P0337

ECCMID
Amsterdam, Netherlands
9-12 April 2016

Activity of Ceftolozane/Tazobactam Tested against Organisms from Urinary Tract Pathogens Collected from 41 Medical Centres in Europe, Turkey and Israel (2014)

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Introduction and Purpose

- Urinary tract infections (UTIs) are usually caused by Gram-negative bacteria; the majority of hospital-associated UTIs are caused by the pathogens *Escherichia coli*, *Klebsiella* spp. and *Pseudomonas aeruginosa*[1]
- Antimicrobial drug resistance because of multidrug-resistant (MDR) and extended-spectrum β-lactamase (ESBL)–producing strains of bacteria is common in complicated UTIs (cUTIs), and its prevalence is increasing[1]; the investigation and availability of new antimicrobial treatments are urgently needed
- Ceftolozane/tazobactam is an antibacterial with activity against *P. aeruginosa*, including MDR strains, and other common Gram-negative pathogens, including most ESBL-producing Enterobacteriaceae[2,3]
- Ceftolozane/tazobactam is approved for the treatment of cUTI including pyelonephritis and complicated intra-abdominal infections (in combination with metronidazole)[4] and is in clinical development for ventilator-associated bacterial pneumonia
- In the current study, we evaluated the activity of ceftolozane/tazobactam and comparator agents against Gram-negative organisms causing UTIs in hospitals in Europe, Turkey and Israel during 2014

Methods

Organism collection

- Organism collection included only aerobic Gram-negative bacilli from hospitalised patients with a diagnosis of UTI
- In 2014, a total of 1,573 unique patient organisms were consecutively collected by the Programme to Assess Ceftolozane/Tazobactam Susceptibility (PACTS) from 41 medical centres across 20 European countries, Turkey and Israel (number of centres) as follows: Austria (1), Belgium (1), Czech Republic (1), Denmark (1), Finland (1), France (4), Germany (5), Greece (1), Ireland (2), Israel (1), Italy (4), Netherlands (1), Norway (1), Poland (1), Portugal (1), Russia (3), Spain (3), Sweden (2), Switzerland (1), Turkey (2), Ukraine (1) and United Kingdom (3)
- Species identification was performed at the participating medical centres and was confirmed at the monitoring laboratory (JMI Laboratories) using MALDI-TOF mass spectrometry (Bruker, Billerica, MA, USA), when necessary

Antimicrobial susceptibility testing

- Isolates were tested for susceptibility to multiple antimicrobial agents at a reference laboratory (JMI Laboratories) by standardized, reference broth microdilution methods, as described in Clinical and Laboratory Standards Institute (CLSI) M07-A10[5]
- Ceftolozane/tazobactam was tested using a fixed dose of 4 mg/L of the β-lactamase inhibitor
- Minimum inhibitory concentration (MIC) results were interpreted according to CLSI criteria in M100-S26[6] (2016) and European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoint tables (version 6.0, January 2016)[7]
  - The ceftolozane/tazobactam CLSI breakpoints applied were ≤2/4 mg/L and ≥8/4 mg/L for Enterobacteriaceae and ≤4/4 mg/L and ≥16/4 mg/L for *P. aeruginosa*, for susceptibility and resistance, respectively
  - EUCAST breakpoints applied for ceftolozane/tazobactam were ≤1/4 mg/L and ≥2/4 mg/L for Enterobacteriaceae and ≤4/4 mg/L and ≥8/4 mg/L for *P. aeruginosa*, for susceptibility and resistance, respectively
  - *E. coli* and *Klebsiella* spp. isolates with MIC ≥2 mg/L for ceftazidime or ceftriaxone or aztreonam were categorized as ESBL phenotypes

Results

- The most frequently isolated Gram-negative pathogens from patients with UTIs were *E. coli* (n = 775; 49.3%), *Klebsiella pneumoniae* (n = 245; 15.6%), *P. aeruginosa* (n = 146; 9.3%), *Proteus mirabilis* (n = 102; 6.5%) and *Enterobacter* spp. (n = 94; 6.0%)
  - Among *E. coli* and *K. pneumoniae* isolates, the ESBL-positive phenotype rates were 12.8% and 37.6%, respectively (**Table 1**)
- Overall, ceftolozane/tazobactam was active against the most prevalent pathogens, with MIC required to inhibit the growth of 50% and 90% of isolates ($MIC_{50/90}$) of 0.25/0.5, 0.5/>32 and 0.5/4 mg/L for *E. coli*, *K. pneumoniae* and *P. aeruginosa*, respectively (**Table 1**)
- Using EUCAST breakpoints (ceftolozane/tazobactam susceptible at ≤1/4 mg/L), 91.0%, 98.5%, 73.1%, 97.1% and 74.5% susceptibility rates were observed for all Enterobacteriaceae, *E. coli*, *K. pneumoniae*, *P. mirabilis* and *Enterobacter* spp., respectively (**Table 2**)
  - Ceftolozane/tazobactam inhibited 87.9% of ESBL-phenotype *E. coli* at the EUCAST susceptibility breakpoint of ≤1 mg/L (**Table 1**)
  - In contrast, only 30.4% of ESBL-phenotype *K. pneumoniae* were susceptible to ceftolozane/tazobactam; this value increased to 39.4% in the ESBL-positive, meropenem-susceptible subpopulation (**Table 1**)
- Meropenem resistance using EUCAST criteria was only 0.8%, 0.0% and 4.5% for Enterobacteriaceae, *E. coli* and *K. pneumoniae*, respectively (**Table 2**)
- Ceftolozane/tazobactam was very active ($MIC_{50/90}$, 0.5/4 mg/L, 93.2% susceptible) against 146 *P. aeruginosa* isolates (**Table 1**)
  - In contrast, susceptibility rates using EUCAST criteria for ceftazidime, piperacillin/tazobactam, meropenem, ciprofloxacin and amikacin were lower at 80.8%, 76.7%, 85.6%, 71.0% and 89.7%, respectively (**Table 2**)
- Colistin susceptibility was 100.0% when tested against *P. aeruginosa* (**Table 2**)
- Similar to other β-lactams, ceftolozane/tazobactam demonstrated limited activity against the small number of *Acinetobacter* spp. and *Stenotrophomonas maltophilia* isolates (**Table 1**)

Table 1. Cumulative ceftolozane/tazobactam MIC distributions and prevalence of the 1,573 tested Gram-negative UTI pathogens

Organism	Isolates, n (%)	Number of isolates (cumulative %) inhibited at ceftolozane/tazobactam MIC, mg/L										MIC_{50}	MIC_{90}
		≤0.12	0.25	0.5	1	2	4	8	16	32	>32		
Enterobacteriaceae (all)†	1402 (89.1)	357 (25.5)	560 (65.4)	289 (86.0)	70 (91.0)‡	40 (93.9)	24 (95.6)	12 (96.4)	12 (97.3)	7 (97.8)	31 (100.0)	0.25	1
Escherichia coli	775 (49.3)	295 (38.1)	366 (85.3)	85 (96.3)	17 (98.5)	4 (99.0)	3 (99.4)	2 (99.6)	1 (99.7)	0 (99.7)	2 (100.0)	0.25	0.5
Non-ESBL phenotype	676 (87.2)§	290 (42.9)	338 (92.9)	43 (99.3)	5 (100.0)							0.25	0.25
ESBL phenotype	99 (12.8)§	5 (5.1)	28 (33.3)	42 (75.8)	12 (87.9)	4 (91.9)	3 (94.9)	2 (97.0)	1 (98.0)	0 (98.0)	2 (100.0)	0.5	2
Klebsiella pneumoniae	245 (15.6)	35 (14.3)	87 (49.8)	45 (68.2)	12 (73.1)	13 (78.4)	12 (83.3)	6 (85.7)	4 (87.3)	5 (89.4)	26 (100.0)	0.5	>32
Non-ESBL phenotype	153 (62.4)‖	34 (22.2)	82 (75.8)	32 (96.7)	3 (98.7)	2 (100.0)						0.25	0.5
ESBL phenotype	92 (37.6)‖	1 (1.1)	5 (6.5)	13 (20.7)	9 (30.4)	11 (42.4)	12 (55.4)	6 (62.0)	4 (66.38)	5 (71.7)	26 (100.0)	4	>32
MEM-S-ESBL phenotype	71 (29.0)‖	1 (1.4)	5 (8.5)	13 (26.8)	9 (39.4)	11 (54.9)	12 (71.8)	6 (80.3)	4 (85.9)	1 (87.3)	9 (100.0)	2	>32
Proteus mirabilis	102 (6.5)		9 (8.8)	82 (89.2)	8 (97.1)	2 (99.0)	1 (100.0)					0.5	1
Enterobacter spp.	94 (6.0)	5 (5.3)	29 (36.2)	22 (59.6)	14 (74.5)	12 (87.2)	4 (91.5)	1 (92.6)	5 (97.9)	1 (98.9)	1 (100.0)	0.5	4
Pseudomonas aeruginosa	146 (9.3)	1 (0.7)	5 (4.1)	79 (58.2)	38 (84.2)	6 (88.4)	7 (93.2)	1 (93.8)	1 (94.5)	3 (96.6)	5 (100.0)	0.5	4
Acinetobacter spp.¶	19 (1.2)	1 (5.3)	0 (5.3)	2 (15.8)	1 (21.1)	1 (26.3)	2 (36.8)	0 (36.8)	3 (52.6)	2 (63.2)	7 (100.0)	16	>32
Stenotrophomonas maltophilia	4 (0.3)							1 (25.0)	0 (25.0)	0 (25.0)	3 (100.0)	>32	—

ESBL = extended-spectrum β-lactamase; MEM = meropenem; MIC = minimum inhibitory concentration; MIC_{50} = minimum inhibitory concentration required to inhibit growth of 50% of isolates; MIC_{90} = minimum inhibitory concentration required to inhibit growth of 90% of isolates; S = susceptible; UTI = urinary tract infection.

†Includes *Citrobacter amalonaticus* (4), *Citrobacter braakii* (1), *Citrobacter freundii* (27), *Citrobacter koseri* (31), *Enterobacter aerogenes* (23), *Enterobacter cloacae* (71), *Escherichia coli* (775), *Klebsiella oxytoca* (55), *Klebsiella pneumoniae* (245), *Klebsiella variicola* (1), *Morganella morganii* (20), *Proteus mirabilis* (102), *Proteus vulgaris* (12), *Providencia rettgeri* (2), *Providencia stuartii* (7), *Serratia liquefaciens* (6), *Serratia marcescens* (20).

‡Underlined results based on the EUCAST susceptibility breakpoint.[7]

§Percentage expressed with total number of *E. coli* as the denominator.

‖Percentage expressed with total number of *K. pneumoniae* as the denominator.

¶Includes *Acinetobacter baumannii-calcoaceticus* spp. complex (15), *Acinetobacter junii* (1), *Acinetobacter pittii* (3).

Table 2. Antimicrobial activity of ceftolozane/tazobactam and comparator agents against Gram-negative pathogens isolated from UTIs collected in Europe, Turkey and Israel, 2014

Organism (n) / antimicrobial agent	MIC, mg/L		%S / %I / %R†	
	MIC_{50}	MIC_{90}	CLSI	EUCAST
Enterobacteriaceae (1,402)				
Ceftolozane/tazobactam	0.25	1	93.9 / 1.7 / 4.4	91.0 / –‡ / 9.0
Ceftriaxone	≤0.06	>8	80.5 / 1.3 / 18.2	80.5 / 1.3 / 18.2
Ceftazidime	0.12	16	86.0 / 2.6 / 11.3	82.7 / 3.4 / 14.0
Cefepime	≤0.5	16	86.4 / 2.6 / 11.0	84.9 / 2.9 / 12.2
Meropenem	≤0.015	0.06	98.3 / 0.1 / 1.6	98.4 / 0.9 / 0.8
Doripenem	≤0.12	≤0.12	98.4 / 0.4 / 1.3	98.4 / 0.4 / 1.3
Aztreonam	≤0.12	>16	83.4 / 1.6 / 15.0	81.7 / 1.6 / 16.6
Piperacillin/tazobactam	2	16	90.1 / 4.3 / 5.6	86.6 / 3.6 / 9.9
Ciprofloxacin	≤0.03	>4	76.1 / 1.7 / 22.2	74.6 / 1.5 / 23.9
Gentamicin	≤1	>8	88.2 / 0.6 / 11.3	87.2 / 1.0 / 11.8
Tigecycline§	0.12	0.5	99.1 / 0.9 / 0.0	95.3 / 3.9 / 0.9
Colistin	≤0.5	>8	– / – / –	85.7 / – / 14.3
***Escherichia coli* (775)**				
Ceftolozane/tazobactam	0.25	0.5	99.0 / 0.4 / 0.6	98.5 / – / 1.5
Ceftriaxone	≤0.06	>8	87.7 / 0.9 / 11.4	87.7 / 0.9 / 11.4
Ceftazidime	0.12	2	91.9 / 2.1 / 6.1	88.8 / 3.1 / 8.1
Cefepime	≤0.5	2	90.3 / 2.3 / 7.4	88.9 / 2.6 / 8.5
Meropenem	≤0.015	0.03	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Doripenem	≤0.12	≤0.12	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Aztreonam	≤0.12	8	89.0 / 1.5 / 9.4	87.6 / 1.4 / 11.0
Piperacillin/tazobactam	2	8	95.2 / 2.6 / 2.2	92.9 / 2.3 / 4.8
Ciprofloxacin	≤0.03	>4	75.7 / 0.3 / 24.0	75.1 / 0.6 / 24.3
Gentamicin	≤1	2	90.7 / 0.5 / 8.8	90.1 / 0.6 / 9.3
Tigecycline§	0.06	0.12	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Colistin	≤0.5	≤0.5	– / – / –	99.2 / 0.0 / 0.8
***Klebsiella pneumoniae* (245)**				
Ceftolozane/tazobactam	0.5	>32	78.4 / 4.9 / 16.7	73.1 / – / 26.9
Ceftriaxone	0.12	>8	63.3 / 0.4 / 36.3	63.3 / 0.4 / 36.3
Ceftazidime	0.25	>32	66.5 / 4.1 / 29.4	63.7 / 2.9 / 33.5
Cefepime	≤0.5	>16	65.3 / 3.7 / 31.0	65.3 / 2.4 / 32.2
Meropenem	0.03	1	91.0 / 0.4 / 8.6	91.4 / 4.1 / 4.5
Doripenem	≤0.12	1	91.4 / 2.0 / 6.5	91.4 / 2.0 / 6.5
Aztreonam	≤0.12	>16	65.3 / 0.8 / 33.9	64.9 / 0.4 / 34.7
Piperacillin/tazobactam	4	>64	76.6 / 6.6 / 16.8	69.3 / 7.4 / 23.4
Ciprofloxacin	0.06	>4	65.7 / 3.3 / 31.0	62.9 / 2.9 / 34.3
Gentamicin	≤1	>8	75.5 / 0.4 / 24.1	75.1 / 0.4 / 24.5
Tigecycline§	0.25	0.5	100.0 / 0.0 / 0.0	96.7 / 3.3 / 0.0
Colistin	≤0.5	1	– / – / –	92.4 / – / 7.6

Organism (n) / antimicrobial agent	MIC, mg/L		%S / %I / %R†	
	MIC_{50}	MIC_{90}	CLSI	EUCAST
***Proteus mirabilis* (102)**				
Ceftolozane/tazobactam	0.5	1	99.0 / 1.0 / 0.0	97.1 / – / 2.9
Ceftriaxone	≤0.06	≤0.06	92.2 / 3.9 / 3.9	92.2 / 3.9 / 3.9
Ceftazidime	0.06	0.12	98.0 / 0.0 / 2.0	92.2 / 5.9 / 2.0
Cefepime	≤0.5	≤0.5	97.1 / 2.0 / 1.0	96.0 / 2.0 / 2.0
Meropenem	0.06	0.12	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Doripenem	≤0.12	0.5	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Aztreonam	≤0.12	≤0.12	100.0 / 0.0 / 0.0	97.1 / 2.9 / 0.0
Piperacillin/tazobactam	≤0.5	1	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Ciprofloxacin	≤0.03	>4	77.5 / 8.8 / 13.7	74.5 / 2.9 / 22.5
Gentamicin	≤1	4	90.2 / 1.0 / 8.8	86.3 / 3.9 / 9.8
Tigecycline§	1	4	89.2 / 10.8 / 0.0	56.9 / 32.4 / 10.8
Colistin	>8	>8	– / – / –	0.0 / – / 100.0
***Enterobacter* spp. (94)**				
Ceftolozane/tazobactam	0.5	4	87.2 / 4.3 / 8.5	74.5 / – / 25.5
Ceftriaxone	0.5	>8	56.4 / 2.1 / 41.5	56.4 / 2.1 / 41.5
Ceftazidime	0.5	>32	66.0 / 6.4 / 27.7	57.4 / 8.5 / 34.0
Cefepime	≤0.5	>16	78.7 / 5.3 / 16.0	75.5 / 5.3 / 19.1
Meropenem	0.03	0.12	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Doripenem	≤0.12	≤0.12	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Aztreonam	0.25	>16	63.8 / 5.3 / 30.9	59.6 / 4.3 / 36.2
Piperacillin/tazobactam	4	64	77.7 / 17.0 / 5.3	66.0 / 11.7 / 22.3
Ciprofloxacin	≤0.03	>4	75.5 / 3.2 / 21.3	75.5 / 0.0 / 24.5
Gentamicin	≤1	>8	84.0 / 0.0 / 16.0	84.0 / 0.0 / 16.0
Tigecycline§	0.25	1	100.0 / 0.0 / 0.0	91.5 / 8.5 / 0.0
Colistin	≤0.5	1	– / – / –	93.4 / 0.0 / 6.6
***Pseudomonas aeruginosa* (146)**				
Ceftolozane/tazobactam	0.5	4	93.2 / 0.6 / 6.2	93.2 / – / 6.8
Ceftazidime	2	32	80.8 / 5.5 / 13.7	80.8 / – / 19.2
Cefepime	2	16	83.6 / 11.0 / 5.5	83.6 / – / 16.4
Meropenem	0.25	8	85.6 / 2.1 / 12.3	85.6 / 7.5 / 6.8
Doripenem	0.5	4	87.7 / 3.4 / 8.9	82.2 / 5.5 / 12.3
Aztreonam	8	>16	63.0 / 16.4 / 20.5	2.1 / 77.4 / 20.5
Piperacillin/tazobactam	4	>64	76.7 / 11.6 / 11.6	76.7 / – / 23.3
Ciprofloxacin	0.12	>4	78.6 / 2.1 / 19.3	71.0 / 7.6 / 21.4
Gentamicin	2	>8	81.5 / 4.8 / 13.7	81.5 / – / 18.5
Amikacin	2	16	93.2 / 3.4 / 3.4	89.7 / 3.4 / 6.8
Colistin	2	2	97.3 / 2.7 / 0.0	100.0 / – / 0.0

CLSI = Clinical and Laboratory Standards Institute; EUCAST = European Committee on Antimicrobial Susceptibility Testing; MIC = minimum inhibitory concentration; MIC_{50} = minimum inhibitory concentration required to inhibit growth of 50% of isolates; MIC_{90} = minimum inhibitory concentration required to inhibit growth of 90% of isolates; R = resistant; I = intermediate; S = susceptible; UTI = urinary tract infection.
†Criteria as published by CLSI [2016][6] and EUCAST [2016][7].
‡"–" = no breakpoint available for interpretation.
§In the absence of a CLSI breakpoint, US Food and Drug Administration breakpoints applied when available.[8]

Conclusions

- Ceftolozane/tazobactam exhibited potent activity against contemporary (2014) aerobic Gram-negative pathogens that cause UTIs in Europe, Turkey and Israel
- Ceftolozane/tazobactam was very active against most Enterobacteriaceae, including many ESBL-phenotype strains; however, activity was compromised against ESBL-phenotype *K. pneumoniae* strains
- Against *P. aeruginosa,* ceftolozane/tazobactam demonstrated *in vitro* activity superior to that of meropenem, piperacillin/tazobactam, ciprofloxacin, amikacin and ceftazidime
- These data support a role for ceftolozane/tazobactam in the treatment of patients with cUTI in Europe, Turkey and Israel

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Acknowledgements

Funding for this research was provided by Merck & Co., Inc., Kenilworth, NJ, USA. Medical writing and editorial assistance was provided by Tracy Cao, PhD, of ApotheCom, Yardley, PA, USA. This assistance was funded by Merck & Co., Inc., Kenilworth, NJ, USA.

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