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In vitro activity of ceftolozane/tazobactam against contemporary extended-spectrum cephalosporin resistant Enterobacteriaceae and multi-drug resistant *Pseudomonas aeruginosa* clinical isolates of Argentina.

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Background

The global increase in the prevalence of multidrug-resistant (MDR) pathogens, such as extended-spectrum cephalosporin-resistant Enterobacteriaceae (EEE) and MDR *Pseudomonas aeruginosa* (PA), is a challenge for health systems. A new antimicrobial to treat infections caused by these pathogens, ceftolozane/tazobactam (C/T), has been approved by the FDA/EMA. Objective: to evaluate the in vitro activity of C/T in comparison with other antimicrobial agents against a representative EEE/MDR-PA collection.

Materials/methods

We included 113 EEE and 180 MDR-PA unique clinical isolates (59 hospitals), recovered from: 1) adult patients with complicated intra-abdominal infection undergoing surgical focus control procedure. 2) infections of the urinary tract (adults). 3) bacteremia in cancer and hematopoietic stem cell transplantation adult patients. 4) extreme-drug resistant isolates (mainly PA) submitted to the NRL. Carbapenemase producers were excluded. The MIC of C/T was determined by gradient strips (Liofilchem), susceptibility to other agents by micro-dilution (Sensititre) or disk diffusion and the results were interpreted with CLSI criteria. The molecular characterization of β-lactamases and mcr genes was carried out by PCR/sequencing. The bacterial identification was confirmed with MALDI-TOF (Bruker). The Chi2 test (Yates correction) was used to compare the activity of C/T vs piperacillin/tazobactam.

Results

Fig.

Bacterial group (n)	C/T			% of susceptible											% of ESBL producers	% of plasmidic AmpC producers	% of mcr-1 producers
	MIC_{50}	MIC_{90}	RANGE	C/T	PTZ	CTX	CAZ	FEP	IMP	MER	ETP	AMK	GEN	CIP			
E. coli (33)	0.5	1	0.38 - 2	100	87	4	39	7	100	100	96	100	54	0	97	0	43
K. pneumoniae (60)	1	8	0.5 - 32	78	31	23	40	30	95	93	83	83	38	21	88	8	5
Other *Enterobact.* (20) [a]	1	2	0.5 - 8	90	78	0	53	17	100	95	90	83	33	32	95	0	ND
All *Enterobacteriaceae* (113)	1	4	0.5 - 32	87	57	13	42	22	97	96	88	88	42	17	92[b]	4[c]	
P. aeruginosa (180)	1	4	0.25 - 256	90	25	ND	35	27	19	17	ND	39	25	19	36[d]	ND	

C/T, ceftolozane/tazobactam; PTZ,piperacillin/tazobactam; CTX, cefotaxime, CAZ, ceftazidime, FEP, cefepime, IMP, imipenem; MER, meropenem; ETP, ertapenem; AMK, amikacin; GEN, gentamicin; CIP, ciprofloxacin; ND: not determined

a) 6 *Enterobacter cloacae*, 5 *Serratia marcescens*, 3 *Salmonella*, 2 *Citrobacter freundii*, 2 *Proteus mirabilis*, 1 *Providencia stuartii*, 1 *Klebsiella oxytoca*. b) EEE-ESBLs: 41% CTX-M-1/15, 20% CTX-M-2, 13% CTX-M unassigned variant, 8% CTX-M-9/14, 4% OXA-1/31, 1% CTX-M-8/24, 1% CTX-M-1/15+CTX-M-9/14, 1% PER, 1% CTX-M-2+PER, 8% uncharacterized ESBL. c) Plasmidic AmpC: DHA. d) PA-ESBLs: 75% OXA-1/31, 16% GES-1, 3% CTX-M-1/15, 3% CTX-M unassigned variant, 3% PER.

High level resistance to C/T (MIC >48mg/L) was observed mainly among GES-1-producing PA. C/T was significantly more active than PTZ among MDR-PA ($p<0.01$) and only the *Klebsiella* subgroup within the EEEs ($p<0.01$).

Conclusions

A uniform sensitivity of C/T was observed among EEE, although differences were detected by bacterial species but not by the type of CTX-M produced. C/T was the most active β-lactam assayed against MDR-PA. C/T could be a potential alternative for the treatment of infections in adult patients such as those caused by EEE and MDR-PA circulating in Argentina.