In vitro activity of ceftolozane/tazobactam against Enterobacterales and *Pseudomonas aeruginosa* isolates obtained from patients with hospital-acquired pneumonia in Germany

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M. Kresken[1,2], B. Körber-Irrgang[1], M. Korte-Berwanger[3,4], N. Pfennigwerth[3], S.G. Gatermann[3], E. Wohlfarth[1], H. Seifert[5], German Carbapenem Resistance Study Group

[1]Antiinfectives Intelligence GmbH, Cologne, Germany | [2]University of Applied Sciences, Cologne, Germany | [3]Ruhr-University Bochum, German National Reference Centre for Multidrug Resistant Gram-negative Bacteria, Bochum, Germany
[4]Landeszentrum Gesundheit Nordrhein-Westfalen, Bochum, Germany | [5]Institute for Medical Microbiology, Immunology and Hygiene, University Hospital Cologne, Cologne, Germany

Contact information (presenting author)
Michael Kresken, PhD
Antiinfectives Intelligence GmbH
c/o Rechtsrheinisches Technologie- und Gründerzentrum (RTZ)
Gottfried-Hagen-Straße 60-62, 51105 Köln (Cologne), Germany
Phone: +49 (0)221 560 917 58 | Fax: +49 (0)221 169 950 87
Email: michael.kresken@antiinfectives-intelligence.de
Web: www.antiinfectives-intelligence.de

PURPOSE / OBJECTIVES

Ceftolozane/tazobactam (Zerbaxa®, CTT) at a dosage of 2g/1g intravenously every 8 hours has been approved for the treatment of adult patients with hospital-acquired pneumonia (HAP), including ventilator-associated pneumonia (VAP) (1). Based on this dosage regimen, the European Committee on Antimicrobial Susceptibility Testing (EUCAST) has established the following minimum inhibitory concentration (MIC) breakpoints for HAP isolates: ≤ 2 mg/l (susceptible) and > 2 mg/l (resistant) for Enterobacterales (ENT) and ≤ 4 mg/l (susceptible) and > 4 mg/l (resistant) for *Pseudomonas aeruginosa* (PAE) (2). We aimed to determine i) the dissemination of carbapenem-resistant ENT and PAE isolates among HAP isolates, and ii) their susceptibilities to CTT and other antibiotics.

MATERIAL & METHODS

138 PAE and 172 ENT collected in 12 laboratories in Germany from January 2016 to April 2017 were included. Isolates were recovered from patients with VAP (n=210) or HAP non-VAP (n=100). Susceptibility testing was performed with the broth microdilution method according to the standard ISO 20776-1 (3). EUCAST breakpoints (v.11.0) were applied for interpretation (2). Genetic testing on the carbapenemase (CP)-producing isolates was performed at the German National Reference Laboratory for Multidrug-resistant Gram-negative Bacteria (4).

RESULTS

77% of the isolates were obtained from intensive care patients.

MIC values and percent susceptibility rates of CTT for PAE and ENT are summarized in **Table 1** and **Table 2**, respectively. CTT inhibited 161/172 (93.6%) ENT at 2 mg/l, and 133/138 (96.4%) PAE at 4 mg/l.

Resistance rates of CTT and comparative antimicrobials are presented in **Table 3**.

83/138 (60.1%) PAE were susceptible to both imipenem (IMI) and meropenem (MER), while 55 (39.9%) were resistant to at least one carbapenem. 22/138 (15.9%) isolates showed resistance to both IMI and MER. A CP was detected in 4 (2.9%) PAE isolates (**Table 4**). CPs detected were VIM-1 (n=1), VIM-2 (n=2), and IMP-1 (n=1). 77.3% isolates with combined resistance to IMI and meropenem were susceptible to CTT (**Table 1**).

Ertapenem resistance among ENT was detected in 4/172 (2.3%) isolates, namely in two *Klebsiella pneumoniae* and in one isolate each of *Enterobacter cloacae* and *Serratia marcescens*. A CP was detected in three isolates (**Table 4**).

CTT was not active against the seven CP-producing isolates, as expected.

TABLE 1: Distributions of CTT MICs for *Pseudomonas aeruginosa* isolates obtained from patients with HAP by assigned group

Group	n	Number of isolates inhibited at given concentration (mg/L)													MIC (mg/L)		
		≤ 0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	>128	50%	90%	% S
Total	138			7	82	32	11	1		1		1		3	0.5	2	96.4
Subgroup I*	83			5	54	20	4								0.5	1	100
Subgroup II	55			2	28	12	7	1		1		1		3	0.5	4	90.9
Subgroup III	22				8	3	5	1		1		1		3	1	>128	77.3

*Subgroup I: susceptible to both IMI and MER, subgroup II: resistant to at least one carbapenem, subgroup III: resistant to both IMI and MER;
% S, % susceptible. The dashed vertical line indicates the EUCAST ≤ 4 mg/l (susceptible) and > 4 mg/l (resistant).

TABLE 2: Distributions of CTT MICs for Enterobacterales isolates obtained from patients with HAP by assigned species or species group

Group	n	Number of isolates inhibited at given concentration (mg/L)													MIC (mg/L)		
		≤ 0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	>128	50%	90%	% S
Total	172		15	77	45	18	6	5	1	2	1	1		1	0.25	1	93.6
E. coli	28		5	15	7	1									0.25	0.5	100
K. pneumoniae	59		3	37	14	1	1	1			1	1			0.25	0.5	94.9
K. oxytoca	22		3	14	3	2									0.25	1	100
K. aerogenes	7			1		1	3	1	1						2	8	71.4
E. cloacae complex[a]	16		1	4	5	1	1	1		2				1	0.5	16	75.0
S. marcescens	16				4	10	1	1							1	2	93.8
Morganellaceae[a]	12			1	10	1									0.5	0.5	100
Citrobacter spp.[b]	12		3	5	2	1		1							0.25	1	91.7

[a]*E. cloacae* (n=14), *E. asburiae* (n=1), *E. kobei* (n=1); [b]*C. amalonaticus* (n=9), *C. murliniae* (n=2), *C. freundii* (n=1); [a]*P. mirabilis* (n=9), *M. morganii* (n=2), *P. stuartii* (n=1); [a]*C. freundii* (n=5), *C. koseri* (n=7);
% S, % susceptible. The dashed vertical line indicates the EUCAST ≤ 2 mg/l (susceptible) and > 2 mg/l (resistant).

TABLE 3: Percent resistant Enterobacterales (n=172) and *Pseudomonas aeruginosa* (n=138) isolates obtained from patients with HAP

Species / species group	n	Antibacterial agent[a]											
		PIT	CTT	CTZ	CTR	CEP	ERT	IMI	MER	CIP	AMI	TOB	COL
E. coli	28	14.3	0	10.7	21.4	17.9	0	0	0	21.4	3.6	14.3	0
K. pneumoniae	59	8.5	5.1	16.9	18.6	16.9	3.4	3.4	3.4	13.6	1.7	10.2	3.4
K. oxytoca	22	13.6	0	0	9.1	0	0	0	0	0	0	0	4.5
K. aerogenes	7	71.4	28.6	71.4	71.4	0	0	0	0	14.3	0	0	0
E. cloacae complex[b]	16	25.0	25.0	37.5	50.0	12.5	6.3	0	6.3	12.5	6.3	12.5	12.5
S. marcescens	16	0	6.3	12.5	12.5	6.3	6.3	6.3	0	18.8	0	6.3	93.8
Morganellaceae[a]	12	8.3	0	0	0	0	0	0	0	8.3	0	8.3	100
Citrobacter spp.[b]	12	16.7	8.3	16.7	16.7	0	0	0	0	0	0	0	0
Total Enterobacterales	172	14.0	6.4	16.3	20.9	10.5	2.3	1.7	1.7	12.2	1.7	8.1	18.6
P. aeruginosa	138	22.5	3.6	20.3	-	15.9	-	39.1	16.7	31.2	1.4	6.5	1.4

[a]PIT, piperacillin/tazobactam; CTT, ceftolozane/tazobactam; CTZ, ceftazidime; CTR, ceftriaxone; CEP, cefepime; ERT, ertapenem; IMI, imipenem; MER, meropenem; CIP, ciprofloxacin; AMI, amikacin; TOB, tobramycin; COL, colistin; [b]*E. cloacae* (n=14), *E. asburiae* (n=1), *E. kobei* (n=1); [a]*P. mirabilis* (n=9), *M. morganii* (n=2), *P. stuartii* (n=1); [a]*C. freundii* (n=5), *C. koseri* (n=7)

TABLE 4: Carbapenemases detected in carbapenem-resistant Enterobacterales and *Pseudomonas aeruginosa* isolates obtained from patients with HAP

Species	n	Type
Enterobacter cloacae	1	NDM-1
Klebsiella pneumoniae	1	OXA-162
	1	KPC-2
Pseudomonas aeruginosa	1*	VIM-1
	2	VIM-2
	1	IMP-1

*This isolate also produced a GES variant.

SUMMARY / CONCLUSIONS

Overall, 2.3% and 2.9% of the ENT and PAE, respectively, harboured a CP, while 37% of the PAE were carbapenem-resistant, CP non-producing isolates.

CTT inhibited > 93% of the ENT and > 96% of the PAE isolates.

Based on these findings, CTT seems to be appropriate for empiric treatment of HAP.

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FURTHER MEMBERS OF THE GERMAN IMIPNEM/RELEBACTAM STUDY GROUP

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