

# Ceftolozane/Tazobactam Activity Against Gram-negative Bacteria Causing Intra-abdominal Infections in European Hospitals (2011-2012): A Report From an International Antimicrobial Surveillance Programme

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## INTRODUCTION

- Intra-abdominal infections (IAIs) are caused by a variety of Gram-negative microorganisms, most commonly, *Escherichia coli* and *Klebsiella pneumoniae*; however, *Pseudomonas aeruginosa*, *Klebsiella oxytoca*, *Enterobacter* spp., and *Proteus mirabilis* are also frequently isolated.<sup>1</sup>
- From a clinical perspective, an important feature of IAI is the increasing rate of antimicrobial drug resistance, which is often due to the presence of extended-spectrum  $\beta$ -lactamase (ESBL)-producing strains, necessitating the investigation of new antimicrobial therapies.
- Ceftolozane/tazobactam (TOL/TAZ), a novel antibacterial consisting of ceftolozane, an antipseudomonal cephalosporin with tazobactam, a well-established  $\beta$ -lactamase inhibitor, has been investigated in Phase 2 and 3 clinical trials for the treatment of patients with complicated IAI.<sup>2,3</sup>
- The aim of this study was to evaluate the activity of TOL/TAZ and comparator agents against a collection of clinically isolated Gram-negative organisms obtained from European patients with IAI, as part of the Program to Assess Ceftolozane/Tazobactam Susceptibility (PACTS).

## METHODS

- A total of 578 nonduplicate bacterial isolates were collected from patients with IAI admitted to 31 hospitals in 15 countries: Belgium, France, Germany, Greece, Ireland, Israel, Italy, Poland, Portugal, Russia, Spain, Sweden, Turkey, UK, and Ukraine during 2011-2012 and forwarded to a central laboratory (JMI Laboratories, North Liberty, IA, USA) for confirmatory identification and susceptibility testing.
- Antimicrobial susceptibility testing was carried out for TOL/TAZ and several comparators that are commonly used to treat IAI in Europe, including piperacillin/tazobactam (PIP/TAZ), ceftazidime (CAZ), meropenem (MEM), and gentamicin (GEN).
- Minimum inhibitory concentration (MIC) values were determined using standard broth microdilution assays with dry-form Sensititre<sup>®</sup> panels (TREK Diagnostic Systems, Oakwood Village, OH, USA), according to Clinical Laboratory Standards Institute methodology.<sup>4,5</sup>
- ESBL phenotypes in *E. coli* and *K. pneumoniae* were defined as having an MIC  $\geq 2$  mg/L for ceftazidime or cefttriaxone or aztreonam.
- Multidrug-resistant (MDR) phenotypes were defined as being nonsusceptible (NS) to  $\geq 1$  agent in  $\geq 3$  antimicrobial drug classes.
- Interpretations of susceptibility (S) for all antimicrobials except for TOL/TAZ were based on the European Committee on Antimicrobial Susceptibility Testing criteria.<sup>6</sup>
- A proposed susceptible breakpoint of 8 mg/L was used for TOL/TAZ, which was tested at a fixed 4 mg/L concentration of TAZ.

## RESULTS

- The most frequently isolated pathogens from patients with IAIs were *E. coli* (n = 291; 50.3%), *K. pneumoniae* (n = 88; 15.2%), and *P. aeruginosa* (n = 53; 9.2%). In *E. coli* and *K. pneumoniae*, the ESBL-positive rates were 14.1% and 35.2%, respectively, and 39.6% of *P. aeruginosa* isolates were classified as MDR.
- Of the 31 isolates of ESBL-positive *K. pneumoniae*, 19.4% were NS to MEM (Table 1) suggesting the presence of the *K. pneumoniae* carbapenemase. This phenotype is still relatively rare, and was observed in 6.8% of *K. pneumoniae* IAI isolates in this European study.
- The MICs required to inhibit the growth of 50%/90% of organisms (MIC<sub>50/90</sub>) for TOL/TAZ against *E. coli*, *K. pneumoniae*, and *P. aeruginosa* were 0.25/0.5, 0.25/32, and 0.5/32 mg/L, respectively. At an MIC of 8 mg/L, TOL/TAZ inhibited 87.8% of ESBL-producing *E. coli*, 54.8% of ESBL-producing *K. pneumoniae* (Table 1), and 71.4% of MDR *P. aeruginosa* (Figure 1). Against levofloxacin (LVX) NS (n = 72) and PIP/TAZ NS (n = 40) *E. coli*, TOL/TAZ inhibited 94.4% and 87.5% of isolates, respectively, at a concentration of 8 mg/L (Table 1).
- TOL/TAZ demonstrated greater activity than PIP/TAZ against all ESBL-positive isolates that were tested, including *E. coli* (MIC<sub>50/90</sub> 0.5/32 vs 16/>64 mg/L), *K. pneumoniae* (MIC<sub>50/90</sub> 4/>32 vs 64/>64 mg/L), and MEM *S. pneumoniae* (2/>32 vs 64/>64 mg/L) (Table 2).
- Against *P. aeruginosa* isolates that were NS to multiple  $\beta$ -lactamases, the MIC<sub>50/90</sub> for TOL/TAZ and PIP/TAZ was 2/>32 and 64/>64 mg/L, respectively (Table 2).

## RESULTS (cont'd)

Table 1. Summary of TOL/TAZ Activity Tested Against Drug-Resistant Isolates of *E. coli*, *K. pneumoniae*, and *P. aeruginosa* Collected From Patients With IAI in Europe (2011-2012)

Organism or Group (No. Tested)	No. of Isolates (Cumulative %) Inhibited at MIC (mg/L) of:													
	$\leq 0.03$	0.06	0.12	0.25	0.5	1	2	4	8	16	32	>32	MIC <sub>50</sub>	MIC <sub>90</sub>
<i>E. coli</i> (291)	0 (0.0)	0 (0.0)	92 (31.6)	147 (82.1)	32 (93.1)	10 (96.6)	2 (97.3)	2 (97.9)	1 (98.3)	0 (98.3)	3 (99.3)	2 (100.0)	0.25	0.5
ESBL-phenotype (41)	0 (0.0)	0 (0.0)	0 (0.0)	8 (19.5)	13 (51.2)	10 (75.6)	2 (80.5)	2 (85.4)	1 (87.8)	0 (87.8)	3 (95.1)	2 (100.0)	0.5	32
LVX NS (72)	0 (0.0)	0 (0.0)	12 (16.7)	29 (56.9)	18 (81.9)	5 (88.9)	2 (91.7)	1 (93.1)	1 (94.4)	0 (94.4)	2 (97.2)	2 (100.0)	0.25	2
PIP/TAZ NS (40)	0 (0.0)	0 (0.0)	2 (5.0)	13 (37.5)	12 (67.5)	4 (77.5)	1 (80.0)	2 (85.0)	1 (87.5)	0 (87.5)	3 (95.0)	2 (100.0)	0.5	32
<i>K. pneumoniae</i> (88)	0 (0.0)	1 (1.1)	16 (19.3)	33 (56.8)	17 (76.1)	2 (78.4)	3 (81.8)	1 (83.0)	1 (84.1)	4 (88.6)	3 (92.1)	7 (100.0)	0.25	32
ESBL-phenotype (31)	0 (0.0)	0 (0.0)	1 (3.2)	5 (19.4)	4 (32.3)	2 (38.7)	3 (48.4)	1 (51.6)	1 (54.8)	4 (67.7)	3 (77.8)	7 (100.0)	4	>32
ESBL-phenotype MEM S (25)	0 (0.0)	0 (0.0)	1 (4.0)	5 (24.0)	4 (40.0)	2 (48.0)	3 (60.0)	1 (64.0)	1 (68.0)	3 (80.0)	2 (88.0)	3 (100.0)	2	>32
ESBL-phenotype MEM NS (6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.6)	2 (33.3)	4 (100.0)	N/A	N/A	
<i>P. aeruginosa</i> (53)	0 (0.0)	0 (0.0)	0 (0.0)	3 (5.7)	25 (52.8)	11 (73.6)	5 (83.0)	3 (88.7)	0 (88.7)	0 (88.7)	2 (92.5)	4 (100.0)	0.5	32
MEM NS (14)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.1)	2 (21.4)	3 (42.9)	2 (57.1)	0 (57.1)	2 (71.4)	4 (100.0)	4	>32	
PIP/TAZ NS (18)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	3 (22.2)	5 (50.0)	3 (66.7)	0 (66.7)	0 (66.7)	2 (77.8)	4 (100.0)	2	>32
LVX NS (12)	0 (0.0)	0 (0.0)	0 (0.0)	1 (8.3)	2 (25.0)	2 (41.7)	1 (50.0)	2 (66.7)	0 (66.7)	0 (66.7)	2 (83.3)	2 (100.0)	2	>32
MDR (21)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.7)	1 (9.5)	5 (33.3)	5 (57.1)	3 (71.4)	0 (71.4)	2 (81.0)	4 (100.0)	2	>32	

Bold text indicates MIC<sub>50</sub>; underlined text indicates MIC<sub>90</sub>.

Table 2. In vitro Activity of TOL/TAZ and Comparator Agents Tested Against Gram-negative Isolates Collected From Patients With IAI in Europe (2011-2012)

Organism	Range (mg/L)	MIC <sub>50</sub> (mg/L)	MIC <sub>90</sub> (mg/L)	%S*	Organism	Range (mg/L)	MIC <sub>50</sub> (mg/L)	MIC <sub>90</sub> (mg/L)	%S*
<i>E. coli</i> (n = 291)	TOL/TAZ 0.12->32	0.25	0.5	98.3	TOL/TAZ 0.25->32	2	>32	71.4	
	MEM $\leq 0.06-0.25$	$\leq 0.06$	$\leq 0.06$	100	MEM 0.12->8	2	8	47.6	
	PIP/TAZ $\leq 0.5-64$	2	16	86.3	PIP/TAZ 4->64	32	>64	4.8	
	GEN $\leq 1-8$	$\leq 1$	2	90.4	GEN $\leq 1-8$	$\leq 1$	>8	57.1	
	CAZ 0.06->32	0.12	4	87.3	CAZ 1->32	32	>32	14.3	
<i>E. coli</i> ESBL phenotype (n = 41)	TOL/TAZ 0.25->32	0.5	32	87.8	TOL/TAZ 1->32	2	>32	66.7	
	MEM $\leq 0.06-0.25$	$\leq 0.06$	0.12	100	MEM 0.12->8	4	8	38.9	
	PIP/TAZ 2->64	16	>64	46.3	PIP/TAZ 16->64	64	>64	0.0	
	GEN $\leq 1-8$	$\leq 1$	>8	75.6	GEN $\leq 1-8$	2	>8	55.5	
	CAZ 1->32	16	>32	9.8	CAZ 8->32	32	>32	N/A	
<i>E. coli</i> LVX NS (n = 72)	TOL/TAZ 0.12->32	0.25	2	94.4	TOL/TAZ 1->32	2	>32	68.4	
	MEM $\leq 0.06-0.12$	$\leq 0.06$	$\leq 0.06$	100	MEM 0.12->8	4	8	42.1	
	PIP/TAZ 1->64	4	64	65.3	PIP/TAZ 16->64	64	>64	0.0	
	GEN $\leq 1-8$	$\leq 1$	>8	80.0	GEN $\leq 1-8$	2	>8	57.9	
	CAZ 0.06->32	4	64	63.9	CAZ 4->32	32	>32	5.3	
<i>K. pneumoniae</i> (n = 88)	TOL/TAZ 0.06->32	0.25	32	84.1	TOL/TAZ 0.5->32	N/A	N/A	33.3	
	MEM $\leq 0.06-8$	$\leq 0.06$	0.12	93.2	MEM 0.5-8	N/A	N/A	11.1	
	PIP/TAZ $\leq 0.5-64$	4	>64	69.3	PIP/TAZ 4->64	N/A	N/A	11.1	
	GEN $\leq 1-8$	$\leq 1$	>8	81.8	GEN 4-8	N/A	N/A	0.0	
	CAZ 0.03->32	0.25	>32	64.8	CAZ 1->32	N/A	N/A	11.1	
<i>K. pneumoniae</i> ESBL phenotype (n = 31)	TOL/TAZ 0.12->32	4	>32	54.8	TOL/TAZ 0.5->32	4	>32	57.1	
	MEM $\leq 0.06-8$	$\leq 0.06$	>8	80.6	MEM 4-8	8	>8	0.0	
	PIP/TAZ 2->64	64	>64	22.6	PIP/TAZ 4->64	64	>64	21.4	
	GEN $\leq 1-8$	8	>8	48.4	GEN $\leq 1-8$	8	>8	42.9	
	CAZ 2->32	32	>32	0.0	CAZ 1->32	32	>32	21.4	
<i>K. pneumoniae</i> MEM S (n = 25)	TOL/TAZ 0.12->32	2	>32	68	TOL/TAZ 0.25->32	2	>32	73.9	
	MEM N/A	N/A	N/A	N/A	MEM 0.12-8	2	8	52.2	
	PIP/TAZ 2->64	64	>64	28	PIP/TAZ 16->64	64	>64	0.0	
	GEN $\leq 1-8$	>8	>8	44	GEN $\leq 1-8$	2	>8	65.2	
	CAZ 2->32	32	>32	0	CAZ 2->32	32	>32	21.7	
<i>K. pneumoniae</i> MEM NS (n = 6)	TOL/TAZ 16->32	N/A	N/A	0	TOL/TAZ 0.25->32	2	>32	66.7	
	MEM N/A	N/A	N/A	N/A	MEM 0.12-8	2	8	50	
	PIP/TAZ >64->64	N/A	N/A	0	PIP/TAZ 4->64	32	>64	16.7	
	GEN $\leq 1-8$	N/A	N/A	66.7%	GEN $\leq 1-8$	4	>8	41.7	
	CAZ 32->32	N/A	N/A	0	CAZ 1->32	16	>32	33.3	
<i>P. aeruginosa</i> (n = 53)	TOL/TAZ 0.25->32	0.5	32	88.7	TOL/TAZ 1->32	2	>32	66.7	
	MEM $\leq 0.06-8$	0.5	8	73.6	MEM $\leq 0.06-8$	0.5	8	38.9	
	PIP/TAZ 2->64	8	>64	56.6	PIP/TAZ 16->64	64	>64	0	
	GEN $\leq 1-8$	$\leq 1$	>8	83.0	GEN $\leq 1-8$	2	>8	55.5	
	CAZ 1->32	2	>32	66.0	CAZ N/A	N/A	N/A	N/A	

BL,  $\beta$ -lactamase; FEP, ceftepime.

\*Susceptibility was determined by using a proposed breakpoint of 8 mg/L for TOL/TAZ.

Table 3. TOL/TAZ %S Against Enterobacteriaceae Isolates (n = 514) Collected From Patients With IAI in Europe (2011-2012)

Country	No. of Isolates	MIC (mg/L)			%S*
		Range	50%	90%	
Belgium	8	0.12-16	-	-	87.5
France	102	0.12->32	0.25	1	96.1
Germany	64	0.12->32	0.25	4	92.2
Greece	28	0.12->32	0.25	1	92.8
Ireland	34	0.12-2	0.25	0.5	100
Israel	3	0.12-0.25	-	-	100
Italy	24	0.12->32	0.25	1	91.7
Poland	8	0.25->32	-	-	25
Portugal	34	0.12-32	0.25	0.5	97.1
Russia	5	0.25-0.5	-	-	100
Spain	91	0.06->32	0.25	0.5	96.7
Sweden	32	0.12-1	0.25	0.5	100
Turkey	30	0.12-32	0.5	8	90
UK	41	0.12-2	0.25	0.5	100
Ukraine	10	0.25-32	0.5	32	80

\*Susceptibility was determined by using a proposed breakpoint of 8 mg/L for TOL/TAZ.

Table 4. TOL/TAZ %S Against *P. aeruginosa* Isolates (n = 53) Collected From Patients With IAI in Europe (2011-2012)

Country	No. of Isolates	MIC (mg/L)			%S*
		Range	50%	90%	
Belgium	1	0.5	-	-	100
France	6	0.5-4	-	-	100
Germany	5	0.5-32	-	-	80
Ireland	3	0.5-4	-	-	100
Israel	2	0.5	-	-	100
Italy	12	0.25->32	0.5	>32	75
Poland	2	2->32	-	-	50
Portugal	1	0.5	-	-	100
Spain	10	0.25-1	0.5	1	100
Sweden	2	1-2	-	-	100
Turkey	4	0.5-2	-	-	100
UK	4	0.5-1	-	-	100
Ukraine	2	0.5->32	-	-	50

\*Susceptibility was determined by using a proposed breakpoint of 8 mg/L for TOL/TAZ.

- In all isolates of *E. coli*, *K. pneumoniae*, and *P. aeruginosa* that were tested (wild-type and resistant phenotype subsets) TOL/TAZ demonstrated greater activity than CAZ, including a 32-fold higher MIC<sub>50</sub> against ESBL-producing *E. coli*, an 8-fold higher MIC<sub>90</sub> against ESBL-producing *K. pneumoniae*, and a 16-fold higher MIC<sub>90</sub> against MDR *P. aeruginosa* (Table 2).
- Small numbers of Enterobacteriaceae isolates with TOL/TAZ MICs >8 mg/L were found in Belgium (n = 1), France (n = 4), Germany (n = 5), Greece (n = 2), Italy (n = 2), Poland (n = 6), Portugal (n = 1), Spain (n = 3), Turkey (n = 3), and Ukraine (n = 2). Poland had the highest proportion of isolates (6/8 tested) with MICs >8 mg/L. Five of these NS isolates were *K. pneumoniae* and 1 was *Enterobacter cloacae*.
- In all countries except Poland, Enterobacteriaceae susceptibility to TOL/TAZ was  $\geq 80\%$ . In Ireland, Israel, Russia, Sweden, and the UK, 100% of isolates were susceptible to TOL/TAZ (Table 3).
- P. aeruginosa* susceptibility to TOL/TAZ was 100% in all countries except