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

Michael Kresken*[1], Barbara Körber-Irrgang[1], Harald Seifert[2]

[1]*Antiinfectives Intelligence Gmbh; Campus of the University of Applied Sciences*

[2]*University of Cologne; German Centre for Infection Research; Institute for Medical Microbiology, Immunology and Hygiene*

Background: *Pseudomonas aeruginosa* is a leading nosocomial Gram-negative pathogen which is often multi-drug resistant. Ceftolozane-tazobactam (C/T) is an antibacterial drug combination of the antipseudomonal cephalosporin ceftolozane and the β-lactamase inhibitor tazobactam. C/T has been approved for the treatment of complicated intra-abdominal infections (IAI) and complicated urinary tract infections (UTI), and is currently being investigated for the treatment of ventilator-associated pneumonia (VAP). The objective of this study was to investigate the *in vitro* activity of C/T against *P. aeruginosa* isolates that were intermediate or resistant (R) to ceftazidime (CAZ), meropenem (MEM) or to both compounds.

Material/methods: 497 *Pseudomonas 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 at a central laboratory. EUCAST breakpoints (v. 6.0) were applied for interpretation. Breakpoints (mg/l) were susceptible (S) ≤4 / R >4 for C/T, S ≤8 / R >8 for ceftazidime and S ≤2 / R >8 for meropenem.

Results: Thirty-six percent of the isolates were obtained from intensive care unit patients. Sixty-five percent of the patients were male. Patients ranged in age from 16 to 94 years (median 67 years). There were 353 (71.0%) ceftazidime-susceptible and meropenem-susceptible isolates, 19 (3.8%) ceftazidime-resistant but meropenem-susceptible isolates, and 84 (16.9%) meropenem non-susceptible (NS, 72 intermediate, 12 resistant) but ceftazidime-susceptible isolates. Forty-one (8.2%) isolates showed non-susceptibility to both drugs.

C/T demonstrated excellent *in vitro* activity against isolates that were susceptible to ceftazidime or meropenem, with $MIC_{50/90}$ values of 1/1 mg/l for meropenem non-susceptible but ceftazidime-susceptible isolates and 2/4 mg/l for ceftazidime-resistant but meropenem-susceptible isolates. C/T also showed remarkable activity against isolates that were resistant to ceftazidime and non-susceptible to meropenem (Table). C/T at 4 mg/l inhibited 98.8% of the meropenem non-susceptible but ceftazidime-susceptible isolates, 94.7% of the ceftazidime-resistant but meropenem-susceptible isolates, and 51.2% of the isolates that were non-susceptible to both drugs. Overall, C/T at 4 mg/l was active against 122/144 (84.7%) isolates that showed reduced susceptibility or resistance to either ceftazidime or meropenem.

Table: Distributions of C/T MICs and cumulative % of isolates inhibited at 4 mg/l

Phenotype (n)	Isolates inhibited at MIC (mg/l)									Cum. % inhibited at 4 mg/l
	≤0.25	0.5	1	2	4	8	16	32	>32	
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

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.