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Ceftolozane/tazobactam activity against drug-resistant Enterobacteriaceae and *Pseudomonas aeruginosa* causing urinary tract and intraabdominal infections in Europe: report from an antimicrobial surveillance programme (2012–15)

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Objectives: To evaluate the *in vitro* activity of ceftolozane/tazobactam and comparators tested against European isolates of Enterobacteriaceae and *Pseudomonas aeruginosa* from hospitalized patients with urinary tract infection or intraabdominal infections.

Methods: A total of 6553 Gram-negative organisms (603 *P. aeruginosa* and 5950 Enterobacteriaceae) were consecutively collected from 41 hospitals located in 17 European countries plus Israel and Turkey. The organisms were tested for susceptibility by broth microdilution methods and the results interpreted according to EUCAST and CLSI breakpoint criteria.

Results: Ceftolozane/tazobactam [$MIC_{50/90}$ 0.25/1 mg/L; 93.5%/91.3% susceptible (S) (CLSI/EUCAST criteria)] and meropenem [$MIC_{50/90}$ ≤0.06/≤0.06 mg/L; 98.1%/98.3% S (CLSI/EUCAST)] were the most active compounds tested against Enterobacteriaceae. Among the Enterobacteriaceae isolates, 1.9% were carbapenem resistant (CRE), 15.2% exhibited an ESBL non-CRE phenotype, 14.6% were MDR, 2.2% were XDR and <0.1% were pan-drug resistant (PDR). Whereas ceftolozane/tazobactam showed activity against ESBL non-CRE phenotype isolates ($MIC_{50/90}$ 0.5/8 mg/L), it lacked useful activity against strains with a CRE ($MIC_{50/90}$ >32/>32 mg/L; 3.6% S) or PDR (MIC_{50} >32 mg/L; 0.0% S) phenotype. Ceftolozane/tazobactam was the most potent ($MIC_{50/90}$ 0.5/4 mg/L) β-lactam agent tested against *P. aeruginosa* isolates, inhibiting 91.7% at an MIC of ≤4 mg/L. *P. aeruginosa* exhibited high rates of resistance to cefepime (20.6%), ceftazidime (23.1%), meropenem (9.0%) and piperacillin/tazobactam (26.9%) (EUCAST criteria). Among these four *P. aeruginosa* resistant phenotypes, 61.3%–70.4% were susceptible to ceftolozane/tazobactam.

Conclusions: Ceftolozane/tazobactam was the most active β-lactam agent tested against *P. aeruginosa* and demonstrated higher *in vitro* activity than currently available cephalosporins and piperacillin/tazobactam when tested against Enterobacteriaceae.

Introduction

Healthcare-associated infections (HCAI) are important causes of morbidity, mortality and excess medical costs worldwide.[1] Over half of all HCAI and associated antibiotic usage may be attributed to the management of lower respiratory tract infections, urinary tract infections (UTI) and intraabdominal infections (IAI).[1,2] The spectrum of aetiological pathogens causing HCAIs is ever-changing and varies from region to region and even from hospital to hospital.[1,3] From the 1970s through 2000, the spectrum of HCAI pathogens shifted from Gram-negative bacilli (GNB) to include both Gram-positive cocci (GPC) and *Candida* spp.[1,3–5] More recently, MDR GNB have become increasingly prevalent in the hospital setting.[6–9] Population-based surveillance of antibiotic resistance in both Europe[10] and the USA[11] has documented increasing resistance among GNB in a large proportion of facilities. Prominent among the resistant species are ESBL- and carbapenem-resistant Enterobacteriaceae (CRE) and MDR (resistant to at least three antimicrobial classes) non-fermenters such as *Pseudomonas aeruginosa*.[6,9,12] Notably, this increase in resistance among GNB reduces the likelihood of appropriate empiric

therapy.[13] It is now well established that delay in initial appropriate therapy is associated with increased morbidity and mortality in patients with severe infections, particularly those caused by ESBL-producing Enterobacteriaceae[14] and *P. aeruginosa*.[13,15]

These findings underscore the continued importance of antibiotic resistance surveillance and the need to assess the potential impact of newly introduced and novel antibacterial agents targeting specific resistance phenotypes.[16,17] Systematic and comprehensive antibiotic resistance surveillance is essential to document the extent of the resistance problem and to inform local, regional, national and global efforts to combat the challenge of resistance.[16]

Ceftolozane/tazobactam is a novel antibacterial agent with activity against *P. aeruginosa*, including antibiotic-resistant strains, and other common GNB, including most ESBL-producing Enterobacteriaceae strains.[17–21] Ceftolozane/tazobactam is not active against *Acinetobacter* spp., *Stenotrophomonas maltophilia*, anaerobes, GPC or Enterobacteriaceae producing carbapenemases, metallo-β-lactamases and some AmpC β-lactamases.[17,22] Ceftolozane/tazobactam has recently been approved for the treatment of complicated IAIs and complicated UTIs.[17] A Phase III clinical trial of ceftolozane/tazobactam in the treatment of nosocomial pneumonia is in progress.

In a previous antimicrobial resistance survey conducted in Europe in 2011–12, we described the *in vitro* activity of ceftolozane/tazobactam tested against isolates of Enterobacteriaceae and *P. aeruginosa* from a variety of infection sites.[19,20] In the present study, we extend these observations and focus on the activity of ceftolozane/tazobactam and selected β-lactam comparators against 6553 isolates of *P. aeruginosa* (603 isolates) and Enterobacteriaceae (5950 isolates) from patients with UTI or IAI hospitalized at 41 European medical centres (19 countries) during the period 2012–15. The analysis includes the activity of ceftolozane/tazobactam against specific resistance phenotypes (e.g. ESBL non-CRE phenotype and MDR strains of Enterobacteriaceae and *P. aeruginosa*) as well as the frequency of resistance patterns among the different European countries.

Materials and methods

Sampling sites and organisms

A total of 6553 GNB, including 5950 Enterobacteriaceae and 603 *P. aeruginosa*, were consecutively collected from 41 large academic medical centres located in 17 European countries plus Turkey and Israel by the Program to Assess Ceftolozane/Tazobactam Susceptibility (PACTS). All organisms were isolated from hospitalized patients with documented UTI or IAI between January 2012 and December 2015 and only one isolate per patient infection episode was included in the surveillance collection. Species identification was performed at each participating medical centre and confirmed by the monitoring laboratory (JMI Laboratories, North Liberty, IA, USA) using the VITEK 2 System (bioMérieux, Hazelwood, MO, USA) or MALDI-TOF MS (Bruker, Billerica, MA, USA), when necessary.

Antimicrobial susceptibility testing

MICs were determined using the reference CLSI broth microdilution method (CLSI, 2015).[23] Quality control (QC) and interpretation of results were performed in accordance with CLSI M100-S26 and EUCAST 2016 guidelines (CLSI, 2016[24]; EUCAST, 2016[25]). *Escherichia coli*, *Klebsiella pneumoniae*, *Klebsiella oxytoca* and *Proteus mirabilis* were grouped as 'ESBL phenotype' based on the CLSI screening criteria for potential ESBL production—i.e. MIC ≥2 mg/L for ceftazidime and/or ceftriaxone and/or aztreonam.[24] CRE were defined as isolates displaying MIC ≥4 mg/L[24] for imipenem (*P. mirabilis* and indole-positive Proteeae were not included due to their intrinsically elevated MIC values) and/or meropenem and/or doripenem. MDR, XDR and pan-drug-resistant (PDR) Enterobacteriaceae isolates were classified according to recently recommended guidelines[26] and using the following antimicrobial class representative agents: ceftriaxone, meropenem, piperacillin/tazobactam, levofloxacin, gentamicin, tigecycline and colistin (seven classes). Results for doripenem, levofloxacin, gentamicin, tigecycline and colistin were used to determine MDR, XDR and PDR phenotypes and are not reported individually. Classifications were based on the following recommended parameters: MDR = non-susceptible (NS; CLSI/EUCAST breakpoints) to at least three antimicrobial classes; XDR = susceptible (S) to two or fewer antimicrobial classes; and PDR = NS to all antimicrobial classes.[26] Classifications of isolates as resistant (R), NS or S to each antimicrobial agent were based on EUCAST breakpoints for tigecycline and colistin and CLSI breakpoints for all other agents. Isolates of *P. aeruginosa* were classified as ceftolozane/tazobactam-NS (MIC >4 mg/L), ceftazidime-NS (MIC >8 mg/L), piperacillin/tazobactam-NS (MIC >16 mg/L) and meropenem-NS (MIC >2 mg/L).

Results

Among the 6553 isolates tested, there were 5950 Enterobacteriaceae isolates (including 3460 *E. coli* isolates, 1112 *Klebsiella* spp. isolates, 432 *Enterobacter* spp. isolates, 256 *Citrobacter* spp. isolates, 368 *P. mirabilis* isolates, 237 indole-positive Proteeae isolates and 77 *Serratia* spp. isolates) and 603 *P. aeruginosa* isolates (Table 1).

Overall activity of ceftolozane/tazobactam

During the years 2012–15, ceftolozane/tazobactam maintained a consistent and potent level of activity against the UTI and IAI target pathogens from the European study sites (Table 1). Among the Enterobacteriaceae isolates tested, 1.9% were CRE, 15.2% exhibited an ESBL non-CRE phenotype, 14.6% were MDR, 2.2% were XDR and <0.1% were PDR (Table 1). An ESBL non-CRE phenotype was observed in 16.2% of *E. coli* and 30.5% of *K. pneumoniae* isolates. An ESBL phenotype was detected in 18.4% of *K. oxytoca* and 8.7% of *P. mirabilis* isolates. Important resistant phenotypes among the *P. aeruginosa* isolates included ceftazidime-NS (23.1%), meropenem-NS (20.9%), cefepime-NS (20.6%) and piperacillin/tazobactam-NS (26.9%) (Table 1).

Against Enterobacteriaceae isolates, ceftolozane/tazobactam MIC values ranged from 0.015 to >32 mg/L, and 91.3%/93.5% of the tested isolates were inhibited at an MIC value of ≤1/≤2 mg/L (EUCAST/CLSI susceptible breakpoint) (Table 1). Whereas ceftolozane/tazobactam showed good activity against ESBL non-CRE phenotype isolates of Enterobacteriaceae ($MIC_{50/90}$ 0.5/8 mg/L), it lacked useful activity against isolates with a CRE ($MIC_{50/90}$ >32/>32 mg/L; 3.6% S) or PDR (MIC_{50} >32 mg/L; 0.0% S) phenotype.

Ceftolozane/tazobactam MIC values ranged from 0.12 to >32 mg/L against isolates of *P. aeruginosa*, and 91.7% of the tested isolates were inhibited at an MIC value of ≤4 mg/L (CLSI and EUCAST breakpoint). Among the four resistant phenotypes, 61.3%–70.4% were susceptible to ceftolozane/tazobactam (Table 1).

Table 1. Antimicrobial activity of ceftolozane/tazobactam tested against the main organisms and organism groups of isolates in this study

	No. of isolates at MIC (mg/L; cumulative %)														
Organisms/organism groups[a]	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	>32	MIC_{50}	MIC_{90}
Enterobacteriaceae (5950)[b]	1 (<0.1)	3 (0.1)	78 (1.4)	1604 (28.3)	2449 (69.5)	1031 (86.8)	269 (91.3)	129 (93.5)	88 (95.0)	71 (96.2)	58 (97.2)	38 (97.8)	131 (100.0)	0.25	1
CRE (112)					0 (0.0)	1 (0.9)	1 (1.8)	2 (3.6)	0 (3.6)	2 (5.4)	6 (10.7)	14 (23.2)	86 (100.0)	>32	>32
ESBL non-CRE phenotype (906)		0 (0.0)	4 (0.4)	44 (5.3)	211 (28.6)	284 (59.9)	136 (74.9)	71 (82.8)	54 (88.7)	33 (92.4)	20 (94.6)	13 (96.0)	36 (100.0)	0.5	8
Enterobacteriaceae MDR (871)		0 (0.0)	1 (0.1)	16 (2.0)	133 (17.2)	219 (42.4)	109 (54.9)	79 (63.9)	62 (71.1)	46 (76.3)	44 (81.4)	34 (85.3)	128 (100.0)	1	>32
Enterobacteriaceae XDR (129)				0 (0.0)	2 (1.6)	7 (7.0)	7 (12.4)	7 (17.8)	8 (24.0)	10 (31.8)	8 (38.0)	10 (45.7)	70 (100.0)	>32	>32
Enterobacteriaceae PDR (3)												0 (0.0)	3 (100.0)	>32	–
E. coli (3460)	1 (<0.1)	2 (0.1)	65 (2.0)	1280 (39.0)	1603 (85.3)	351 (95.4)	88 (98.0)	29 (98.8)	11 (99.1)	11 (99.5)	7 (99.7)	8 (99.9)	4 (100.0)	0.25	0.5
ESBL non-CRE phenotype (559)		0 (0.0)	3 (0.5)	37 (7.2)	169 (37.4)	201 (73.3)	81 (87.8)	27 (92.7)	11 (94.6)	11 (96.6)	7 (97.9)	8 (99.3)	4 (100.0)	0.5	2
Klebsiella spp. (1112)	0 (0.0)	1 (0.1)	9 (0.9)	210 (19.8)	386 (54.5)	196 (72.1)	68 (78.2)	43 (82.1)	38 (85.5)	20 (87.3)	17 (88.8)	18 (90.5)	106 (100.0)	0.25	32
K. pneumoniae (917)	0 (0.0)	1 (0.1)	7 (0.9)	139 (16.0)	315 (50.4)	172 (69.1)	61 (75.8)	32 (79.3)	34 (83.0)	18 (85.0)	15 (86.6)	18 (88.5)	105 (100.0)	0.25	>32
ESBL non-CRE phenotype (280)		0 (0.0)	1 (0.4)	6 (2.5)	37 (15.7)	66 (39.3)	45 (55.4)	28 (65.4)	34 (77.5)	17 (83.6)	11 (87.5)	5 (89.3)	30 (100.0)	1	>32
K. oxytoca (190)		0 (0.0)	2 (1.1)	70 (37.9)	70 (74.7)	22 (86.3)	6 (89.5)	11 (95.3)	4 (97.4)	2 (98.4)	2 (99.5)	0 (99.5)	1 (100.0)	0.25	2
ESBL phenotype (35)			0 (0.0)	1 (2.9)	2 (8.6)	8 (31.4)	4 (42.9)	11 (74.3)	4 (85.7)	2 (91.4)	2 (97.1)	0 (97.1)	1 (100.0)	2	8
Enterobacter spp. (432)			0 (0.0)	35 (8.1)	133 (38.9)	86 (58.8)	47 (69.7)	36 (78.0)	28 (84.5)	24 (90.0)	25 (95.8)	7 (97.5)	11 (100.0)	0.5	8
E. cloacae (278)			0 (0.0)	19 (6.8)	90 (39.2)	55 (59.0)	31 (70.1)	18 (76.6)	14 (81.7)	20 (88.8)	18 (95.3)	4 (96.8)	9 (100.0)	0.5	16
E. aerogenes (105)			0 (0.0)	11 (10.5)	37 (45.7)	20 (64.8)	8 (72.4)	11 (82.9)	10 (92.4)	1 (93.3)	4 (97.1)	2 (99.0)	1 (100.0)	0.5	4
Citrobacter spp. (256)		0 (0.0)	2 (0.8)	54 (21.9)	129 (72.3)	30 (84.0)	7 (86.7)	1 (87.1)	5 (89.1)	12 (93.8)	8 (96.9)	3 (98.0)	5 (100.0)	0.25	8
C. koseri (101)			0 (0.0)	28 (27.7)	62 (89.1)	11 (100.0)								0.25	0.5
C. freundii (111)		0 (0.0)	1 (0.9)	19 (18.0)	47 (60.4)	13 (72.1)	7 (78.4)	1 (79.3)	3 (82.0)	10 (91.0)	5 (95.5)	3 (98.2)	2 (100.0)	0.25	8
P. mirabilis (368)			0 (0.0)	5 (1.4)	93 (26.6)	237 (91.0)	17 (95.7)	6 (97.3)	6 (98.9)	3 (99.7)	0 (99.7)	0 (99.7)	1 (100.0)	0.5	0.5
ESBL phenotype (32)				0 (0.0)	3 (9.4)	9 (37.5)	6 (56.2)	5 (71.9)	5 (87.5)	3 (96.9)	0 (96.9)	0 (96.9)	1 (100.0)	1	8
Indole-positive Proteeae (237)		0 (0.0)	1 (0.4)	20 (8.9)	99 (50.6)	85 (86.5)	20 (94.9)	6 (97.5)	0 (97.5)	1 (97.9)	0 (97.9)	1 (98.3)	4 (100.0)	0.25	1
Serratia spp. (77)				0 (0.0)	6 (7.8)	42 (62.3)	20 (88.3)	8 (98.7)	0 (98.7)	0 (98.7)	0 (98.7)	1 (100.0)		0.5	2
P. aeruginosa (603)			0 (0.0)	5 (0.8)	46 (8.5)	318 (61.2)	119 (80.9)	40 (87.6)	25 (91.7)	10 (93.4)	6 (94.4)	9 (95.9)	25 (100.0)	0.5	4
ceftazidime-NS (139)					0 (0.0)	4 (2.9)	31 (25.2)	34 (49.6)	22 (65.5)	9 (71.9)	5 (75.5)	9 (82.0)	25 (100.0)	4	>32
meropenem-NS (126)				0 (0.0)	4 (3.2)	13 (13.5)	34 (40.5)	21 (57.1)	11 (65.9)	6 (70.6)	6 (75.4)	9 (82.5)	22 (100.0)	2	>32
cefepime-NS (124)					0 (0.0)	3 (2.4)	18 (16.9)	31 (41.9)	24 (61.3)	10 (69.4)	5 (73.4)	9 (80.6)	24 (100.0)	4	>32
TZP-NS (162)					0 (0.0)	13 (8.0)	41 (33.3)	35 (54.9)	25 (70.4)	10 (76.5)	6 (80.2)	9 (85.8)	23 (100.0)	2	>32

[a]Abbreviations: CRE, carbapenem-resistant Enterobacteriaceae; PDR, pan drug resistant; NS, non-susceptible; TZP, piperacillin/tazobactam.

[b]Organisms include: *Citrobacter amalonaticus* (7), *Citrobacter braakii* (8), *Citrobacter farmeri* (1), *Citrobacter freundii* (111), *Citrobacter freundii* species complex (19), *Citrobacter koseri* (101), *Citrobacter werkmanii* (1), *Citrobacter youngae* (3), *Enterobacter aerogenes* (105), *Enterobacter amnigenus* (3), *Enterobacter asburiae* (6), *Enterobacter cancerogenus* (2), *Enterobacter cloacae* (278), *Enterobacter cloacae* species complex (38), *Escherichia coli* (3460), *Hafnia alvei* (4), *Klebsiella oxytoca* (190), *Klebsiella pneumoniae* (917), *Klebsiella variicola* (5), *Morganella morganii* (137), *Pantoea agglomerans* (1), *Proteus mirabilis* (368), *Proteus penneri* (2), *Proteus vulgaris* (64), *Providencia alcalifaciens* (1), *Providencia rettgeri* (11), *Providencia stuartii* (24), *Raoultella planticola* (1), *Serratia fonticola* (1), *Serratia liquefaciens* (7), *Serratia marcescens* (69), unspeciated *Citrobacter* (5).

Activities of ceftolozane/tazobactam and comparators against Enterobacteriaceae

Ceftolozane/tazobactam ($MIC_{50/90}$ 0.25/1 mg/L) inhibited 93.5% of the 5950 Enterobacteriaceae isolates tested at ≤2 mg/L and 95.0% of the isolates at ≤4 mg/L (CLSI susceptible and intermediate breakpoint criteria, respectively) (Table 1). Enterobacteriaceae isolates displayed susceptibility rates to other β-lactam agents ranging from 84.4%/80.2% for ceftazidime, 84.9%/83.0% for cefepime, 89.1%/85.1% for piperacillin/tazobactam and 98.1%/98.3% for meropenem using CLSI/EUCAST breakpoints. Using MIC_{90} values, ceftolozane/tazobactam was 16-fold more active than cefepime and ceftazidime (both MIC_{90} 16 mg/L), was 32-fold more potent than piperacillin/tazobactam (MIC_{90} 32 mg/L), and was second in potency to meropenem (MIC_{90} ≤0.06 mg/L) (Table 2). Against 906 (15.2%) ESBL non-CRE phenotype Enterobacteriaceae isolates, meropenem [$MIC_{50/90}$ ≤0.06/≤0.06 mg/L; 99.2%/100.0% S (CLSI/EUCAST criteria)] and ceftolozane/tazobactam ($MIC_{50/90}$ 0.5/8 mg/L; 82.8%/74.9% S) were the only agents to retain clinically useful activity of the antimicrobials assessed (Table 2).

In total 3460 *E. coli* isolates were evaluated, 98.8%/98.0% of which were susceptible to ceftolozane/tazobactam ($MIC_{50/90}$ 0.25/0.5 mg/L) by CLSI/EUCAST interpretive guidelines. Meropenem [$MIC_{50/90}$ ≤0.06/≤0.06 mg/L; 100.0%/100.0% S (CLSI/EUCAST)] and piperacillin/tazobactam ($MIC_{50/90}$ 2/8 mg/L; 94.0%/90.5% S) showed good activity against *E. coli*, followed by cefepime ($MIC_{50/90}$ ≤0.5/8 mg/L; 87.5%/85.9% S) and ceftazidime ($MIC_{50/90}$ 0.12/8 mg/L; 89.9%/85.4% S) (Table 2). Among ESBL non-CRE phenotype isolates of *E. coli* (16.2%), resistance rates to cefepime, ceftazidime and piperacillin/tazobactam were elevated (Table 2). Meropenem retained potent activity ($MIC_{50/90}$ ≤0.06/≤0.06 mg/L; 100.0% S) against ESBL non-CRE phenotype isolates of *E. coli*. Ceftolozane/tazobactam inhibited 92.7% of the ESBL non-CRE phenotype *E. coli* isolates at ≤2 mg/L (Tables 1 and 2).

Ceftolozane/tazobactam showed potent activity against non-ESBL phenotype isolates of *K. pneumoniae* [$MIC_{50/90}$ 0.25/0.5 mg/L; highest MIC 2 mg/L (data not shown)] and retained activity against many ESBL non-CRE phenotype isolates ($MIC_{50/90}$ 1/>32 mg/L; 65.4%/55.4% S) (Tables 1 and 2). Among the β-lactam comparator agents tested, only meropenem was more active than ceftolozane/tazobactam against *Klebsiella* species irrespective of the resistant phenotype (Table 2). Ceftolozane/tazobactam was also active against other frequently isolated Enterobacteriaceae including *K. oxytoca* ($MIC_{50/90}$ 0.25/2 mg/L), *Enterobacter* spp. ($MIC_{50/90}$ 0.5/8 mg/L), *Citrobacter* spp. ($MIC_{50/90}$ 0.25/8 mg/L), *P. mirabilis* ($MIC_{50/90}$ 0.5/0.5 mg/L), indole-positive Proteeae ($MIC_{50/90}$ 0.25/1 mg/L) and *Serratia* spp. ($MIC_{50/90}$ 0.5/2 mg/L) (Tables 1 and 2).

Previously (2012) we have shown that among European isolates of Enterobacteriaceae from patients with pneumonia, the rates of MDR and XDR phenotypes varied markedly from country to country.[19] As seen in Table 3, resistance rates among Enterobacteriaceae causing either UTI or IAI also show considerable variability among the European nations evaluated. The occurrence of CRE, MDR and XDR Enterobacteriaceae was highest in Poland (29.9%, 72.2% and 32.0%, respectively) and lowest in Austria (0.0%, 3.1% and 0.0%, respectively), Denmark (0.0%, 4.2% and 0.0%, respectively), Finland (0.0%, 1.9% and 0.0%, respectively) and Switzerland (0.0%, 2.1% and 0.0%, respectively) (Table 3). The highest rates of ESBL non-CRE phenotype Enterobacteriaceae were found in isolates from Poland (32.5%) and Turkey (36.2%) and the lowest were in isolates from Austria (0.0%), Finland (1.9%) and Switzerland (2.1%). The frequency of CRE was <1.0% in 14 of the 19 countries contributing to the survey. Among the five major Western European countries (France, Germany, Italy, Spain and the UK), the occurrence of MDR Enterobacteriaceae was higher in Italy (18.4%) when compared with the other four countries (6.4%–12.6%) (Table 3). These data are comparable to those reported in 2012 for respiratory tract isolates of Enterobacteriaceae from Europe.[19]

Activities of ceftolozane/tazobactam and comparators against P. aeruginosa

Ceftolozane/tazobactam was the most potent ($MIC_{50/90}$ 0.5/4 mg/L) β-lactam agent tested against 603 *P. aeruginosa* isolates, inhibiting 91.7% at a MIC of ≤4 mg/L (Tables 1 and 2). Based on the MIC_{90} value, ceftolozane/tazobactam was 2-fold more active than meropenem (MIC_{90} 8 mg/L), 4-fold more active than cefepime (MIC_{90} 16 mg/L), 8-fold more active than ceftazidime (MIC_{90} 32 mg/L) and at least 32-fold more active than piperacillin/tazobactam (MIC_{90} >64 mg/L) (Table 2). Overall susceptibility rates (by CLSI/EUCAST criteria; Table 2) for cefepime (79.4%/79.4%), ceftazidime (76.9%/76.9%), meropenem (79.1%/79.1%) and piperacillin/tazobactam (73.1%/73.1%) were all below that of ceftolozane/tazobactam at ≤4 mg/L (91.7%/91.7%; Table 2).

Ceftolozane/tazobactam retained moderate activity against isolates of *P. aeruginosa* that were NS to the other antipseudomonal β-lactam agents (Table 2): ceftazidime-NS (65.5% susceptible), meropenem-NS (65.9%), cefepime-NS (61.3%) and piperacillin/tazobactam-NS (70.4%). None of the other β-lactam agents inhibited >40.7% of these resistant phenotype isolates.

As observed in 2011–12,[20] *P. aeruginosa* susceptibility to antipseudomonal β-lactams varied markedly among the European nations that participated in the survey (Table 4). The lowest susceptibility rates for ceftazidime and meropenem were observed in Poland (46.9% and 34.4%, respectively) and Portugal (52.6% and 44.7%). Decreased susceptibility rates to ceftazidime and meropenem were also noted in Greece (61.1% for both compounds), Israel (69.2% and 76.9%, respectively), Italy (73.3% and 78.7%), Russia (20.0% for ceftazidime) and Turkey (63.6% and 70.5%). Ceftolozane/tazobactam activity was also compromised when tested against *P. aeruginosa* isolates from Greece (61.1% susceptible), Poland (75.0%), Portugal (63.2%) and Russia (60.0%), but it provided 100.0% coverage against isolates from 11 of the 19 countries (Table 4). *P. aeruginosa* isolates from the five most populous Western European countries (i.e. France, Germany, Italy, Spain and the UK; 332 isolates) were more susceptible to ceftolozane/tazobactam (96.4%), ceftazidime (81.9%) and meropenem (84.9%) than isolates from 6 of the remaining 14 countries (Table 4).

Discussion

The results of the present study both confirm and extend those previously reported concerning the *in vitro* activity of ceftolozane/tazobactam against European isolates of Enterobacteriaceae and *P. aeruginosa*.[19–21] Ceftolozane/tazobactam was the most active of the tested β-lactam agents against *P. aeruginosa* and was second

Table 2. Activity of ceftolozane/tazobactam and comparator antimicrobial agents when tested against Enterobacteriaceae and *P. aeruginosa* from European hospitals (2012–15)

	MIC (mg/L)		%S/%I/%R	
Organism (no. tested)/antimicrobial agent	50%	90%	CLSI	EUCAST
Enterobacteriaceae (5950)				
ceftolozane/tazobactam	0.25	1	93.5/1.5/5.0	91.3/–/8.7
cefepime	≤0.5	16	84.9/3.6/11.4	83.0/3.8/13.2
ceftazidime	0.25	16	84.4/2.7/12.8	80.2/4.2/15.6
meropenem	≤0.06	≤0.06	98.1/0.2/1.7	98.3/0.8/1.0
piperacillin/tazobactam	2	32	89.1/4.1/6.8	85.1/4.0/10.9
ESBL non-CRE phenotype (906)				
ceftolozane/tazobactam	0.5	8	82.8/6.0/11.3	74.9/–/25.1
cefepime	16	>16	23.1/18.8/58.1	15.1/17.1/67.8
ceftazidime	16	>32	33.8/14.7/51.5	10.5/23.3/66.2
meropenem	≤0.06	≤0.06	99.2/0.8/0.0	100.0/0.0/0.0
piperacillin/tazobactam	8	>64	70.8/10.8/18.4	57.2/13.6/29.2
E. coli (3460)				
ceftolozane/tazobactam	0.25	0.5	98.8/0.3/0.9	98.0/–/2.0
cefepime	≤0.5	8	87.5/3.1/9.3	85.9/3.3/10.9
ceftazidime	0.12	8	89.9/2.5/7.7	85.4/4.4/10.1
meropenem	≤0.06	≤0.06	100.0/0.0/0.0	100.0/0.0/0.0
piperacillin/tazobactam	2	8	94.0/2.9/3.2	90.5/3.4/6.0
ESBL non-CRE phenotype (559)				
ceftolozane/tazobactam	0.5	2	92.7/2.0/5.4	87.8/–/12.2
cefepime	16	>16	23.2/18.6/58.2	15.0/17.5/67.6
ceftazidime	8	>32	37.2/15.4/47.4	9.8/27.4/62.8
meropenem	≤0.06	≤0.06	100.0/0.0/0.0	100.0/0.0/0.0
piperacillin/tazobactam	8	64	81.1/9.3/9.5	66.6/14.5/18.9
Klebsiella spp. (1112)				
ceftolozane/tazobactam	0.25	32	82.1/3.4/14.5	78.2/–/21.8
cefepime	≤0.5	>16	68.8/5.6/25.6	67.1/4.2/28.7
ceftazidime	0.25	>32	70.3/4.0/25.6	66.5/3.9/29.7
meropenem	≤0.06	0.5	91.1/0.9/8.0	92.0/3.1/4.9
piperacillin/tazobactam	4	>64	74.8/5.4/19.8	69.3/5.4/25.2
K. pneumoniae (917)				
ceftolozane/tazobactam	0.25	>32	79.3/3.7/17.0	75.8/–/24.2
cefepime	≤0.5	>16	63.4/6.0/30.6	62.4/3.6/34.0
ceftazidime	0.25	>32	64.6/4.7/30.8	60.3/4.3/35.4
meropenem	≤0.06	2	89.2/1.1/9.7	90.3/3.7/6.0
piperacillin/tazobactam	4	>64	73.2/6.4/20.4	66.7/6.5/26.8
ESBL phenotype (373)				
ceftolozane/tazobactam	4	>32	49.1/9.1/41.8	41.6/–/58.4
cefepime	>16	>16	9.9/14.7/75.3	7.8/8.6/83.6
ceftazidime	32	>32	12.9/11.5/75.6	2.4/10.5/87.1
meropenem	≤0.06	>8	73.5/2.7/23.9	76.1/9.1/14.7
piperacillin/tazobactam	64	>64	40.7/11.9/47.4	30.1/10.6/59.3
ESBL non-CRE phenotype (280)				
ceftolozane/tazobactam	1	>32	65.4/12.1/22.5	55.4/–/44.6
cefepime	>16	>16	13.2/19.6/67.1	10.4/11.4/78.2
ceftazidime	16	>32	17.1/15.4/67.5	3.2/13.9/82.9
meropenem	≤0.06	0.12	97.5/2.5/0.0	100.0/0.0/0.0
piperacillin/tazobactam	16	>64	54.3/15.9/29.7	40.2/14.1/45.7
K. oxytoca (190)				
ceftolozane/tazobactam	0.25	2	95.3/2.1/2.6	89.5/–/10.5

Continued

Table 2 *Continued*

Organism (no. tested)/antimicrobial agent	MIC (mg/L)		%S/%I/%R	
	50%	90%	CLSI	EUCAST
cefepime	≤0.5	2	94.2/3.7/2.1	88.9/7.4/3.7
ceftazidime	0.12	1	97.4/1.1/1.6	95.3/2.1/2.6
meropenem	≤0.06	≤0.06	100.0/0.0/0.0	100.0/0.0/0.0
piperacillin/tazobactam	2	≥64	82.0/1.1/16.9	81.5/0.5/18.0
ESBL phenotype (35)				
ceftolozane/tazobactam	2	8	74.3/11.4/14.3	42.9/–/57.1
cefepime	2	16	68.6/20.0/11.4	40.0/40.0/20.0
ceftazidime	1	8	85.7/5.7/8.6	74.3/11.4/14.3
meropenem	≤0.06	≤0.06	100.0/0.0/0.0	100.0/0.0/0.0
piperacillin/tazobactam	>64	>64	8.6/2.9/88.6	8.6/0.0/91.4
Enterobacter spp. (432)				
ceftolozane/tazobactam	0.5	8	78.0/6.5/15.5	69.7/–/30.3
cefepime	≤0.5	16	80.6/7.6/11.8	76.4/8.8/14.8
ceftazidime	0.5	>32	62.3/3.9/33.8	58.1/4.2/37.7
meropenem	≤0.06	0.12	97.5/0.5/2.1	97.9/1.9/0.2
piperacillin/tazobactam	4	>64	73.3/15.1/11.6	65.0/8.4/26.7
E. cloacae (278)				
ceftolozane/tazobactam	0.5	16	76.6/5.0/18.3	70.1/–/29.9
cefepime	≤0.5	16	79.1/10.1/10.8	74.8/10.8/14.4
ceftazidime	0.5	>32	65.1/2.5/32.4	61.5/3.6/34.9
meropenem	≤0.06	0.12	97.5/0.7/1.8	98.2/1.4/0.4
piperacillin/tazobactam	4	>64	75.1/11.2/13.7	67.9/7.2/24.9
E. aerogenes (105)				
ceftolozane/tazobactam	0.5	4	82.9/9.5/7.6	72.4/–/27.6
cefepime	≤0.5	1	93.3/1.9/4.8	91.4/3.8/4.8
ceftazidime	0.5	>32	62.9/6.7/30.5	58.1/4.8/37.1
meropenem	≤0.06	≤0.06	99.0/0.0/1.0	99.0/1.0/0.0
piperacillin/tazobactam	4	64	71.4/23.8/4.8	63.8/7.6/28.6
Citrobacter spp. (256)				
ceftolozane/tazobactam	0.25	8	87.1/2.0/10.9	86.7/–/13.3
cefepime	≤0.5	1	97.7/0.8/1.6	94.5/3.9/1.6
ceftazidime	0.25	>32	83.2/1.6/15.2	82.0/1.2/16.8
meropenem	≤0.06	≤0.06	98.8/0.4/0.8	99.2/0.4/0.4
piperacillin/tazobactam	2	64	87.1/4.7/8.2	83.6/3.5/12.9
C. koseri (101)				
ceftolozane/tazobactam	0.25	0.5	100.0/0.0/0.0	100.0/0.0/0.0
cefepime	≤0.5	≤0.5	100.0/0.0/0.0	100.0/0.0/0.0
ceftazidime	0.12	0.25	100.0/0.0/0.0	100.0/0.0/0.0
meropenem	≤0.06	≤0.06	100.0/0.0/0.0	100.0/0.0/0.0
piperacillin/tazobactam	2	8	100.0/0.0/0.0	98.0/2.0/0.0
C. freundii (111)				
ceftolozane/tazobactam	0.25	8	79.3/2.7/18.0	78.4/–/21.6
cefepime	≤0.5	1	97.3/0.9/1.8	91.9/6.3/1.8
ceftazidime	0.5	>32	73.0/2.7/24.3	70.3/2.7/27.0
meropenem	≤0.06	≤0.06	99.1/0.0/0.9	99.1/0.0/0.9
piperacillin/tazobactam	4	>64	78.4/7.2/14.4	73.9/4.5/21.6
P. mirabilis (368)				
ceftolozane/tazobactam	0.5	0.5	97.3/1.6/1.1	95.7/–/4.3
cefepime	≤0.5	≤0.5	96.2/1.4/2.4	94.0/3.0/3.0
ceftazidime	0.06	0.12	96.7/0.5/2.7	92.7/4.1/3.3
meropenem	≤0.06	0.12	100.0/0.0/0.0	100.0/0.0/0.0

Continued

Table 2 *Continued*

Organism (no. tested)/antimicrobial agent	MIC (mg/L)		%S/%I/%R	
	50%	90%	CLSI	EUCAST
piperacillin/tazobactam	≤0.5	1	100.0/0.0/0.0	99.2/0.8/0.0
ESBL phenotype (32)				
ceftolozane/tazobactam	1	8	71.9/15.6/12.5	56.2/–/43.8
cefepime	2	>16	56.2/15.6/28.1	31.2/34.4/34.4
ceftazidime	4	32	62.5/6.2/31.2	15.6/46.9/37.5
meropenem	≤0.06	0.12	100.0/0.0/0.0	100.0/0.0/0.0
piperacillin/tazobactam	1	8	100.0/0.0/0.0	93.8/6.2/0.0
Indole-positive Proteeae (237)				
ceftolozane/tazobactam	0.25	1	97.5/0.0/2.5	94.9/–/5.1
cefepime	≤0.5	≤0.5	95.8/1.7/2.5	94.9/2.1/3.0
ceftazidime	0.12	8	89.8/3.8/6.4	84.7/5.1/10.2
meropenem	≤0.06	0.12	99.6/0.0/0.4	99.6/0.0/0.4
piperacillin/tazobactam	≤0.5	2	97.5/2.1/0.4	96.2/1.3/2.5
Serratia spp. (77)				
ceftolozane/tazobactam	0.5	2	98.7/0.0/1.3	88.3/–/11.7
cefepime	≤0.5	≤0.5	97.4/2.6/0.0	94.8/5.2/0.0
ceftazidime	0.25	0.5	97.4/0.0/2.6	94.8/2.6/2.6
meropenem	≤0.06	0.12	97.4/0.0/2.6	97.4/2.6/0.0
piperacillin/tazobactam	2	16	90.9/6.5/2.6	85.7/5.2/9.1
P. aeruginosa (603)				
ceftolozane/tazobactam	0.5	4	91.7/1.7/6.6	91.7/–/8.3
cefepime	2	16	79.4/11.1/9.5	79.4/–/20.6
ceftazidime	2	32	76.9/5.5/17.6	76.9/–/23.1
meropenem	0.5	8	79.1/6.3/14.6	79.1/12.0/9.0
piperacillin/tazobactam	4	>64	73.1/12.8/14.1	73.1/–/26.9
Ceftazidime-NS (139)				
ceftolozane/tazobactam	4	>32	65.5/6.5/28.1	65.5/–/34.5
cefepime	16	>16	23.7/39.6/36.7	23.7/–/76.3
ceftazidime	32	>32	0.0/23.7/76.3	0.0/–/100.0
meropenem	4	>8	39.6/10.8/49.6	39.6/28.1/32.4
piperacillin/tazobactam	>64	>64	8.6/37.4/54.0	8.6/–/91.4
Meropenem-NS (126)				
ceftolozane/tazobactam	2	>32	65.9/4.8/29.4	65.9/–/34.1
cefepime	16	>16	32.5/33.3/34.1	32.5/–/67.5
ceftazidime	32	>32	33.3/12.7/54.0	33.3/–/66.7
meropenem	8	>8	0.0/30.2/69.8	0.0/57.1/42.9
piperacillin/tazobactam	64	>64	23.8/31.0/45.2	23.8/–/76.2
Cefepime-NS (124)				
ceftolozane/tazobactam	4	>32	61.3/8.1/30.6	61.3/–/38.7
cefepime	16	>16	0.0/54.0/46.0	0.0/–/100.0
ceftazidime	32	>32	14.5/8.9/76.6	14.5/–/85.5
meropenem	8	>8	31.5/10.5/58.1	31.5/32.3/36.3
piperacillin/tazobactam	>64	>64	4.0/29.1/66.9	4.0/–/96.0
Piperacillin/tazobactam-NS (162)				
ceftolozane/tazobactam	2	>32	70.4/6.2/23.5	70.4/–/29.6
cefepime	16	>16	26.5/38.9/34.6	26.5/–/73.5
ceftazidime	32	>32	21.6/13.0/65.4	21.6/–/78.4
meropenem	4	>8	40.7/13.6/45.7	40.7/30.2/29.0
piperacillin/tazobactam	>64	>64	0.0/47.5/52.5	0.0/–/100.0

Table 3. Geographical distribution of carbapenem-resistant (CRE), ESBL non-CRE, MDR, XDR and pan-drug-resistant (PDR) Enterobacteriaceae isolates from European patients with UTI or IAI (2012–15)

		Isolates with resistant phenotype (%)				
Country	No. tested	CRE	ESBL non-CRE	MDR	XDR	PDR
Austria	64	0.0	0.0	3.1	0.0	0.0
Belgium	181	0.6	21.0	17.1	1.1	0.0
Denmark	95	0.0	6.3	4.2	0.0	0.0
Finland	104	0.0	1.9	1.9	0.0	0.0
France	800	0.1	6.8	7.8	0.4	0.0
Germany	828	0.6	12.8	12.6	0.6	0.0
Greece	241	5.4	13.7	14.9	3.3	0.4
Ireland	426	0.5	26.5	23.9	1.4	0.0
Israel	164	1.2	23.8	17.1	1.8	0.0
Italy	495	3.8	16.8	18.4	5.3	0.0
Netherlands	5	0.0	20.0	40.0	0.0	0.0
Poland	194	29.9	32.5	72.2	32.0	0.0
Portugal	225	0.0	19.1	22.2	1.8	0.0
Russia	29	0.0	20.7	31.0	3.4	0.0
Spain	660	0.2	7.7	6.4	0.2	0.0
Sweden	369	0.3	4.9	2.7	0.0	0.0
Switzerland	47	0.0	2.1	2.1	0.0	0.0
Turkey	434	1.8	36.2	22.6	1.6	0.5
UK	589	0.2	15.6	9.7	0.2	0.0
Five major countries[a]	3372	0.8	11.4	10.6	1.1	0.0
Overall	5950	1.9	15.2	14.6	2.2	<0.1

[a]France, Germany, Italy, Spain, United Kingdom.

to meropenem against Enterobacteriaceae. Whereas ceftolozane/tazobactam had little activity against CRE, XDR or PDR isolates of Enterobacteriaceae, it retained activity against most ESBL non-CRE phenotype isolates, second only to meropenem. Likewise, ceftolozane/tazobactam was more active than the other antipseudomonal β-lactam agents tested against isolates of *P. aeruginosa* that were NS to cefepime, meropenem or piperacillin/tazobactam.

In agreement with previous surveys,[18–21] we found a great deal of variation in resistance rates to ceftazidime and meropenem with higher rates of resistance among European countries in the southern (Greece and Portugal) and eastern (Poland) countries versus northern countries (such as Germany, Ireland, Sweden and the UK). This pertains to both Enterobacteriaceae and *P. aeruginosa* (Tables 3 and 4) and has been shown to correlate with regional differences in β-lactamase production.[20]

Whereas the spread of CRE is a major concern in Europe, the prevalence is variable.[20,27] Higher prevalence rates of CRE have been reported in Greece, Italy, Turkey and Israel, with lower rates in the northern nations.[20,27] Our results confirm these observations with CRE rates exceeding 1% in Greece (5.4%), Israel (1.2%), Italy (3.8%), Poland (29.9%) and Turkey (1.8%) (Table 3). Notably, CRE were not identified in 7 of the 19 countries participating in the survey. High and variable rates of ESBL non-CRE phenotype and MDR Enterobacteriaceae are consistent with those previously reported by Farrell *et al.*,[19] Sader *et al.*[20] and Canton *et al.*[27]

In summary, these data for ceftolozane/tazobactam collected in 2012–15 from 41 medical centres in 17 European countries plus Israel and Turkey demonstrated sustained potency and spectrum against Enterobacteriaceae and *P. aeruginosa* when compared to previous European studies.[20,21] These data suggest that ceftolozane/tazobactam may be an important treatment option for UTI and IAI caused by both wild-type and MDR strains of *P. aeruginosa* and Enterobacteriaceae.[17] One of the more important aspects of this survey is the confirmation of extensive variation in antibiotic-resistant phenotypes of GNB across Europe. This finding emphasizes the need for ongoing surveillance and application of antimicrobial stewardship to prevent the further spread of β-lactam resistance.[16]

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Transparency declarations

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Table 4. Antimicrobial activity of ceftolozane/tazobactam, ceftazidime and meropenem against European isolates of *P. aeruginosa* stratified by country

	Percentage susceptible[a]		
Country (no. tested)	ceftolozane/tazobactam	ceftazidime	meropenem
Austria (7)	100.0	85.7	85.7
Belgium (15)	86.7	80.0	73.3
Denmark (29)	100.0	96.6	100.0
Finland (16)	100.0	93.8	100.0
France (50)	100.0	82.0	92.0
Germany (92)	93.5	83.7	83.7
Greece (18)	61.1	61.1	61.1
Ireland (21)	100.0	81.0	81.0
Israel (13)	100.0	69.2	76.9
Italy (75)	92.0	73.3	78.7
Netherlands (1)	100.0	100.0	100.0
Poland (32)	75.0	46.9	34.4
Portugal (38)	63.2	52.6	44.7
Russia (5)	60.0	20.0	100.0
Spain (51)	100.0	80.4	90.2
Sweden (23)	100.0	91.3	87.0
Switzerland (9)	100.0	88.9	100.0
Turkey (44)	88.6	63.6	70.5
UK (64)	100.0	90.6	84.4
Five major countries (332)[b]	96.4	81.9	84.9
Overall (603)	91.7	76.9	78.9

[a]Percentage susceptible at the following MIC breakpoints (CLSI, 2016[24]): ceftolozane/tazobactam $\leq$4 mg/L; ceftazidime $\leq$8 mg/L; meropenem $\leq$2 mg/L.
[b]France, Germany, Italy, Spain and United Kingdom.

AstraZeneca, Basilea, Bayer, BD, Biomodels, Cardeas, CEM-102 Pharma, Cempra, Cidara, Cormedix, CSA Biotech, Cubist, Debiopharm, Dipexium, Duke, Durata, Entasis, Fortress, Fox Chase Chemical, GSK, Medpace, Melinta, Micurx, Motif, N8 Medical, Nabriva, Nexcida, Novartis, Paratek, Pfizer, Polyphor, Rempex, Scynexis, Shionogi, Spero Therapeutics, Symbal Therapeutics, Synlogic, TGV Therapeutics, The Medicines Company, Theravance, ThermoFisher, Venatorx, Wockhardt, Zavante. Some JMI employees are advisors/consultants for Allergan, Astellas, Cubist, Pfizer, Cempra and Theravance. There are no speakers' bureaus or stock options to declare.

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