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New and old beta-lactamase inhibitors

CEFTOLOZANE/TAZOBACTAM ACTIVITY AGAINST GRAM-NEGATIVE BACTERIA CAUSING INTRA-ABDOMINAL INFECTIONS IN EUROPEAN HOSPITALS (2011-2012): A REPORT FROM AN INTERNATIONAL ANTIMICROBIAL SURVEILLANCE PROGRAM

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Objectives: Ceftolozane/tazobactam (TOL/TAZ) is a novel antibacterial with activity against common Gram-negative pathogens, including most extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae and *Pseudomonas aeruginosa*, as well as drug-resistant strains, and is currently under Phase 3 clinical development. As part of the Program to Assess Ceftolozane/Tazobactam Susceptibility (PACTS), this study evaluated the activity of TOL/TAZ and comparator agents against a collection of clinically isolated Gram-negative organisms obtained from patients with intra-abdominal infections (IAIs) in European hospitals.

Methods: During 2011-2012, a total of 578 unique bacterial isolates were collected consecutively from patients with IAI in 31 hospitals in 11 European countries, plus Russia, Turkey, Ukraine and Israel. Susceptibility testing for TOL/TAZ and other antibacterial agents (including gentamicin [GEN], piperacillin/tazobactam [PIP/TAZ], ceftazidime [CAZ], meropenem [MEM] and colistin) commonly used to treat patients with IAIs in Europe was performed using broth microdilution methodology according to CLSI M07-A9 document. Antimicrobial susceptibility (S) rates of Gram-negative organisms were based on EUCAST (2013) interpretative criteria. A proposed TOL/TAZ susceptible breakpoint of 8 mg/L was used. TOL/TAZ was tested at a fixed 4 mg/L concentration of TAZ.

Results: The distribution of organisms in these IAI specimens was 50.3% *Escherichia coli* (14.1% ESBL-positive), 15.2% *Klebsiella pneumoniae* (35.2% ESBL-phenotype) and 9.2% *P. aeruginosa* (39.6% classified as multidrug resistant [MDR]). TOL/TAZ showed greater activity than PIP/TAZ, GEN and CAZ against these organisms (Table). Against *E. coli,* including ESBL–phenotype isolates, the S rate to TOL/TAZ was 98.3% and 87.8%, respectively (S to MEM was 100%). Of the commonly used antibacterials, TOL/TAZ was second only to MEM (84.1% and 93.2%, respectively) against *K. pneumoniae*, including against ESBL–phenotype isolates. Against *P. aeruginosa,* with the exception of colistin (data not shown), TOL/TAZ was the most active agent tested, inhibiting 88.7% of isolates at an MIC of <=8 mg/L. A per-country analysis showed that S to TOL/TAZ was >=90% in Enterobacteriaceae isolates obtained from IAI patients in all countries except 3 (Belgium, Poland and Ukraine). For *P. aeruginosa*, small numbers of isolates with TOL/TAZ MICs >8 mg/L were found in Germany (1), Italy (3), Poland (1) and Ukraine (1). In all other countries, *P. aeruginosa* S to TOL/TAZ was 100%.
Conclusion: Antimicrobial S varied among European countries. At an MIC of <=8 mg/L TOL/TAZ provides greater *in vitro* activity against *P. aeruginosa* than MEM and was second only to MEM amongst other antibacterials commonly used for the treatment of Enterobacteriaceae causing IAIs in European hospitals (2011-12). TOL/TAZ could represent a valuable treatment option for these pathogens.

	MIC_{50}/MIC_{90} (mg/L)/%Susceptible				
Organism	**TOL/TAZ[a]**	**MEM[b]**	**PIP/TAZ[b]**	**GEN[b]**	**CAZ[b]**
E. coli (n = 291)	0.25/0.5/98.3	≤0.06/≤0.06/100	2/16/86.3	≤1/2/90.4	0.12/4/87.3
E. coli ESBL-phenotype (n = 41)	0.5/32/87.8	≤0.06/0.12/100	16/>64/46.3	≤1/>8/75.6	16/>32/9.8
K. pneumoniae (n = 88)	0.25/32/84.1	≤0.06/0.12/93.2	4/>64/69.3	≤1/>8/81.8	0.25/>32/64.8
K. pneumoniae ESBL-phenotype (n = 31)	4/>32/54.8	≤0.06/>8/80.6	64/>64/22.6	8/>8/48.4	32/>32/0.0
P. aeruginosa (n = 53)	0.5/32/88.7	0.5/8/73.6	8/>64/56.6	≤1/>8/83.0	2/>32/66.0
P. aeruginosa MDR[c] (n = 21)	2/>32/71.4	2/8/47.6	32/>64/4.8	≤1/>8/57.1	32/>32/14.3

[a]Proposed susceptible breakpoint of 8 mg/L of TOL/TAZ used for comparative purposes.
[b]Susceptible breakpoint established by EUCAST (2013).
[c]MDR bacteria were classified according to Magiorakos AP, et al. *Clin Microbiol Infect* 2012;18:268-281.