Poster No.

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

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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 (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 objectives of this study were i) to investigate the comparative *in vitro* activity of C/T and three other broad-spectrum anti-Gram-negative antimicrobials 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 (4) at a central laboratory, while Etest® MICs of C/T were determined at the local laboratories. EUCAST breakpoints (v. 6.0) were applied for interpretation (5). Breakpoints (mg/L) of C/T were susceptible (S) ≤4 mg/L / resistant (R) >4 mg/L for PAE and S ≤1 mg/L / R >1 mg/L for Enterobacteriaceae. ESBL testing was performed according to CLSI criteria (6).

Results

Thirty-four percent of the 1,299 isolates were obtained from patients on intensive care units. Sixty-two percent 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 **(Table 1)**. 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 2)**. 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 **(Tables 1 and 2)**. MICs of C/T determined by Etest® were usually 0.5-1 log_2 dilution steps lower than those obtained by BMD **(Tables 1 and 2)**. Resistance rates as determined by Etest® were 2–2.9% lower for *E. coli*, *K. oxytoca*, and *S. marcescens*, similar and identical for PAE and *P. mirabilis*, respectively, and 2.1% and 8.3% higher for *K. pneumoniae* and *E. cloacae*, respectively, when compared to the resistance rates as determined by BMD **(Table 1)**. In total, however, the categorical agreement between the two methods 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. However, more closely linked resistance rates of Etest® and BMD would have been achieved, if EUCAST had been defined an intermediate category.

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References

1. Cluck D et al. 2015. Am J Health Syst Pharm. 72:2135-46.
2. Ceftolozane: www.clicialtrials.gov (assessed 23th June 2014).
3. Zhanel GG et al. 2014. Drugs. 74:31-51.
4. ISO 20776-1: 2006. German version EN ISO 20776-1:2006. Beuth-Verlag, Berlin.
5. European Committee on Antimicrobial Susceptibility Testing (EUCAST). 2015. Breakpoint tables v 6.0.
6. Clinical and Laboratory Standards Institute (CLSI). 2015. CLSI document M100-S25. Wayne, PA, USA.

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* For research use only. The performance characteristics of this product have not been established.

Table 1: ***In vitro*** **activity of C/T in comparison to three other broad-spectrum β-lactams against Gram-negative bacteria as determined by BMD and susceptibility testing of C/T with Etest®**

Species* (no tested)	Drug	Method	MIC_{50} (mg/L)	MIC_{90} (mg/L)	Percent of isolates		
					S	I	R
P. aeruginosa (n=497)	C/T	BMD	0.5	2	95.6	–	4.4
		Etest®	0.5	1	95.8	–	4.2
	P/T	BMD	8	64	83.7	–	16.3
	CAZ		2	16	87.9	–	12.1
	MEM		0.5	8	74.8	17.9	7.2
E. coli (n=202)	C/T	BMD	0.25	0.5	96.0	–	4.0
		Etest®	0.19	0.38	98.5	–	1.5
	P/T	BMD	2	8	91.6	2.0	6.4
	CAZ		0.25	8	83.2	6.4	10.4
	MEM		≤0.03	≤0.03	100	0	0
K. pneumoniae (n=233)	C/T	BMD	0.25	1	93.1	–	6.9
		Etest®	0.19	1	91.0	–	9.0
	P/T	BMD	2	16	83.3	6.9	9.9
	CAZ		0.12	8	82.8	2.6	14.6
	MEM		≤0.03	≤0.03	100	0	0
K. oxytoca (n=68)	C/T	BMD	0.25	2	86.8	–	13.2
		Etest®	0.19	1.5	89.7	–	10.3
	P/T	BMD	2	≥512	73.5	1.5	25.0
	CAZ		0.12	1	91.2	8.8	0.0
	MEM		≤0.03	≤0.03	100	0	0
P. mirabilis (n=56)	C/T	BMD	0.5	0.5	100	–	0
		Etest®	0.38	0.75	100	–	0
	P/T	BMD	0.25	0.5	100	0	0
	CAZ		≤0.06	0.12	100	0	0
	MEM		≤0.03	0.06	100	0	0
E. cloacae (n=73)	C/T	BMD	0.5	16	69.9	–	30.1
		Etest®	0.5	12	61.6	–	38.4
	P/T	BMD	4	128	60.3	9.6	30.1
	CAZ		1	64	54.8	5.5	39.7
	MEM		≤0.03	0.12	98.6	0,0	1.4
S. marcescens (n=49)	C/T	BMD	0.5	2	89.8	–	10.2
		Etest®	0.5	1	91.8	–	8.2
	P/T	BMD	2	32	75.5	4.1	20.4
	CAZ		0.25	1	95.9	0,0	4.1
	MEM		≤0.03	0.06	95.9	0,0	4.1

Abbreviations: C/T, ceftolozane-tazobactam; P/T, piperacillin-tazobactam; CAZ, ceftazidime; MEM, meropenem; BMD, broth microdilution

*Species representing more than 30 isolates are listed.

Table 2: ***In vitro*** **activity of C/T in comparison to three other broad-spectrum β-lactams against CAZ-resistant *P. aeruginosa* and Enterobacteriaceae with an ESBL phenotype as determined by BMD, and susceptibility testing of C/T with Etest®**

Species, phenotype (no tested)	Drug	Method	MIC_{50} (mg/L)	MIC_{90} (mg/L)	Percent of isolates		
					S	I	R
P. aeruginosa, CAZ-R (n=60)	C/T	BMD	2	128	65.0	–	35.0
		Etest®	1.5	>256	66.7	–	33.3
	P/T	BMD	128	256	6.7	–	93.3
	CAZ		32	128	0	–	100
	MEM		8	64	31.7	28.3	40.0
E. coli, ESBL+ (n=32)	C/T	BMD	0.5	2	81.3	–	18.8
		Etest®	0.38	1	93.8	–	6.3
	P/T	BMD	4	32	75.0	9.4	15.6
	CAZ		8	32	0.0	37.5	62.5
	MEM		≤0.03	≤0.03	100	0	0
K. pneumoniae, ESBL+ (n=40)	C/T	BMD	1	4	62.5	–	37.5
		Etest®	1	8	52.5	–	47.5
	P/T	BMD	16	≥512	37.5	17.5	45.0
	CAZ		16	128	2.5	15.0	82.5
	MEM		≤0.03	0.12	100	0	0
K. oxytoca, ESBL+ (n=11)	C/T	BMD	2	4	45.5	–	54.5
		Etest®	0.75	3	63.6	–	36.4
	P/T	BMD	≥512	≥512	0	0	100
	CAZ		0.5	2	63.6	36.4	0.0
	MEM		≤0.03	0.06	100	0	0
P. mirabilis, ESBL+ (n=1)	C/T	BMD	–	–	100	–	0
		Etest®	–	–	100	–	0
	P/T	BMD	–	–	100	0	0
	CAZ		–	–	100	0	0
	MEM		–	–	100	0	0

Abbreviations: C/T, ceftolozane-tazobactam; P/T, piperacillin-tazobactam; CAZ, ceftazidime; MEM, meropenem; BMD, broth microdilution, ESBL+, ESBL phenotype

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