Antimicrobial Activity of Ceftolozane-Tazobactam Tested against Contemporary (2012–2017) Gram-Negative Isolates from Patients Hospitalised with Pneumonia in European Medical Centres

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INTRODUCTION

- Ceftolozane-tazobactam (C-T) is a combination of an antipseudomonal cephalosporin and a well-described β-lactamase inhibitor
  - Ceftolozane-tazobactam has activity against most common β-lactam resistance mechanisms employed by *Pseudomonas aeruginosa*, including AmpC production (PDC), up-regulated efflux pumps, and porin reductions (OprD loss)
  - Ceftolozane-tazobactam also has activity against most ESBL-producing *Enterobacteriaceae* (new taxonomy: Enterobacterales)
- Ceftolozane-tazobactam has been approved in >50 countries by the US Food and Drug Administration (2014) and the European Medicines Agency (2015) for treatment of complicated urinary tract infections, including acute pyelonephritis, and complicated intra-abdominal infections in combination with metronidazole
  - Clinical trials in hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia are in progress (clinicaltrials.gov Identifier: NCT02070757)
- The Program to Assess Ceftolozane-Tazobactam Susceptibility (PACTS) monitors the in vitro activity of C-T among clinical isolates obtained from patients worldwide
- In the current study, gram-negative isolates were collected consecutively from patients hospitalised with pneumonia in Europe from 2012–2017

MATERIALS AND METHODS

- A total of 7,556 gram-negative isolates, including 4,005 *Enterobacteriaceae* and 2,358 *P. aeruginosa*, were collected in 2012–2017 from patients hospitalised with pneumonia in 40 European hospitals from 22 countries (Belarus, Belgium, Czech Republic, Denmark, France, Germany, Greece, Hungary, Ireland, Israel, Italy, the Netherlands, Poland, Portugal, Russia, Slovenia, Spain, Sweden, Switzerland, Turkey, the United Kingdom, and Ukraine)
- All isolates were tested for ceftolozane-tazobactam susceptibility by CLSI broth microdilution at JMI Laboratories
- Other antibiotics tested were amikacin (AMK), cefepime (FEP), ceftazidime (CAZ), colistin (COL), levofloxacin (LVX), meropenem (MER), and piperacillin-tazobactam (TZP)
  - Ceftolozane-tazobactam and piperacillin-tazobactam were tested with a fixed 4 mg/L concentration of tazobactam
  - EUCAST 2018 clinical breakpoints were applied
- Resistant phenotypes included *Enterobacteriaceae* resistant to doripenem, imipenem, or meropenem (CRE) and extended-spectrum beta-lactamase not resistant to carbapenems (ESBL, non-CRE)
  - For *P. aeruginosa*, the phenotypes analysed were CAZ-nonsusceptible (CAZ-NS), MER-NS, FEP-NS, TZP-NS, and NS to the 4 β-lactams (BL-NS)
  - Multidrug-resistant (MDR) isolates were identified as NS to 3 or more antimicrobial classes

RESULTS

- The top 3 overall species isolated from European patients hospitalised with pneumonia were *P. aeruginosa* (33.6%), *Klebsiella pneumoniae* (14.2%), and *Escherichia coli* (13.2%) as shown in Figure 1
  - The rate of these resistant gram-negative pathogens was variable across different countries
  - *Acinetobacter baumannii-calcoaceticus* was primarily from patients in Russia and Turkey, which comprised 43% of all *A. baumannii-calcoaceticus* isolates in Europe
- The overall % susceptible of ceftolozane-tazobactam and comparators are shown in Table 1, including resistant phenotypes
  - For *Enterobacteriaceae*, amikacin and meropenem were the most active agents tested
  - For *P. aeruginosa*, ceftolozane-tazobactam and colistin were the most active agents tested
- MIC distributions for the main pathogens for ceftolozane-tazobactam for all isolates are shown in Table 2
- The % susceptible for ceftolozane-tazobactam and comparators for *Enterobacteriaceae* combined, *E. coli*, *K. pneumoniae*, and *P. aeruginosa* are shown in Figure 2

Figure 1 Frequency of pathogens isolated from European patients hospitalised with pneumonia

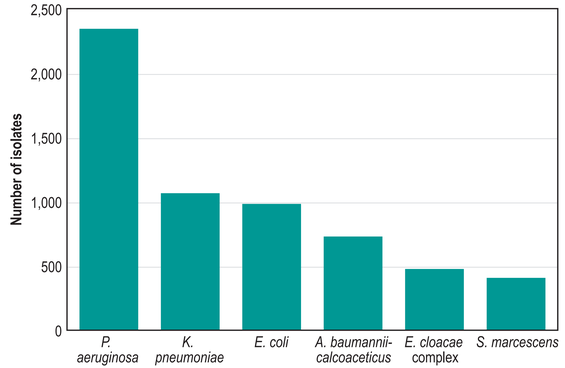


Table 1 Susceptibilities of ceftolozane-tazobactam and comparators against *P. aeruginosa* and *Enterobacteriaceae* in this study

		% susceptible[a]							
Species	n	Ceftolozane-tazobactam	Cefepime	Ceftazidime	Meropenem	Piperacillin-tazobactam	Levofloxacin	Amikacin	Colistin
Enterobacteriaceae	4,005	83.7	77.7	72.8	95.9	75.1	72.8	93.3	76.1
ESBL, non-CRE	664	63.0	14.3	10.7	99.1	39.9	28.2	82.8	92.4
MDR	1,072	45.1	23.4	16.0	82.9	22.5	18.4	73.4	70.1
E. coli	997	97.2	79.3	79.9	100.0	83.4	62.8	95.8	99.6
ESBL, non-CRE	222	87.4	12.2	9.9	100.0	59.9	18.5	86.4	99.5
K. pneumoniae	1,075	67.4	53.9	52.5	86.3	57.1	56.9	83.1	91.2
ESBL, non-CRE	372	45.2	6.5	1.3	98.4	27.3	26.6	79.5	92.9
Pseudomonas aeruginosa	2,358	88.0	73.7	70.0	65.3	65.6	55.0	80.5	99.3
MDR	1,002	70.7	37.6	32.6	19.8	22.0	11.1	54.8	98.6
Ceftazidime-NS	706	61.6	22.9	0.0	28.9	5.5	23.5	54.3	98.6
Cefepime-NS	621	57.8	0.0	12.4	22.4	5.5	16.1	47.0	98.9
Meropenem-NS	817	66.8	41.0	38.6	0.0	29.0	18.7	53.8	98.9
Piperacillin-tazobactam-NS	810	65.7	27.5	17.7	28.4	0.0	22.7	55.5	98.9
β-lactam-NS	425	43.5	0.0	0.0	0.0	0.0	7.1	35.5	99.1

[a] EUCAST (2018)

Table 2 MIC distribution of ceftolozane-tazobactam for pneumonia pathogens

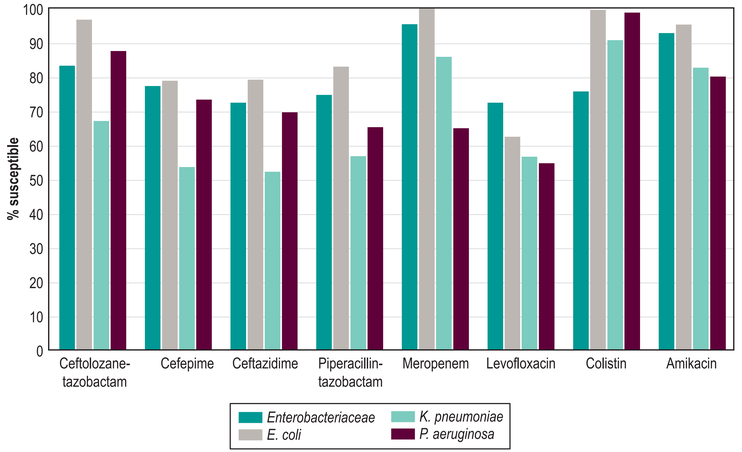
		Number (%) at ceftolozane-tazobactam MIC in mg/L													
Organism/organism group	Total isolates	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	>32	MIC_{50}	MIC_{90}
Enterobacteriaceae	4,005	0 (0.0)	27 (0.7)	724 (18.8)	1,410 (54.0)	840 (74.9)	353 (83.7)	161 (87.8)	119 (90.7)	84 (92.8)	54 (94.2)	53 (95.5)	180 (100.0)	0.25	4
E. cloacae spp.	484		0 (0.0)	34 (7.0)	205 (49.4)	73 (64.5)	45 (73.8)	27 (79.3)	26 (84.7)	34 (91.7)	21 (96.1)	9 (97.9)	10 (100.0)	0.5	8
E. coli	997	0 (0.0)	15 (1.5)	344 (36.0)	453 (81.4)	110 (92.5)	47 (97.2)	12 (98.4)	4 (98.8)	5 (99.3)	3 (99.6)	1 (99.7)	3 (100.0)	0.25	0.5
K. pneumoniae	1,075	0 (0.0)	5 (0.5)	149 (14.3)	331 (45.1)	153 (59.3)	87 (67.4)	54 (72.5)	55 (77.6)	22 (79.6)	22 (81.7)	37 (85.1)	160 (100.0)	0.5	>32
S. marcescens	414		0 (0.0)	1 (0.2)	32 (8.0)	244 (66.9)	101 (91.3)	26 (97.6)	4 (98.6)	6 (100.0)				0.5	1
P. aeruginosa	2,358	0 (0.0)	4 (0.2)	15 (0.8)	151 (7.2)	1,048 (51.7)	519 (73.7)	211 (82.6)	127 (88.0)	38 (89.6)	29 (90.8)	38 (92.5)	178 (100.0)	0.5	16

EUCAST (2018) susceptible breakpoint shaded

CONCLUSIONS

- *Pseudomonas aeruginosa*, *K. pneumoniae,* and *E. coli* were the most common gram-negative clinical isolates from patients hospitalised with pneumonia in Europe
- Ceftolozane-tazobactam demonstrated potent activity against gram-negative isolates from European patients hospitalised with pneumonia
- For *Enterobacteriaceae* isolates, amikacin and meropenem were the most active agents followed by ceftolozane-tazobactam
  - Amikacin, colistin, and meropenem were the most active agents against ESBL, non-CRE isolates
- For *P. aeruginosa*, ceftolozane-tazobactam was the most potent β-lactam tested and second in activity to colistin
- Ceftolozane-tazobactam was the most active β-lactam tested against MDR isolates
- Although clinical data are needed to confirm these findings, these data suggest that ceftolozane-tazobactam may be a useful treatment option against gram-negative pathogens obtained from patients hospitalised with pneumonia

Figure 2 Percent susceptible for ceftolozane-tazobactam and comparators for *Enterobacteriaceae, E. coli, K. pneumoniae,* and *P. aeruginosa* for isolates from patients hospitalised with pneumonia



Acknowledgements

Funding for this research was provided by Merck & Co., Inc., Kenilworth, NJ, USA

References

Clinical and Laboratory Standards Institute (2018). *M100Ed28E. Performance standards for antimicrobial susceptibility testing: 28th informational supplement.* Wayne, PA: CLSI.

Clinical and Laboratory Standards Institute (2018). *M07Ed11E. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard—eleventh edition.* Wayne, PA: CLSI.

EUCAST (2018). Breakpoint tables for interpretation of MICs and zone diameters. Version 8.0, January 2018. Available at: http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_8.0_Breakpoint_Tables.pdf. Accessed January 2018.

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Presented at the ECCMID 2018; April 21–24, 2018; Madrid, Spain