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Paper Poster Session

New antibiotics against Gram-negative bacteria

In vitro activity of ceftolozane-tazobactam against *Pseudomonas aeruginosa* and Enterobacteriaceae isolates recovered from hospitalized patients in Germany

Michael Kresken*¹, Barbara Körber-Irrgang¹, Harald Seifert², German Ceftolozan/Tazobactam Study Group¹

¹*Antiinfectives Intelligence GmbH, Campus of the University of Applied Sciences, Rheinbach, Germany*

²*Institut Für Medizinische Mikrobiologie, Immunologie und Hygiene, Uniklinik Köln, Köln, Germany*

Background: *Pseudomonas aeruginosa* (PAE) is a leading nosocomial Gram-negative pathogen which is often multi-drug resistant. Ceftolozane-tazobactam (C/T) is an antibacterial drug combination of ceftolozane, a novel antipseudomonal cephalosporin, 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 objectives of this study were i) to investigate the comparative in vitro activity of C/T against PAE and various Enterobacteriaceae species, and ii) to compare MICs of C/T determined by standard broth microdilution (BMD) versus the Etest®. (Etest® - RUO* - bioMerieux S.A., Marcy l'Etoile, France).

Material/methods: 497 PAE and 802 Enterobacteriaceae 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 by BMD according to the standard ISO 20776-1 at a central laboratory, while Etest® MICs of C/T were determined at the local laboratories. EUCAST breakpoints (v. 5.0) were applied for interpretation. Breakpoints (mg/L) of C/T were S \leq 4 / R > 4 for PAE and S \leq 1 / R > 1 for Enterobacteriaceae. ESBL testing was performed according to CLSI criteria.

Results: Thirty-four percent of the 1,299 isolates were obtained from patients on intensive care units. More than 60% of the patients were male. Patients ranged in age from 16 to 95 years (median 67 years). C/T demonstrated excellent *in vitro* activity against PAE, with MIC_{50/90} values of 0.5/2 mg/L. In comparison, MIC_{50/90} values of piperacillin-tazobactam (P/T), ceftazidime (CAZ), and meropenem (MEM) for PAE were 8/64, 2/16, and 0.5/8 mg/L, respectively. C/T also showed remarkable activity against CAZ-resistant PAE isolates (Table). An ESBL phenotype was confirmed for 32/202 (15.8%) *E. coli*, 40/233 (17.2%) *K. pneumoniae*, 11/68 (16.2%) *K. oxytoca*, and 1/56 (1.8%) *P. mirabilis*. C/T was at least as active as P/T or CAZ against Enterobacteriaceae isolates (Table). MICs of C/T determined by Etest® were usually 0.5-1 log₂ lower than those obtained by BMD. The categorical agreement between the methods, however, was excellent, with 99.8% for PAE and 95.9% for Enterobacteriaceae isolates.

Conclusions: In comparison to other broad-spectrum β -lactams with antipseudomonal activity, C/T showed superior activity against PAE. It also exhibited good activity against Enterobacteriaceae including isolates with an ESBL phenotype. Consequently, C/T may be an option for the empirical treatment of infections in which PAE and/or Enterobacteriaceae play a major role. The Etest® method seems to be suitable to test the susceptibility of PAE and Enterobacteriaceae to C/T.

* For Research Use Only. The performance characteristics of this product have not been established.

Table: Comparative *in vitro* activity of ceftolozane-tazobactam

Bacterial species, phenotype (n)	% susceptible / % resistant			
	C/T	P/T	CAZ	MEM
<i>P. aeruginosa</i> , all (497)	95.6 / 4.4	83.7 / 16.3	87.9 / 12.1	74.8 / 7.2
<i>P. aeruginosa</i> , CAZ-R (60)	65.0 / 35.0	6.7 / 93.3	0 / 100	31.7 / 40.0
<i>E. coli</i> , all (202)	96.0 / 4.0	91.6 / 6.4	83.2 / 10.4	100 / 0
<i>E. coli</i> , ESBL pos. (32)	81.3 / 18.6	75.0 / 15.6	0 / 62.5	100 / 0
<i>K. pneumoniae</i> , all (233)	93.1 / 6.9	83.3 / 9.9	82.8 / 14.6	100 / 0
<i>K. pneumoniae</i> , ESBL pos. (40)	62.5 / 37.5	37.5 / 45.0	2.5 / 82.5	100 / 0
<i>K. oxytoca</i> , all (68)	86.8 / 13.2	73.5 / 25.0	91.2 / 0	100 / 0
<i>P. mirabilis</i> , all (56)	100 / 0	100 / 0	100 / 0	100 / 0
<i>E. cloacae</i> , all (73)	69.9 / 30.1	60.3 / 30.1	54.8 / 39.7	98.6 / 1.4
<i>S. marcescens</i> , all (49)	89.8 / 10.2	75.5 / 20.4	95.9 / 4.1	95.9 / 4.1