9/52.7	38.2/6.3/55.6
Tigecycline[b]	0.5	2	94.9/4.8/0.3	82.9/12.0/5.1
Colistin	0.5	>8	-/-/-	69.8/0.0/30.2
XDR (136)				
Ceftolozane/tazobactam	>32	>32	18.4/5.9/75.7[b]	-/-/-
Ceftazidime	>32	>32	10.3/2.9/86.8	5.2/5.2/89.6
Cefepime	>16	>16	13.2/8.1/78.7	5.9/10.3/83.8
Ceftriaxone	>8	>8	0.7/1.5/97.8	0.7/1.5/97.8
Meropenem	4	>8	42.1/0.8/57.1	42.9/16.5/40.6
Piperacillin/tazobactam	>64	>64	19.1/13.2/67.7	16.2/2.9/80.9
Levofloxacin	>4	>4	2.9/3.7/93.4	0.7/2.2/97.1
Gentamicin	>8	>8	34.6/4.4/61.0	16.2/18.4/65.4
Tigecycline[b]	1	4	89.7/10.3/0.0	60.3/29.4/10.3
Colistin	>8	>8	-/-/-	36.0/0.0/64.0
Escherichia coli (2184)				
Ceftolozane/tazobactam	0.25	0.5	98.5/0.5/1.0[b]	-/-/-
Ceftazidime	0.25	8	88.1/2.3/9.6	83.3/4.8/11.9
Cefepime	≤0.5	16	85.0/3.8/11.2	83.3/3.4/13.3
Ceftriaxone	≤0.06	>8	81.9/0.2/17.9	81.9/0.2/17.9
Meropenem	≤0.06	≤0.06	100.0/0.0/0.0	100.0/0.0/0.0
Piperacillin/tazobactam	2	16	92.0/3.6/4.4	87.6/4.4/8.0
Levofloxacin	≤0.12	>4	70.5/2.0/27.5	70.2/0.3/29.5
Gentamicin	≤1	>8	88.6/0.4/11.0	88.0/0.6/11.4
Tigecycline[b]	0.12	0.25	100.0/0.0/0.0	100.0/0.0/0.0
Colistin	0.5	0.5	-/-/-	99.6/0.0/0.4

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

Organism (No. Tested)/ Antimicrobial Agent	MIC (mg/L)		%S/%I/%R	
	50%	90%	CLSI[a]	EUCAST[a]
ESBL-phenotype (406)				
Ceftolozane/tazobactam	0.5	2	92.1/2.7/5.2[b]	-/-/-
Ceftazidime	16	>32	36.2/12.3/51.5	10.1/26.1/63.8
Cefepime	>16	>16	20.7/19.3/60.0	13.3/15.8/70.9
Ceftriaxone	>8	>8	2.7/1.2/96.1	2.7/1.2/96.1
Meropenem	≤0.06	≤0.06	100.0/0.0/0.0	100.0/0.0/0.0
Piperacillin/tazobactam	8	>64	78.1/11.1/10.8	62.8/15.3/21.9
Levofloxacin	>4	>4	22.4/2.2/75.4	22.2/0.2/77.6
Gentamicin	≤1	>8	64.2/0.2/35.6	63.7/0.5/35.8
Tigecycline[b]	0.12	0.25	100.0/0.0/0.0	100.0/0.0/0.0
Colistin	0.5	0.5	-/-/-	99.8/0.0/0.2
Klebsiella pneumoniae (874)				
Ceftolozane/tazobactam	0.5	>32	76.5/2.7/20.8[b]	-/-/-
Ceftazidime	0.25	>32	61.8/4.4/33.8	58.4/3.4/38.2
Cefepime	≤0.5	>16	61.9/4.8/33.3	60.4/3.4/36.2
Ceftriaxone	0.12	>8	60.1/0.5/39.4	60.1/0.5/39.4
Meropenem	≤0.06	>8	86.0/0.3/13.7	86.3/3.0/10.7
Piperacillin/tazobactam	4	>64	68.6/6.1/25.3	61.6/7.0/31.4
Levofloxacin	≤0.12	>4	69.7/3.0/27.3	67.4/2.3/30.3
Gentamicin	≤1	>8	76.5/0.5/23.0	74.6/1.9/23.5
Tigecycline[b]	0.25	1	99.0/0.9/0.1	95.8/3.2/1.0
Colistin	0.5	1	-/-/-	92.1/0/7.9
ESBL-phenotype (372; includes 122 meropenem nonsusceptible isolates)				
Ceftolozane/tazobactam	4	>32	44.9/6.2/48.9[b]	-/-/-
Ceftazidime	>32	>32	10.2/10.5/79.3	2.2/8.0/89.8
Cefepime	>16	>16	11.0/11.0/78.0	7.5/8.1/84.4
Ceftriaxone	>8	>8	6.2/1.3/92.5	6.2/1.3/92.5
Meropenem	≤0.06	>8	66.8/0.8/32.4	67.6/7.1/25.3
Piperacillin/tazobactam	>64	>64	33.2/10.9/55.9	21.9/11.3/66.8
Levofloxacin	>4	>4	35.8/4.9/59.3	32.5/3.3/64.2
Gentamicin	>8	>8	47.2/1.0/51.8	42.6/4.6/52.8
Tigecycline[b]	0.5	1	99.2/0.5/0.3	93.8/5.4/0.8
Colistin	0.5	>8	-/-/-	83.3/0.0/16.7
Klebsiella oxytoca (188)				
Ceftolozane/tazobactam	0.25	1	95.2/2.1/2.7[b]	-/-/-
Ceftazidime	0.12	1	96.3/0.0/3.7	93.6/2.7/3.7
Cefepime	≤0.5	1	95.2/3.7/1.1	91.0/5.8/3.2
Ceftriaxone	≤0.06	8	83.0/2.1/14.9	83.0/2.1/14.9
Meropenem	≤0.06	≤0.06	100.0/0.0/0.0	100.0/0.0/0.0
Piperacillin/tazobactam	2	>64	82.7/1.1/16.2	82.7/0.0/17.3
Levofloxacin	≤0.12	0.5	94.7/2.1/3.2	92.0/2.7/5.3
Gentamicin	≤1	≤1	98.4/0.5/1.1	98./0.0/1.6
Tigecycline[b]	0.12	0.5	100.0/0.0/0.0	98.5/0.5/0.0
Colistin	0.5	0.5	-/-/-	98.9/0.0/1.1

[a]Criteria as published by the CLSI [2015] and EUCAST [2015].
[b]In the absence of CLSI breakpoint, USA-FDA breakpoints were applied when available [Zerbaxa Product Insert, 2014; Tygacil Product Insert, 2012].
[c]"-/-/-" breakpoint not available.

Table 3. Antimicrobial Activity of Ceftolozane/Tazobactam, Ceftazidime, and Meropenem Against Enterobacteriaceae Strains Stratified by Country and MDR Status (2013)

Country (No. Tested)	Ceftolozane/Tazobactam	Ceftazidime	Meropenem	%MDR/%XDR/ %PDR[b]
	$MIC_{50/90}$ (% at ≤2/4/≤4/4 mg/L)	$MIC_{50/90}$ (% at ≤1 mg/L)[a]	$MIC_{50/90}$ (% at ≤2 mg/L)[a]	
Belgium (156)	0.25/2 (91.0/94.9)	0.25/32 (76.9)	≤0.06/≤0.06 (98.1)	11.5/1.3/0.0
Czech Republic (66)	0.25/2 (93.9/93.9)	0.12/32 (77.3)	≤0.06/≤0.06 (100.0)	16.7/1.5/0.0
France (317)	0.25/1 (94.3/96.5)	0.12/16 (83.0)	≤0.06/≤0.06 (99.7)	10.7/1.9/0.0
Germany (838)	0.25/1 (93.6/95.1)	0.12/16 (83.3)	≤0.06/≤0.06 (99.5)	10.6/0.8/0.0
Greece (144)	0.25/8 (88.9/89.6)	0.25/>32 (75.7)	≤0.06/0.12 (93.1)	20.1/4.2/0.0
Ireland (379)	0.25/1 (95.0/96.3)	0.25/16 (77.0)	≤0.06/≤0.06 (100.0)	14.5/0.8/0.0
Israel (140)	0.25/1 (92.9/94.3)	0.25/32 (67.1)	≤0.06/≤0.06 (96.4)	25.0/5.7/0.0
Italy (728)	0.25/32 (83.8/85.9)	0.25/>32 (66.6)	≤0.06/0.25 (90.8)	25.6/7.4/0.1
Poland (96)	1/>32 (56.3/58.3)	16/>32 (43.8)	≤0.06/8 (75.3)	50.0/31.3/0.0
Portugal (188)	0.25/1 (97.3/98.4)	0.12/16 (85.1)	≤0.06/≤0.06 (100.0)	16.5/1.1/0.0
Russia (165)	0.5/32 (79.4/81.8)	2/>32 (47.9)	≤0.06/0.12 (98.8)	43.6/2.4/0.0
Spain (581)	0.25/1 (96.0/97.4)	0.25/2 (89.0)	≤0.06/≤0.06 (99.7)	8.3/0.5/0.0
Sweden (270)	0.25/0.5 (98.2/98.9)	0.12/0.5 (94.8)	≤0.06/≤0.06 (100.0)	3.0/0.0/0.0
Turkey (361)	0.25/2 (91.1/94.5)	0.25/32 (70.4)	≤0.06/≤0.06 (97.8)	18.8/2.2/0.3
UK (405)	0.25/1 (98.3/99.0)	0.12/4 (86.7)	≤0.06/≤0.06 (100.0)	7.7/0.3/0.0
Ukraine (41)	0.25/2 (95.1/95.1)	0.25/8 (78.0)	≤0.06/≤0.06 (97.6)	9.8/2.4/0.0
Overall (4875)	**0.25/2 (91.7/93.4)**	**0.25/32 (78.0)**	**≤0.06/≤0.06 (97.4)**	**15.7/2.8/0.05**

[a]Susceptible breakpoint established by EUCAST (2015).
[b]Multidrug-resistant (MDR), extensively drug-resistant (XDR), and pandrug-resistant (PDR) bacteria were classified according to Magiorakos AP, et al. (2012). *Clin Microbiol Infect.* 18:268-81.

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 EU nations.
- At an MIC of ≤2/4 and ≤4/4 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.

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