P0338

ECCMID
Amsterdam, Netherlands
9-12 April 2016

Ceftolozane/Tazobactam Activity against Intra-Abdominal Pathogens Collected from 41 Medical Centres in Europe, Turkey and Israel (2014)

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Introduction and Purpose

- Intra-abdominal infections (IAIs) can be mono- or polymicrobial and often include anaerobes and aerobic bacteria[1]
- Gram-negative bacilli (increasingly multidrug-resistant [MDR] strains) play a prominent role in IAIs; *Escherichia coli* is the pathogen most frequently isolated (in ~50% of cases), followed by other Enterobacteriaceae and *Pseudomonas aeruginosa*[1]
- Antimicrobial drug resistance because of the presence of MDR and extended-spectrum β-lactamase (ESBL)–producing strains of bacteria is becoming increasingly common in complicated IAIs (cIAIs)[1]
- The increase in the rate of antimicrobial drug resistance has led to the investigation and recent availability of new antimicrobial treatments such as β-lactam/β-lactamase inhibitor combinations
- 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 complicated urinary tract infection (cUTI) including pyelonephritis and cIAI (in combination with metronidazole)[4]; clinical development in patients with ventilator-associated nosocomial bacterial pneumonia is ongoing
- In the current study, we evaluated the activity of ceftolozane/tazobactam and comparator agents against Gram-negative organisms causing IAIs in hospitals in Europe, Turkey and Israel during 2014

Methods

Organism collection

- Organism collection included only aerobic Gram-negative bacilli collected from hospitalised patients with a diagnosis of IAI
- In 2014, a total of 566 Gram-negative, non-duplicate, non-consecutive clinical isolates were collected by the Programme to Assess Ceftolozane/Tazobactam Susceptibility (PACTS) from single patients with IAI in 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
- Only one strain per patient infection episode was included in this surveillance study

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 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]
  - 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 of ≥2 mg/L for ceftazidime or ceftriaxone or aztreonam were categorized as ESBL phenotypes

Results

- *E. coli* (n = 279; 49.3%), *Klebsiella pneumoniae* (n = 71; 12.5%), *P. aeruginosa* (n = 51; 9.0%), *Enterobacter cloacae* (n = 36; 6.4%) and *Proteus mirabilis* (n = 22; 3.9%) were the most frequently isolated Gram-negative pathogens from patients with IAIs (**Table 1**)
- In *E. coli* and *K. pneumoniae*, the ESBL-positive rates were 18.6% and 40.8%, respectively (**Table 1**)
- Ceftolozane/tazobactam was active against the most commonly isolated pathogens with MIC required to inhibit 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**)
- When applying the EUCAST breakpoints (ceftolozane/tazobactam susceptible at ≤1/4 mg/L), 87.1%, 94.3%, 74.6%, 90.9% and 69.4% susceptibility rates were noted for all tested Enterobacteriaceae, *E. coli*, *K. pneumoniae*, *P. mirabilis* and *E. cloacae,* respectively (**Table 2**)
  - Among ESBL-phenotype *E. coli*, ceftolozane/tazobactam inhibited 69.2% at the EUCAST susceptibility breakpoint of ≤1 mg/L (**Table 1**)
  - In contrast, only 41.4% of ESBL-phenotype *K. pneumoniae* were susceptible to ceftolozane/tazobactam, and 63.2% of the ESBL-positive, meropenem-susceptible subpopulation were susceptible (**Table 1**)
- Meropenem resistance (EUCAST criteria) in Enterobacteriaceae ranged from 0% (*E. coli, P. mirabilis and E. cloacae*) to 5.6% (*K. pneumoniae*), with 1.0% resistance overall (**Table 2**)
- Ceftolozane/tazobactam was very active ($MIC_{50/90}$, 0.5/4 mg/L; 90.2% susceptible) against *P. aeruginosa* (**Table 1**)
  - In contrast, susceptibility rates (EUCAST criteria) for ceftazidime, piperacillin/tazobactam, meropenem and ciprofloxacin were lower at 70.6%, 72.5%, 78.4% and 78.4%, respectively (**Table 2**)
  - Colistin and amikacin had the highest susceptibility rates at 100.0% and 94.1%, respectively (**Table 2**)
- Ceftolozane/tazobactam demonstrated limited activity against the *Acinetobacter* spp. and *Stenotrophomonas maltophilia* isolated (**Table 1**), which made up only 3.3% of IAI pathogens

Table 1. Cumulative ceftolozane/tazobactam MIC distributions and prevalence of the 566 tested Gram-negative IAI 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)†	496 (87.6)	117 (23.6)	212 (66.3)	71 (80.6)	32 (87.1)‡	15 (90.1)	7 (91.5)	12 (94.0)	10 (96.0)	6 (97.2)	14 (100.0)	0.25	2
Escherichia coli	279 (49.3)	97 (34.8)	137 (83.9)	19 (90.7)	10 (94.3)	5 (96.1)	1 (96.4)	4 (97.8)	4 (99.3)	2 (100.0)		0.25	0.5
Non-ESBL phenotype	227 (81.4)§	96 (42.3)	122 (96.0)	9 (100.0)								0.25	0.25
ESBL phenotype	52 (18.6)§	1 (1.9)	15 (30.8)	10 (50.0)	10 (69.2)	5 (78.8)	1 (80.8)	4 (88.5)	4 (96.2)	2 (100.0)		0.5	16
Klebsiella pneumoniae	71 (12.5)	12 (16.9)	21 (446.5)	15 (67.6)	5 (74.6)	1 (76.1)	2 (78.9)	2 (81.7)	1 (83.1)	3 (87.3)	9 (100.0)	0.5	>32
Non-ESBL phenotype	42 (59.2)‖	12 (28.6)	19 (73.8)	8 (92.9)	2 (97.6)	1 (100.0)						0.25	0.5
ESBL phenotype	29 (40.8)‖		2 (6.9)	7 (31.0)	3 (41.4)	0 (41.4)	2 (48.3)	2 (55.2)	1 (58.6)	3 (69.0)	9 (100.0)	8	>32
MEM-S-ESBL phenotype	19 (26.8)‖		2 (10.5)	7 (47.4)	3 (63.2)	0 (63.2)	2 (73.7)	2 (84.2)	0 (84.2)	0 (84.2)	3 (100.0)	1	>32
Enterobacter cloacae	36 (6.4)	1 (2.8)	13 (38.9)	7 (58.3)	4 (69.4)	2 (75.0)	2 (80.6)	2 (86.1)	2 (91.7)	1 (94.4)	2 (100.0)	0.5	16
Proteus mirabilis	22 (3.9)	0 (0.0)	7 (31.8)	11 (81.8)	2 (90.9)	2 (100.0)						0.5	1
Klebsiella oxytoca	17 (3.0)	4 (23.5)	10 (82.4)	3 (100.0)								0.25	0.5
Pseudomonas aeruginosa	51 (9.0)	1 (2.0)	1 (3.9)	30 (62.7)	5 (72.5)	5 (82.4)	4 (90.2)	4 (98.0)	0 (98.0)	0 (98.0)	1 (100.0)	0.5	4
Acinetobacter spp.¶	12 (2.1)	1 (8.3)	0 (8.3)	0 (8.3)	0 (8.3)	0 (8.3)	1 (16.7)	2 (33.3)	5 (50.0)	0 (50.0)	6 (100.0)	16	>32
Stenotrophomonas maltophilia	7 (1.2)					1 (14.3)	0 (14.3)	0 (14.3)	1 (28.6)	2 (57.1)	3 (100.0)	32	—

ESBL = extended-spectrum β-lactamase; IAI = intra-abdominal infection; 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.

†Includes *Citrobacter braakii* (2), *Citrobacter freundii* (17), *Citrobacter koseri* (1), *Enterobacter aerogenes* (15), *Enterobacter amnigenus* (1), *Enterobacter asburiae* (1), *E. cloacae* (41), *E. coli* (279), *K. oxytoca* (17), *K. pneumoniae* (71), *Morganella morganii* (10), *P. mirabilis* (22), *Proteus vulgaris* (6), *Providencia rettgeri* (1), *Providencia stuartii* (3), *Serratia fonticola* (1), *Serratia marcescens* (8).

‡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 (10), *Acinetobacter junii* (1), *Acinetobacter johnsonii* (1).

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

Organism (n) / antimicrobial agent	MIC, mg/L		%S / %I / %R†	
	MIC_{50}	MIC_{90}	CLSI	EUCAST
Enterobacteriaceae (496)				
Ceftolozane/tazobactam	0.25	2	90.1 / 1.4 / 8.5	87.1 / –‡ / 12.9
Ceftriaxone	≤0.06	>8	75.8 / 2.2 / 22.0	75.8 / 2.2 / 22.0
Ceftazidime	0.25	32	83.1 / 3.2 / 13.7	77.6 / 5.4 / 16.9
Cefepime	≤0.5	>16	83.1 / 3.2 / 13.7	77.6 / 5.4 / 16.9
Meropenem	≤0.015	0.06	96.4 / 0.6 / 3.0	97.0 / 2.0 / 1.0
Doripenem	≤0.12	≤0.12	96.4 / 0.6 / 3.0	96.4 / 0.6 / 3.0
Aztreonam	≤0.12	>16	79.6 / 2.2 / 18.1	77.6 / 2.0 / 20.4
Piperacillin/tazobactam	2	>64	84.9 / 3.2 / 11.9	80.2 / 4.6 / 15.1
Ciprofloxacin	≤0.03	>4	79.8 / 1.2 / 19.0	77.4 / 2.4 / 20.2
Gentamicin	≤1	>8	88.1 / 0.8 / 11.1	86.7 / 1.4 / 11.9
Tigecycline§	0.12	0.5	99.4 / 0.6 / 0.0	96.2 / 3.2 / 0.6
Colistin	≤0.5	>8	– / – / –	87.3 / – / 12.7
***Escherichia coli* (279)**				
Ceftolozane/tazobactam	0.25	0.5	96.1 / 0.4 / 3.6	94.3 / – / 5.7
Ceftriaxone	≤0.06	>8	82.4 / 1.1 / 16.5	82.4 / 1.1 / 16.5
Ceftazidime	0.25	4	90.3 / 2.5 / 7.2	82.8 / 7.5 / 9.7
Cefepime	≤0.5	16	84.9 / 3.2 / 11.8	82.8 / 2.9 / 14.3
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	>16	83.9 / 2.2 / 14.0	81.7 / 2.2 / 16.1
Piperacillin/tazobactam	2	32	90.0 / 2.5 / 7.5	85.7 / 4.3 / 10.0
Ciprofloxacin	≤0.03	>4	78.1 / 0.0 / 21.9	75.5 / 2.5 / 21.9
Gentamicin	≤1	>8	88.9 / 0.0 / 11.1	86.7 / 2.2 / 11.1
Tigecycline§	0.06	0.12	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Colistin	≤0.5	≤0.5	– / – / –	99.6 / 0.0 / 0.4
***Klebsiella pneumoniae* (71)**				
Ceftolozane/tazobactam	0.5	>32	76.1 / 2.8 / 21.1	74.6 / – / 25.4
Ceftriaxone	0.12	>8	62.0 / 0.0 / 38.0	62.0 / 0.0 / 38.0
Ceftazidime	0.25	>32	64.8 / 7.0 / 28.2	60.6 / 4.2 / 35.2
Cefepime	≤0.5	>16	62.0 / 5.6 / 32.4	62.0 / 0.0 / 38.0
Meropenem	0.03	8	83.1 / 2.8 / 14.1	85.9 / 8.5 / 5.6
Doripenem	≤0.12	4	83.1 / 2.8 / 14.1	83.1 / 2.8 / 14.1
Aztreonam	≤0.12	>16	62.0 / 2.8 / 35.2	62.0 / 0.0 / 38.0
Piperacillin/tazobactam	4	>64	70.4 / 1.4 / 28.2	64.8 / 5.6 / 29.6
Ciprofloxacin	≤0.03	>4	70.4 / 2.8 / 26.8	66.2 / 4.2 / 29.6
Gentamicin	≤1	>8	78.9 / 0.0 / 21.1	78.9 / 0.0 / 21.1
Tigecycline§	0.25	0.5	100.0 / 0.0 / 0.0	95.8 / 4.2 / 0.0
Colistin	≤0.5	2	– / – / –	93.0 / – / 7.0

Organism (n) / antimicrobial agent	MIC, mg/L		%S / %I / %R†	
	MIC_{50}	MIC_{90}	CLSI	EUCAST
***Proteus mirabilis* (22)**				
Ceftolozane/tazobactam	0.5	1	100.0 / 0.0 / 0.0	90.9 / – / 9.1
Ceftriaxone	≤0.06	≤0.06	90.9 / 0.0 / 9.1	90.9 / 0.0 / 9.1
Ceftazidime	0.06	0.12	95.5 / 0.0 / 4.5	95.5 / 0.0 / 4.5
Cefepime	≤0.5	≤0.5	95.5 / 0.0 / 4.5	90.9 / 4.5 / 4.5
Meropenem	0.06	0.12	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Doripenem	≤0.12	0.25	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	≤0.5	100.0 / 0.0 / 0.0	100.0 / 0.0 / 0.0
Ciprofloxacin	≤0.03	>4	77.3 / 0.0 / 22.7	77.3 / 0.0 / 22.7
Gentamicin	≤1	>8	77.3 / 9.1 / 13.6	77.3 / 0.0 / 22.7
Tigecycline§	1	2	90.9 / 9.1 / 0.0	50.0 / 40.9 / 9.1
Colistin	>8	>8	– / – / –	0.0 / – / 100.0
***Enterobacter cloacae* (36)**				
Ceftolozane/tazobactam	0.5	16	75.0 / 5.6 / 19.4	69.4 / – / 30.6
Ceftriaxone	1	>8	52.8 / 8.3 / 38.9	52.8 / 8.3 / 38.9
Ceftazidime	0.5	>32	66.7 / 2.8 / 30.6	61.1 / 5.6 / 33.3
Cefepime	≤0.5	16	83.3 / 5.6 / 11.1	80.6 / 5.6 / 13.9
Meropenem	0.03	0.12	94.4 / 0.0 / 5.6	94.4 / 5.6 / 0.0
Doripenem	≤0.12	0.25	94.4 / 0.0 / 5.6	94.4 / 0.0 / 5.6
Aztreonam	0.25	>16	69.4 / 2.8 / 27.8	69.4 / 0.0 / 30.6
Piperacillin/tazobactam	4	>64	75.0 / 8.3 / 16.7	69.4 / 5.6 / 25.0
Ciprofloxacin	≤0.03	>4	83.3 / 2.8 / 13.9	80.6 / 2.8 / 16.7
Gentamicin	≤1	≤1	91.7 / 2.8 / 5.6	91.7 / 0.0 / 8.3
Tigecycline§	0.25	1	100.0 / 0.0 / 0.0	94.4 / 5.6 / 0.0
Colistin	≤0.5	1	– / – / –	91.7 / – / 8.3
***Pseudomonas aeruginosa* (51)**				
Ceftolozane/tazobactam	0.5	4	90.2 / 7.8 / 2.0	90.2 / – / 9.8
Ceftazidime	2	>32	70.6 / 5.9 / 23.5	70.6 / – / 29.4
Cefepime	2	>16	74.5 / 7.8 / 17.6	74.5 / – / 25.5
Meropenem	0.5	16	78.4 / 5.9 / 15.7	78.4 / 9.8 / 11.8
Doripenem	1	>4	78.4 / 5.9 / 15.7	70.6 / 7.8 / 21.6
Aztreonam	8	>16	54.9 / 9.8 / 35.3	0.0 / 64.7 / 35.3
Piperacillin/tazobactam	4	>64	72.5 / 3.9 / 23.5	72.5 / – / 27.5
Ciprofloxacin	0.12	4	88.2 / 0.0 / 11.8	78.4 / 9.8 / 11.8
Gentamicin	≤1	4	90.2 / 0.0 / 9.8	90.2 / – / 9.8
Amikacin	2	4	96.1 / 0.0 / 3.9	94.1 / 2.0 / 3.9
Colistin	2	2	100.0 / 0.0 / 0.0	100.0 / – / 0.0

CLSI = Clinical and Laboratory Standards Institute; EUCAST = European Committee on Antimicrobial Susceptibility Testing; IAI = intra-abdominal infection; 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.
†Criteria as published by the 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 demonstrated potent activity against contemporary aerobic Gram-negative pathogens causing IAIs in European, Turkish and Israeli hospitals
- Ceftolozane/tazobactam was active against many Enterobacteriaceae, including some ESBL-phenotype strains; however, activity was compromised against ESBL-phenotype *K. pneumoniae* strains and meropenem-susceptible subsets
- Against *P. aeruginosa*, ceftolozane/tazobactam demonstrated *in vitro* activity superior to that of meropenem, piperacillin/tazobactam, ceftazidime, cefepime and ciprofloxacin but was less active than colistin and amikacin
- These recent (2014) data support a role for ceftolozane/tazobactam in the treatment of patients with cIAIs

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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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