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Antimicrobial Activity of Ceftolozane/Tazobactam from the PACTS Programme Tested against *Pseudomonas aeruginosa* Isolated from Patients Hospitalised in Intensive Care Units in Europe, Turkey and Israel (2013-2014)

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Introduction and Purpose

- Ceftolozane/tazobactam is an antibacterial consisting of ceftolozane, a novel antipseudomonal cephalosporin, and tazobactam, a well-established β-lactamase inhibitor[1]
- Ceftolozane exerts its bactericidal activity by inhibiting essential penicillin-binding proteins, resulting in inhibition of cell wall synthesis and subsequent cell death[1]
- Compared with ceftazidime and cefepime, ceftolozane demonstrates greater activity against *Pseudomonas aeruginosa*[2-5]
  - Ceftolozane is stable against many *P. aeruginosa* resistance mechanisms, including porin deficiencies and mutations[1]
  - Up-regulated efflux has little effect on ceftolozane because ceftolozane is not a substrate for the efflux pumps commonly found in *P. aeruginosa* and because its low affinity for pseudomonal AmpC maintains activity in AmpC-hyper-producing *P. aeruginosa*[6]
- Tazobactam is a potent inhibitor of most common class A and some class C β-lactamases; binding to the active site of these enzymes protects ceftolozane from hydrolysis and broadens coverage to include most extended-spectrum β-lactamase–producing Enterobacteriaceae[3]
- Ceftolozane/tazobactam has been approved by the US Food and Drug Administration for the treatment of complicated urinary tract infections and, in combination with metronidazole, for the treatment of complicated intra-abdominal infections[1]; a Phase 3 trial for the treatment of nosocomial pneumonia is under way
- In this study, we evaluated the *in vitro* activities of ceftolozane/tazobactam, ceftazidime, piperacillin/tazobactam (P/T), meropenem and other comparator agents against clinical *P. aeruginosa* isolates obtained from intensive care unit (ICU) patients in Europe, Turkey and Israel during 2013 and 2014

Methods

Organism collection

- 502 *P. aeruginosa* isolates were consecutively collected from ICU patients from 38 medical centres located in 21 countries (number of centres) during 2013-2014: Belgium (1), Czech Republic (1), Denmark (1), Finland (1), France (4), Germany (4), Greece (1), Ireland (2), Israel (1), Italy (4), Netherlands (1), Norway (1), Poland (1), Portugal (1), Russia (3), Spain (3), Sweden (1), Switzerland (1), Turkey (2), Ukraine (1) and United Kingdom (3)

Antimicrobial susceptibility testing

- Antimicrobial susceptibility of ceftolozane combined with tazobactam (at a fixed concentration of 4 mg/L) and several comparator agents was determined using broth microdilution methods as described in Clinical and Laboratory Standards Institute (CLSI) M07-A10[7]
- Validated minimum inhibitory concentration (MIC) panels were manufactured by ThermoFisher 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 recent guidelines based on non-susceptibility (EUCAST breakpoints)[8] to ceftazidime, meropenem, piperacillin/tazobactam, levofloxacin, gentamicin and colistin
  - Classifications were based on the following recommended parameters: MDR = non-susceptible to ≥3 antimicrobial classes; XDR = susceptible to ≤2 antimicrobial classes; PDR = non-susceptible to all antimicrobial classes[9]
- 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-S26[10] and the European Committee on Antimicrobial Susceptibility Testing (EUCAST; 2016) guidelines[8]; all QC results were within published ranges

Results

- Overall, ceftolozane/tazobactam was the second most potent agent against *P. aeruginosa* after colistin
  - Ceftolozane/tazobactam MIC required to inhibit the growth of 50% and 90% of isolates ($MIC_{50/90}$) was 1/4 mg/L; 90.2% of the isolates were susceptible by EUCAST criteria (**Tables 1 and 2**)
  - Colistin $MIC_{50/90}$ was 2/2 mg/L; 100% of the isolates were susceptible by EUCAST criteria (**Table 2**)
- Susceptibility rates for all other agents (% susceptible by EUCAST criteria; **Table 2**) were much lower: ceftazidime: 70.7%; cefepime: 75.1%; meropenem: 64.9%; doripenem: 56.7%; P/T: 67.5%; levofloxacin: 57.5%; amikacin: 83.3%; and gentamicin: 79.3%
- Ceftolozane/tazobactam retained activity (% susceptible) against many isolates in resistant (R) phenotype subsets of *P. aeruginosa*, inhibiting 68.0% of ceftazidime-R, 45.7% of meropenem-R, 30.8% of ceftazidime-R and meropenem-R, 70.6% of P/T-R and 31.4% of ceftazidime-, meropenem- and P/T-R subsets (**Table 1**)
- Overall, 197 isolates (39.2%) were classified as MDR and 88 (17.5%) as XDR; no isolates were found to be PDR
  - Ceftolozane/tazobactam retained activity against many MDR strains ($MIC_{50/90}$, 2/>32 mg/L; 75.1% susceptible) and XDR strains ($MIC_{50/90}$, 4/>32 mg/L; 52.3% susceptible; **Table 1**)
  - With the exception of colistin, resistance rates (by EUCAST criteria) for other agents ranged from 28.9% (amikacin) to 73.6% (doripenem) against MDR strains and 52.3% (amikacin) to 96.6% (levofloxacin) against XDR strains (**Table 2**)
- In countries with >10 isolates, the highest susceptibility to ceftazidime or meropenem was observed in Ireland (100.0% and 92.3%, respectively), Greece (90.0% for ceftazidime) and France (85.7% for meropenem; **Table 3**)
  - Ceftolozane/tazobactam susceptibility was 100.0% and 92.5% in Ireland and Greece, respectively (**Table 3**)
- In countries with >10 isolates, resistance rates to ceftazidime and meropenem were high (>40.0%) in Poland, Belgium and Russia; although ceftolozane/tazobactam was more active than comparators against *P. aeruginosa* in these countries, activity was lower than in other countries (**Table 3**)
  - Ceftolozane/tazobactam (overall MIC_{50}, 1 mg/L) was generally 4-fold more active than ceftazidime (MIC_{50}, 4 mg/L) and inhibited >90.0% of isolates at MIC of ≤4 mg/L in 8 countries (**Table 3**)
- In countries with >10 isolates, MDR/XDR rates (**Table 3**) were highest in Poland (81.0%/50.0%), Belgium (70.4%/37.0%) and Russia (65.2%/52.2%) and were lowest in Ireland (7.7%/0.0%), France (29.6%/8.2%) and Greece (12.5%/7.5%)

Table 1. Cumulative MIC distributions of ceftolozane/tazobactam tested against *Pseudomonas aeruginosa*, including various resistant subsets

Organism / resistant subset, n	Number of isolates (cumulative %) inhibited at ceftolozane/tazobactam MIC, mg/L										
	0.25	0.5	1	2	4	8	16	32	>32	MIC_{50}	MIC_{90}
Pseudomonas aeruginosa (502)	13 (2.6)	233 (49.0)	116 (72.1)	57 (83.5)	34 (90.2)†	6 (91.4)	5 (92.4)	5 (93.4)	33 (100.0)	1	4
MDR (197)	1 (0.5)	21 (11.2)	53 (38.1)	48 (62.4)	25 (75.1)	6 (78.2)	5 (80.7)	5 (83.2)	33 (100.0)	2	>32
XDR (88)	0 (0.0)	1 (1.1)	9 (11.4)	22 (36.4)	14 (52.3)	2 (54.5)	3 (58.0)	5 (63.6)	32 (100.0)	4	>32
CAZ-S (355)	13 (3.7)	232 (69.0)	98 (96.6)	9 (99.2)	1 (99.4)	1 (99.7)	1 (100.0)			0.5	1
CAZ-R (147)	0 (0.0)	1 (0.7)	18 (12.9)	48 (45.6)	33 (68.0)	5 (71.4)	4 (74.1)	5 (77.6)	33 (100.0)	4	>32
MEM-S (325)	12 (3.7)	200 (65.2)	76 (88.6)	23 (95.7)	13 (99.7)	0 (99.7)	1 (100.0)			0.5	2
MEM-R (70)	0 (0.0)	3 (4.3)	10 (18.6)	9 (31.4)	10 (45.7)	3 (50.0)	3 (54.3)	5 (61.4)	27 (100.0)	8	>32
CAZ-R and MEM-R (52)	0 (0.0)	0 (0.0)	1 (1.9)	6 (13.5)	9 (30.8)	2 (34.6)	2 (38.5)	5 (48.1)	27 (100.0)	>32	>32
P/T-S (339)	13 (3.8)	227 (70.8)	87 (96.5)	11 (99.7)	0 (99.7)	0 (99.7)	0 (99.7)	0 (99.7)	1 (100.0)	0.5	1
P/T-R (163)	0 (0.0)	6 (3.7)	29 (21.5)	46 (49.7)	34 (70.6)	6 (74.2)	5 (77.3)	5 (80.4)	32 (100.0)	4	>32
CAZ-, MEM-, and P/T- R (51)	0 (0.0)	0 (0.0)	1 (2.0)	6 (13.7)	9 (31.4)	2 (35.3)	2 (39.2)	5 (49.0)	26 (100.0)	>32	>32
Cefepime-S (377)	13 (3.4)	233 (65.3)	103 (92.6)	22 (98.4)	1 (98.7)	1 (98.9)	0 (98.9)	0 (98.9)	4 (100.0)	0.5	1
Cefepime-R (125)	0 (0.0)	0 (0.0)	13 (10.4)	35 (38.4)	33 (64.8)	5 (68.8)	5 (72.8)	5 (76.8)	29 (100.0)	4	>32
Levofloxacin-S (288)	12 (4.2)	191 (70.5)	55 (89.6)	16 (95.1)	13 (99.7)	0 (99.7)	1 (100.0)			0.5	2
Levofloxacin-R (175)	1 (0.6)	24 (14.3)	48 (41.7)	36 (62.3)	20 (73.7)	5 (76.6)	4 (78.9)	4 (81.1)	33 (100.0)	2	>32
Gentamicin-S (398)	12 (3.0)	230 (60.8)	86 (82.4)	34 (91.0)	24 (97.0)	4 (98.0)	3 (98.7)	0 (98.7)	5 (100.0)	0.5	2
Gentamicin-R (104)	1 (1.0)	3 (3.8)	30 (32.7)	23 (54.8)	10 (64.4)	2 (66.3)	2 (68.3)	5 (73.1)	28 (100.0)	2	>32

CAZ = ceftazidime; MDR = multidrug-resistant; MEM = meropenem; MIC = minimum inhibitory concentration; MIC_{50} = minimum inhibitory concentration required to inhibit growth of 50% of isolates; MIC_{90} = minimum inhibitory concentration required to inhibit growth of 90% of isolates; P/T = piperacillin/tazobactam; R = resistant; S = susceptible; XDR = extensively drug-resistant.

†Underlined results based on the EUCAST susceptibility breakpoints for ceftolozane/tazobactam.[8]

Table 2. Activity of ceftolozane/tazobactam and comparator antimicrobial agents when tested against *Pseudomonas aeruginosa* isolated from ICU patients from European, Turkish and Israeli hospitals (2013-2014)

Organism (n) / antimicrobial agent	MIC, mg/L		%S / %I / %R†	
	MIC_{50}	MIC_{90}	CLSI	EUCAST
Pseudomonas aeruginosa (502)				
Ceftolozane/tazobactam	1	4	90.2 / 1.2 / 8.6	90.2 / –‡ / 9.8
Ceftazidime	4	>32	70.7 / 5.4 / 23.9	70.7 / – / 29.3
Cefepime	4	>16	75.1 / 14.7 / 10.2	75.1 / – / 24.9
Meropenem	1	>8	64.9 / 10.0 / 25.1	64.9 / 21.2 / 14.0
Doripenem	1	>4	68.3 / 13.6 / 18.2	56.7 / 11.6 / 31.7
Piperacillin/tazobactam	8	>64	67.5 / 14.7 / 17.7	67.5 / – / 32.5
Levofloxacin	1	>4	65.1 / 4.4 / 30.5	57.5 / 7.6 / 34.9
Amikacin	2	32	88.4 / 3.4 / 8.2	83.3 / 5.2 / 11.6
Gentamicin	2	>8	79.3 / 4.6 / 16.1	79.3 / – / 20.7
Colistin	2	2	98.8 / 1.2 / 0.0	100.0 / – / 0.0
MDR (197)				
Ceftolozane/tazobactam	2	>32	75.1 / 3.0 / 21.8	75.1 / – / 24.9
Ceftazidime	32	>32	38.6 / 10.2 / 51.3	38.6 / – / 61.4
Cefepime	16	>16	43.1 / 32.0 / 24.9	43.1 / – / 56.9
Meropenem	8	>8	21.3 / 16.8 / 61.9	21.3 / 43.7 / 35.0
Doripenem	4	>4	26.4 / 28.4 / 45.2	11.7 / 14.7 / 73.6
Piperacillin/tazobactam	64	>64	31.0 / 31.5 / 37.6	31.0 / – / 69.0
Levofloxacin	>4	>4	27.4 / 7.1 / 65.5	16.2 / 11.2 / 72.6
Amikacin	8	>32	71.1 / 8.1 / 20.8	58.9 / 12.2 / 28.9
Gentamicin	8	>8	49.7 / 10.2 / 40.1	49.7 / – / 50.3
Colistin	2	2	98.5 / 1.5 / 0.0	100.0 / – / 0.0
XDR (88)				
Ceftolozane/tazobactam	4	>32	52.3 / 2.3 / 45.5	52.3 / – / 47.7
Ceftazidime	32	>32	11.4 / 15.9 / 72.7	11.4 / – / 88.6
Cefepime	16	>16	22.7 / 36.4 / 40.9	22.7 / – / 77.3
Meropenem	>8	>8	4.5 / 14.8 / 80.7	4.5 / 42.0 / 53.4
Doripenem	>4	>4	6.8 / 17.0 / 76.1	1.1 / 5.7 / 93.2
Piperacillin/tazobactam	>64	>64	9.1 / 37.5 / 53.4	9.1 / 0.0 / 90.9
Levofloxacin	>4	>4	3.4 / 6.8 / 89.8	1.1 / 2.3 / 96.6
Amikacin	32	>32	47.7 / 11.4 / 40.9	29.5 / 18.2 / 52.3
Gentamicin	>8	>8	21.6 / 13.6 / 64.8	21.6 / – / 78.4
Colistin	2	2	96.6 / 3.4 / 0.0	100.0 / – / 0.0

CLSI = Clinical and Laboratory Standards Institute; EUCAST = European Committee on Antimicrobial Susceptibility Testing; ICU = intensive care unit; MDR = multidrug-resistant; MIC = minimum inhibitory concentration; MIC_{50} = minimum inhibitory concentration required to inhibit growth of 50% of isolates; MIC_{90} = minimum inhibitory concentration required to inhibit growth of 90% of isolates; R = resistant; I = intermediate; S = susceptible; XDR = extensively drug-resistant.

†Criteria as published by the CLSI (2016)[10] and EUCAST (2016).[8]

‡"–" = no breakpoint available for interpretation.

Table 3. Antimicrobial activity of ceftolozane/tazobactam, ceftazidime and meropenem against *Pseudomonas aeruginosa* strains stratified by country and MDR status (2013-2014)

Country (n)	Ceftolozane/ tazobactam	Ceftazidime	Meropenem	%MDR / %XDR‡
	$MIC_{50/90}$ (%S)†	$MIC_{50/90}$ (%S)†	$MIC_{50/90}$ (%S)†	
Belgium (27)	2 / >32 (70.4)	32 / >32 (37.0)	8 / >8 (30.8)	70.4 / 37.0
Czech Republic (9)	1 / – (–)	4 / – (–)	2 / – (–)	55.6 / 33.3
Denmark (2)	0.5 / – (–)	2 / – (–)	0.12 / – (–)	0.0 / 0.0
Finland (1)	– / –§	– / –	– / –	0.0 / 0.0
France (98)	0.5 / 2 (98.0)	2 / 32 (73.5)	0.5 / 4 (85.7)	29.6 / 8.2
Germany (30)	1 / 4 (96.7)	4 / 32 (86.7)	1 / >8 (53.3)	43.3 / 10.0
Greece (40)	0.5 / 1 (92.5)	2 / 8 (90.0)	0.5 / 8 (82.5)	12.5 / 7.5
Ireland (13)	0.5 / 1 (100.0)	2 / 4 (100.0)	0.25 / 2 (92.3)	7.7 / 0.0
Israel (19)	0.5 / 4 (100.0)	4 / >32 (68.4)	2 / >8 (63.2)	47.4 / 15.8
Italy (45)	0.5 / 32 (86.7)	4 / >32 (73.3)	0.5 / >8 (73.3)	26.7 / 13.3
Netherlands (4)	1 / – (–)	4 / – (–)	1 / – (–)	50.0 / 0.0
Norway (2)	0.5 / – (–)	2 / – (–)	0.12 / – (–)	0.0 / 0.0
Poland (42)	1 / >32 (69.0)	8 / >32 (54.8)	8 / >8 (23.8)	81.0 / 50.0
Portugal (12)	2 / 32 (66.7)	32 / >32 (41.7)	1 / >8 (66.7)	41.7 / 33.3
Russia (23)	1 / >32 (60.9)	16 / 32 (43.5)	4 / >8 (43.5)	65.2 / 52.2
Spain (70)	0.5 / 2 (97.1)	2 / 32 (77.1)	1 / 8 (62.9)	38.6 / 7.1
Sweden (2)	1 / – (–)	1 / – (–)	0.12 / – (–)	50.0 / 50.0
Switzerland (4)	0.5 / – (–)	2 / – (–)	0.25 / – (–)	0.0 / 0.0
Turkey (40)	1 / 4 (97.5)	4 / 32 (72.5)	2 / 8 (65.0)	35.0 / 22.5
Ukraine (2)	0.5 / – (–)	2 / – (–)	0.12 / – (–)	0.0 / 0.0
United Kingdom (17)	0.5 / 2 (100.0)	2 / 32 (70.6)	1 / >8 (58.8)	35.3 / 0.0
Overall (502)	1 / 4 (90.2)	4 / >32 (70.7)	1 / >8 (64.7)	39.2 / 17.5

MDR = multidrug-resistant; $MIC_{50/90}$ = minimum inhibitory concentration required to inhibit growth of 50% and 90% of isolates; S = susceptible; XDR = extensively drug-resistant.

MIC is expressed as mg/L.

†Susceptible breakpoint established by EUCAST (2016)[8], and % susceptibility is provided only for countries with more than 10 isolates.

‡MDR and XDR bacteria were classified based on Magiorakos AP et al.[9]

§"–" = data not available because of the limited number of isolates.

Conclusions

- Antimicrobial susceptibility and MDR/XDR rates of *P. aeruginosa* varied widely among isolates obtained from ICU patients in Europe, Turkey and Israel
- Resistance to ceftazidime and meropenem was generally elevated and particularly high in some European countries, such as Poland, Portugal, Belgium and Russia
- At the EUCAST susceptibility breakpoint of ≤4 mg/L, ceftolozane/tazobactam provides greater coverage than currently available β-lactams for the treatment of *P. aeruginosa* infections and could represent a valuable addition to treatment options for this pathogen

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