Poster No.

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In vitro activity of ceftolozane-tazobactam against *Pseudomonas aeruginosa* isolates non-susceptible to ceftazidime or meropenem

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Background

Pseudomonas aeruginosa is a leading nosocomial Gram-negative pathogen which is often multidrug resistant. Ceftolozane-tazobactam (C/T) is an antibacterial drug combination of the antipseudomonal cephalosporin ceftolozane and the β-lactamase inhibitor tazobactam (1). C/T has been approved for the treatment of complicated intra-abdominal infections (IAI) and complicated urinary tract infections (UTI) (2), and is currently being investigated for the treatment of ventilator-associated pneumonia (VAP) (1, 3).

The objective of this study was to investigate the comparative *in vitro* activity of C/T and three other broad-spectrum β-lactams as well as colistin against *P. aeruginosa* isolates that were intermediate or resistant (R) to ceftazidime (CAZ), meropenem (MEM) or to both compounds.

Material/methods

497 *P. aeruginosa* isolates collected in 10 laboratories in Germany from October 2014 to April 2015 were included. Isolates were recovered from patients with bloodstream infections, lower respiratory tract infections, IAI or UTI. Identification of the isolates was performed by MALDI-TOF. MICs were determined using the broth microdilution method according to the standard ISO 20776-1 (4) at a central laboratory. EUCAST breakpoints (v. 6.0) were applied for interpretation (5).

Results

There were 353 (71%) CAZ-susceptible (S) and MEM-S isolates, 19 (3.8%) CAZ-R but MEM-S isolates, and 84 (16.9%) MEM-non-susceptible (NS, 72 intermediate, 12 resistant) but CAZ-S isolates. Forty-one (8.2%) isolates showed non-susceptibility to both drugs.

C/T demonstrated excellent *in vitro* activity against CAZ-S isolates, with $MIC_{50/90}$ values of 0.5/1 mg/L for isolates that were also MEM-S and 1/1 mg/L for isolates that where MEM-NS. Moreover C/T showed remarkable activity against CAZ-R isolates, with $MIC_{50/90}$ values of 2/4 mg/L and 4/>32 mg/L for MEM-S and MEM-NS isolates, respectively (**Tables 1 & 2**).

C/T at 4 mg/L inhibited 98.8% of the CAZ-S but MEM-NS isolates, 94.7% of the CAZ-R but MEM-S isolates, and 51.2% of the isolates that were NS to both drugs.

Overall, C/T at 4 mg/l was active against 122/144 (84.7%) isolates that were NS or R to either CAZ or MEM (**Table 1**).

In comparison piperacillin-tazobactam (P/T) inhibited 82.1% of the CAZ-S but MEM-NS isolates, but only 10.5% of the CAZ-R but MEM-S isolates, and 4.9% of the isolates that were NS to both drugs (**Table 2**). Overall activity of P/T against isolates that were NS or R to either CAZ or MEM was 50.7% (n=73/144, data not shown). Colistin was active against all strains tested except one CAZ-R but MEM-NS isolate.

Conclusions

C/T exhibited good activity against *P. aeruginosa* isolates with reduced susceptibility or resistance to either ceftazidime or meropenem. Consequently, C/T may be a first-line option for the empirical treatment of infections in which *P. aeruginosa* is suspected or for targeted therapy if resistance to comparator drugs is detected.

Table 1: Distribution of C/T MICs and cumulative % of *P. aeruginosa* isolates inhibited at 4 mg/l

Phenotype (n)	MIC [mg/L]									Cum. % inhibited at 4 mg/L
	≤0.25	0.5	1	2	4	8	16	32	>32	
All isolates (497)	22	291	123	34	5	4	2	3	13	95.6
CAZ-S, MEM-S (353)	20	255	75	3						100
CAZ-S, MEM-NS (84)	2	34	41	6				1		98.8
CAZ-R, MEM-S (19)			2	14	2				1	94.7
CAZ-R, MEM-NS (41)		2	5	11	3	4	2	2	12	51.2
Isolates NS or R to CAZ or MEM or to both drugs (144)	2	36	48	31	5	4	2	3	13	84.7

Abbreviations: Cum. %, cumulative per cent; S, susceptible; NS, non-susceptible; R, resistant; C/T, ceftolozane/tazobactam; CAZ, ceftazidime; MEM, meropenem

Table 2: *In vitro* activity of C/T in comparison to three other broad-spectrum β-lactams and colistin against different resistant phenotypes of *P. aeruginosa*

Species, phenotype (no tested)	Drug	MIC_{50} (mg/L)	MIC_{90} (mg/L)	Percent of isolates		
				S	I	R
All isolates (n=497)	C/T	0.5	2	95.6	–	4.4
	P/T	8	>32	83.7	–	16.3
	CAZ	2	16	87.9	–	12.1
	MEM	0.5	8	74.8	17.9	7.2
	COL	1	2	99.8	–	0.2
CAZ-S, MEM-S (n=353)	C/T	0.5	1	100	–	0
	P/T	4	16	97.2	–	2.8
	CAZ	2	4	100	–	0
	MEM	0.25	1	100	0	0
	COL	1	2	100	–	0
CAZ-S, MEM-NS (n=84)	C/T	1	1	98.8	–	1.2
	P/T	8	32	82.1	–	17.9
	CAZ	4	8	100	–	0
	MEM	4	16	0	85.7	14.3
	COL	1	1	100	–	0
CAZ-R, MEM-S (n=19)	C/T	2	4	94.7	–	5.3
	P/T	>32	>32	10.5	–	89.5
	CAZ	32	>32	0	–	100
	MEM	0.5	2	100	0	0
	COL	1	1	100	–	0
CAZ-R, MEM-NS (n=41)	C/T	4	>32	51.2	–	48.8
	P/T	>32	>32	4.9	–	95.1
	CAZ	32	>32	0	–	100
	MEM	16	>32	0	41.5	58.5
	COL	1	2	97.6	–	2.4

Abbreviations: S, susceptible; I, intermediate; NS, non-susceptible; R, resistant; C/T, ceftolozane/tazobactam; CAZ, ceftazidime; COL, colistin; MEM, meropenem; P/T, piperacillin-tazobactam

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Disclosures

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