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

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ABSTRACT

OBJECTIVE: To evaluate the anti-*P. aeruginosa* activity of ceftolozane/tazobactam, ceftazidime, meropenem, and other comparator agents against isolates from 15 European (EU) countries and Israel. Ceftolozane is a novel oxyimino-aminothiazolyl cephalosporin with potent anti-pseudomonal activity. Tazobactam, a penicillanic acid-sulfone, is a well-established β-lactamase inhibitor that extends the spectrum of β-lactam agents. Ceftolozane/tazobactam is currently being investigated for treatment of ventilator-associated bacterial pneumonia, and was recently approved for complicated intra-abdominal infections (in combination with metronidazole) and complicated urinary tract infections in the USA.

METHODS: A total of 1266 *P. aeruginosa* isolates were consecutively collected during 2013 from 34 medical centers located in 15 EU countries, including Turkey, Russia, 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 11 in Ukraine to 197 in Spain. Ceftolozane/tazobactam (overall $MIC_{50/90}$, 0.5/4 mg/L) was generally 4-fold more active than ceftazidime ($MIC_{50/90}$, 2/>32 mg/L) and inhibited 93.4% and 91.5% of all isolates, at MIC values of ≤8 mg/L and ≤4 mg/L, respectively. In contrast, susceptibility to ceftazidime was 75.4%. Similarly, susceptibility to meropenem was 71.0% overall. The highest combined susceptibility rates observed for ceftazidime and meropenem were 90.5%/90.5% (Sweden) and 91.3%/82.6% (Ireland), respectively. Susceptibility (by EUCAST criteria) to both ceftazidime and meropenem was extremely low (≤50%) in Belgium and Poland and below 70% in Portugal and Russia. Overall susceptibility rates (by EUCAST criteria) to piperacillin/tazobactam, doripenem, ciprofloxacin, and amikacin were 69.2, 66.1, 65.6, and 86.1%, respectively. MDR rates (26.0% overall) varied widely, ranging from 9.5% in Sweden to 64.8% in Poland (Ukraine 0.0% but only 11 isolates). XDR rates were >30% in Belgium, Poland, Portugal, and Russia. Only 2 PDR isolates were found in Italy.

CONCLUSION: Antimicrobial susceptibility, MDR and XDR of *P. aeruginosa* varied widely among EU countries. MDR, XDR, and resistance rates to ceftazidime and meropenem were generally elevated and particularly high in some EU nations. At MIC values of ≤4 and ≤8 mg/L, ceftolozane/tazobactam had higher susceptibility rates than β-lactams currently available for treatment of *P. aeruginosa* infections.

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 and cefepime.
- Ceftolozane has been demonstrated to be stable against many *P. aeruginosa* resistance mechanisms, including some organisms with porin deficiencies or mutations. Unregulated efflux has little effect on ceftolozane, as ceftolozane is not a substrate for the efflux pumps commonly found in *P. aeruginosa* and its low affinity for pseudomonal AmpC maintains activity in AmpC-hyperproducing *P. aeruginosa*.
- 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.
- Ceftolozane/tazobactam has 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 against clinical *P. aeruginosa* isolates collected from hospitals in Europe (EU) and Israel during 2013.

MATERIALS AND METHODS

Organism Collection

- A total of 1266 clinically significant, consecutively collected, nonduplicate isolates of *P. aeruginosa* were evaluated from the following infection types: pneumonias 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 testing conducted according to the methodology of the Clinical and Laboratory Standards Institute (CLSI) was performed to determine antimicrobial susceptibility of ceftolozane combined with tazobactam at a fixed concentration of 4 mg/L and of 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 ensure proper test conditions and procedures.
- Multidrug-resistant (MDR), extensively drug-resistant (XDR), and pandrug-resistant (PDR) *P. aeruginosa* 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, 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-S24 guidelines and all QC results were within published ranges.

RESULTS

- Overall, ceftolozane/tazobactam (inhibited 91.5% and 93.4% of 1266 *P. aeruginosa* strains at ≤4/4 and ≤8/4 mg/L, respectively) was the second most potent agent, next to colistin (MIC required to inhibit the growth of 50%/90% of organisms [$MIC_{50/90}$], 1/2 mg/L and 99.8% isolates were susceptible by EUCAST criteria).
- Susceptibility rates for all other agents (% susceptible; **Table 1**) were much lower; ceftazidime (75.4%), cefepime (76.8%), meropenem (71.0%), doripenem (66.1% EUCAST, 74.5% CLSI), piperacillin/tazobactam (P/T; 69.2%), ciprofloxacin (65.6% EUCAST, 70.1% CLSI), levofloxacin (60.0% EUCAST, 67.8% CLSI), amikacin (86.1% EUCAST, 90.2% CLSI), and gentamicin (82.1%).
- Ceftolozane/tazobactam retained activity against many isolates in resistant phenotype subsets of *P. aeruginosa*, inhibiting 69.5/75.6% of ceftazidime nonsusceptible (NS), 73.0/79.0% of meropenem-NS, 59.2/66.8% of ceftazidime- and meropenem-NS, 72.8/79.2% of P/T-NS, and 58.8/66.7% of ceftazidime- and meropenem- and P/T-NS subsets at MIC values of ≤4/≤8 mg/L (**Table 2**).
- Overall, 329 (26.0%) isolates were classified as MDR, 236 (18.6%) as XDR, and only 2 isolates (1 each from Catania and Genoa in Italy) were found to be PDR. Ceftolozane/tazobactam retained activity against many MDR strains ($MIC_{50/90}$, 4/>32 mg/L; 68.4% and 75.1% inhibited at ≤4 and ≤8 mg/L, respectively), and XDR strains ($MIC_{50/90}$, 4/>32 mg/L; 58.9% and 67.0% inhibited at ≤4 and ≤8 mg/L, respectively, **Table 2**). With the exception of colistin, resistance rates (EUCAST) for other agents ranged from 35.5% (amikacin) to 94.2% (piperacillin/tazobactam) against MDR strains, and 44.4% (amikacin) to 97.5% (piperacillin/tazobactam) against XDR strains (**Table 1**).

RESULTS (cont'd)

Table 1. Activity of Ceftolozane/Tazobactam and Comparator Antimicrobial Agents When Tested Against *Pseudomonas aeruginosa* From European Hospitals (2013)

Organism (No. Tested)/ Antimicrobial Agent	MIC (mg/L)		%S/%I/%R	
	50%	90%	CLSI[a]	EUCAST[a]
P. aeruginosa (1266)				
Ceftolozane/tazobactam	0.5	4	91.5/2.0/6.5[b]	-/-/-[c]
Ceftazidime	2	>32	75.4/4.5/20.1	75.4/0/24.6
Cefepime	4	>16	76.8/11.5/11.7	76.8/0/23.2
Meropenem	0.5	>8	71.0/7.6/21.4	71.0/16.2/12.8
Doripenem	0.5	8	74.5/9.7/15.8	66.1/8.4/25.5
Piperacillin/tazobactam	8	>64	69.2/12.1/18.7	69.2/0/30.8
Levofloxacin	0.5	>4	67.8/5.8/26.4	60.0/7.8/32.2
Ciprofloxacin	0.25	>4	70.1/4.9/25.0	65.6/4.5/29.9
Amikacin	2	16	90.2/3.2/6.6	86.1/4.1/9.8
Gentamicin	≤1	>8	82.1/2.7/15.2	82.1/0/17.9
Colistin	1	2	99.6/0.2/0.2	99.8/0.1/0.1
MDR (329)				
Ceftolozane/tazobactam	4	>32	68.4/6.7/24.9[b]	-/-/-
Ceftazidime	32	>32	22.8/13.7/63.5	22.8/0.0/77.2
Cefepime	16	>16	23.1/36.5/40.4	23.1/0.0/76.9
Meropenem	8	>8	16.7/12.2/71.1	16.7/36.8/46.5
Doripenem	8	>8	19.8/22.5/57.7	10.0/9.7/80.3
Piperacillin/tazobactam	>64	>64	5.8/33.4/60.8	5.8/0.0/94.2
Levofloxacin	>4	>4	16.4/8.8/74.8	7.6/8.8/83.6
Ciprofloxacin	>4	>4	19.8/6.4/73.8	15.2/4.6/80.2
Amikacin	8	>32	64.4/11.3/24.3	51.4/13.1/35.5
Gentamicin	>8	>8	39.2/7.6/53.2	39.2/0.0/60.8
Colistin	2	2	98.5/0.6/0.9	99.1/0.0/0.9
XDR (236)				
Ceftolozane/tazobactam	32	>32	58.9/8.1/33.0[b]	-/-/-
Ceftazidime	32	>32	10.6/15.7/73.7	10.6/0.0/89.4
Cefepime	16	>16	14.8/35.6/49.6	14.8/0.0/85.2
Meropenem	>8	>8	8.5/11.0/80.5	8.5/36.9/54.6
Doripenem	8	>8	11.0/19.9/69.1	4.2/6.8/89.0
Piperacillin/tazobactam	>64	>64	2.5/28.4/69.1	2.5/0.0/97.5
Levofloxacin	>4	>4	6.8/7.2/86.0	0.9/5.9/93.2
Ciprofloxacin	>4	>4	9.3/5.1/85.6	5.9/3.4/90.7
Amikacin	16	>32	55.5/14.0/30.5	42.0/13.6/44.4
Gentamicin	>8	>8	27.1/7.2/65.7	27.1/0.0/72.9
Colistin	2	2	97.9/0.9/1.2	98.7/0.0/1.3

[a]According to the susceptible breakpoints established by CLSI (2015) and EUCAST (2015).
[b]Ceftolozane/tazobactam USA FDA-approved breakpoint for *P. aeruginosa*: Susceptible ≤4/4 mg/L, Intermediate 8/4 mg/L, Resistant ≥16/4 mg/L.
[c] "-" breakpoint not available.

Table 2. Cumulative MIC Distributions of Ceftolozane/Tazobactam Tested Against *Pseudomonas aeruginosa*, Including Various Resistance Subsets

Organism/Resistant Subset (No. Tested)	Number 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}
P. aeruginosa (1266)	3 (0.2)	41 (3.5)	650 (54.8)	271 (76.2)	113 (85.2)	80 (91.5)	25 (93.4)	18 (94.9)	16 (96.1)	49 (100.0)	0.5	4
MDR (329)	0 (0.0)	1 (0.3)	10 (3.3)	65 (23.1)	86 (49.2)	63 (68.4)	22 (75.1)	17 (80.2)	16 (85.1)	49 (100.0)	4	>32
XDR (236)	0 (0.0)	0 (0.0)	3 (1.3)	27 (12.7)	62 (39.0)	47 (58.9)	19 (67.0)	15 (73.3)	15 (79.7)	48 (100.0)	4	>32
PDR (2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (50.0)	0 (50.0)	0 (50.0)	0 (50.0)	0 (50.0)	0 (50.0)	1 (100.0)	1	
CAZ-S (955)	3 (0.3)	41 (4.6)	645 (72.2)	225 (95.7)	22 (98.0)	6 (98.6)	6 (99.3)	5 (99.8)	2 (100.0)		0.5	1
CAZ-NS (311)	0 (0.0)	0 (0.0)	5 (1.6)	46 (16.4)	91 (45.7)	74 (69.5)	19 (75.6)	13 (79.7)	14 (84.2)	49 (100.0)	4	>32
MEM-S (897)	3 (0.3)	39 (4.7)	581 (69.5)	190 (90.6)	49 (96.1)	26 (99.0)	3 (99.3)	2 (99.6)	0 (99.6)	4 (100.0)	0.5	1
MEM-NS (366)	0 (0.0)	1 (0.3)	67 (18.6)	81 (40.7)	64 (58.2)	54 (73.0)	22 (79.0)	16 (83.3)	16 (87.7)	45 (100.0)	2	>32
CAZ- & MEM-NS (211)	0 (0.0)	0 (0.0)	1 (0.5)	20 (10.0)	54 (35.6)	50 (59.2)	16 (66.8)	11 (72.0)	14 (78.7)	45 (100.0)	4	>32
P/T-S (876)	3 (0.3)	40 (4.9)	629 (76.7)	187 (98.1)	14 (99.7)	1 (99.8)	0 (99.8)	1 (99.9)	0 (99.9)	1 (100.0)	0.5	1
P/T-NS (389)	0 (0.0)	1 (0.3)	20 (5.4)	84 (27.0)	99 (52.4)	79 (72.8)	25 (79.2)	18 (83.6)	16 (87.7)	48 (100.0)	2	>32
CAZ-, MEM- & P/T- NS (204)	0 (0.0)	0 (0.0)	1 (0.5)	17 (8.8)	52 (34.3)	50 (58.8)	16 (66.7)	10 (71.6)	14 (78.4)	14 (100.0)	4	>32
Cefepime-S (972)	3 (0.3)	41 (4.5)	650 (71.4)	238 (95.9)	26 (98.6)	3 (98.9)	4 (99.3)	3 (99.6)	0 (99.6)	4 (100.0)	0.5	1
Cefepime-NS (294)	0 (0.0)	0 (0.0)	0 (0.0)	33 (11.2)	87 (40.8)	77 (67.0)	21 (74.2)	15 (79.3)	16 (84.7)	45 (100.0)	4	>32
Levofloxacin-S (856)	2 (0.2)	35 (4.3)	563 (70.1)	174 (90.4)	37 (94.7)	30 (98.3)	6 (99.0)	4 (99.4)	3 (99.8)	2 (100.0)	0.5	1
Levofloxacin-NS (407)	1 (0.3)	5 (1.5)	85 (22.4)	97 (46.2)	76 (64.9)	50 (77.2)	19 (81.8)	14 (85.3)	13 (88.5)	47 (100.0)	2	>32
Gentamicin-S (1039)	3 (0.3)	39 (4.0)	636 (65.3)	218 (86.2)	70 (93.0)	49 (97.7)	13 (98.9)	3 (99.2)	0 (99.2)	8 (100.0)	0.5	2
Gentamicin-NS (227)	0 (0.0)	2 (0.9)	14 (7.1)	53 (30.4)	43 (49.3)	31 (63.0)	12 (68.3)	15 (74.9)	16 (819)	41 (100.0)	4	>32

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; P/T, piperacillin/tazobactam.

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

Country (No. Tested)	Ceftolozane/Tazobactam $MIC_{50/90}$ (% at ≤4/4/≤8/4 mg/L)	Ceftazidime $MIC_{50/90}$ (% at ≤8 mg/L)[a]	Meropenem $MIC_{50/90}$ (% at ≤2 mg/L)[a]	%MDR/%XDR/ %PDR[b]
Belgium (40)	1/>32 (72.5/72.5)	8/>32 (50.0)	4/>8 (41.0)	52.5/35.4/0.0
Czech Rep. (22)	0.5/4 (95.5/100.0)	2/16 (81.8)	0.5/8 (63.6)	27.3/18.2/0.0
France (76)	0.5/2 (98.7/100.0)	2/32 (77.6)	0.5/4 (88.2)	14.5/9.2/0.0
Germany (168)	0.5/2 (98.2/99.4)	2/32 (85.7)	0.5/8 (74.4)	17.9/10.7/0.0
Greece (44)	0.5/8 (88.6/90.9)	2/16 (88.6)	0.5/8 (84.1)	15.9/9.1/0.0
Ireland (46)	0.5/2 (97.8/100.0)	2/8 (91.3)	0.5/4 (82.6)	15.2/4.4/0.0
Israel (66)	0.5/4 (97.0/98.5)	4/>32 (72.7)	0.5/>8 (71.2)	31.8/19.7/0.0
Italy (160)	0.5/4 (91.3/94.4)	4/>32 (71.9)	0.5/>8 (72.3)	31.9/25.6/1.3
Poland (71)	2/16 (81.7/85.9)	16/>32 (46.5)	8/>8 (22.5)	64.8/53.5/0.0
Portugal (60)	1/32 (71.7/73.3)	2/>32 (60.0)	2/>8 (51.7)	38.3/36.7/0.0
Russia (71)	1/>32 (71.8/73.2)	8/>32 (52.1)	1/>8 (63.4)	40.9/33.8/0.0
Spain (197)	0.5/4 (94.9/96.5)	2/32 (80.7)	0.5/8 (78.7)	18.3/14.2/0.0
Sweden (42)	0.5/2 (97.6/100.0)	2/8 (90.5)	0.25/2 (90.5)	9.5/2.4/0.0
Turkey (111)	1/4 (91.9/95.5)	2/32 (82.9)	0.5/>8 (73.6)	23.4/13.5/0.0
UK (81)	0.5/2 (100.0/100.0)	2/32 (84.0)	0.5/>8 (75.3)	13.6/6.2/0.0
Ukraine (11)	0.5/2 (100.0/100.0)	4/>32 (63.6)	0.5/0.5 (100.0)	0.0/0.0/0.0
Overall (1266)	**0.5/4 (91.5/93.4)**	**2/>32 (75.4)**	**0.5/>8 (71.0)**	**26.0/18.6/0.2**

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

- The highest susceptibility rates for ceftazidime and meropenem were observed in Sweden (90.5% and 90.5%, respectively) and Ireland (91.3% and 82.6%, respectively). Ceftolozane/tazobactam inhibited 97.6/100.0% and 97.8/100.0% of strains at ≤4/≤8 mg/L in Sweden and Ireland, respectively (**Table 3**).
- Resistance rates to ceftazidime and meropenem were high (>40%) in Poland, Portugal, Belgium, and Russia, and although ceftolozane/tazobactam was more active than comparators against *P. aeruginosa* from these countries, activity was lower (**Table 3**).
- Ceftolozane/tazobactam (overall MIC_{50}, 0.5 mg/L) was generally 4-fold more active than ceftazidime (MIC_{50}, 2 mg/L) and inhibited >90% of isolates at MIC of ≤4 mg/L in 11 countries (**Table 3**).
- MDR/XDR rates (**Table 3**) were highest in Poland (64.8/53.5%), Belgium (52.5/35.4%), and Russia (40.9/33.8%), and lowest in Sweden (9.5/2.4%) and the UK (13.6/6.2%).

CONCLUSIONS

- Antimicrobial susceptibility and MDR/XDR rates of *P. aeruginosa* varied widely among EU countries.
- Resistance to ceftazidime and meropenem was generally elevated and particularly high in some EU nations, such as Poland, Portugal, Belgium, and Russia.
- At MIC values of ≤4/4 and ≤8/4 mg/L, ceftolozane/tazobactam provides greater coverage than β-lactams currently available for treatment of *P. aeruginosa* infections and could represent a valuable addition to treatment options for this pathogen.

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