Susceptibility Trends of Ceftolozane-Tazobactam and Comparators When Tested against European Gram-Negative Bacterial Surveillance Isolates Collected from 2012–2018

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Introduction

- Ceftolozane-tazobactam (C-T) is an antipseudomonal cephalosporin combined with a β-lactamase inhibitor
  - C-T has activity against most common β-lactam resistance mechanisms employed by *Pseudomonas aeruginosa* (PSA), including AmpC production (PDC), up-regulated efflux pumps, and porin reductions (OprD loss)
  - C-T also has activity against most extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae
- C-T has been approved in >60 countries for treatment of complicated urinary tract infections and acute pyelonephritis and for complicated intra-abdominal infections (with metronidazole) in adults
- Hospital-acquired pneumonia, including ventilator-associated pneumonia, clinical treatment trials have recently concluded and regulatory filings are in progress (clinicaltrials.gov Identifier: NCT02070757)
- The Program to Assess Ceftolozane-Tazobactam Susceptibility (PACTS) monitors C-T resistance worldwide
- In this study, we analysed resistance trends in Europe over the 7 years of PACTS for gram-negative (GN) isolates

Materials and Methods

- In 2012–2018, 40,008 GN isolates, including 29,952 Enterobacteriaceae (ENT) and 7,288 PSA, were collected from 53 medical centres in 26 countries
- Infection types were bloodstream (BSI), pneumonia in hospitalized patients (PIHP), skin and skin structure (SSSI), intra-abdominal, and urinary tract (UTI)
- Isolates were tested for susceptibility (S) by the CLSI broth microdilution method at JMI Laboratories
- Antimicrobials tested were C-T, amikacin (AMK), cefepime (FEP), ceftazidime (CAZ), colistin (COL), levofloxacin (LEV), meropenem (MEM), and piperacillin-tazobactam (PIP-TAZ)
- Phenotypes analysed were
  - Carbapenem-resistant ENT (CRE), ENT screen-positive for ESBL, non-CRE (ESBL)
  - Ceftazidime nonsusceptible, meropenem nonsusceptible, cefepime nonsusceptible, piperacillin-tazobactam nonsusceptible, and β-lactam nonsusceptible to all 4 β-lactam comparators
  - Multidrug-resistant (MDR) isolates were identified as nonsusceptible to 3 or more antimicrobial classes
  - Extensively-drug resistant (XDR) isolates were identified as nonsusceptible to all but ≤2 antimicrobial classes

Results

- The most common infection type from which GN pathogens were isolated was BSI (10,796) followed by PIHP (10,497), SSSI (7,936) and UTI (7,259)
  - The top 3 species overall were *Escherichia coli* (13,823), PSA (7,288), and *Klebsiella pneumoniae* (5,784)
- The overall MIC frequency distributions for C-T and comparators are shown in Table 1 for PSA, *E. coli* and *K. pneumoniae*
- COL and C-T were the most active agents against PSA (Figure 1 and Table 1)
  - C-T %S ranged from 87.8% in 2012 to 94.2% in 2018 and was 90.1% for all years
  - COL %S was >98.5% for the entire period and 99.3%S overall
- For ENT, AMK and MEM were the most active with >94.0%S (Figure 2)
- For ENT, C-T %S ranged from 87.9% in 2014 to 90.4% in 2018
  - LEV was the least active agent tested against ENT and PSA with %S ranging from 71.3-75.9% for ENT and 59.6-63.2% for PSA
  - For *E. coli*, C-T, AMK, COL, and MEM were >97%S overall (Table 1)
    - LEV was least active (69.6%S)
  - For *K. pneumoniae*, only COL was >90%S (93.6%)
    - MEM and AMK were 87.1%S and 86.4%S, C-T had 71.8%S
- The PSA MDR rate varied from 24.5% in 2014 to 30.7% in 2012 (Figure 3)
  - There was a slight downward trend in frequency of MDR and XDR isolates
- During the period analysed, the MDR ENT rate varied from 17.5% in 2014 to 21.0% in 2017 (Figure 4)
  - The CRE rates varied from 2.1-3.8%
  - ESBL, non-CRE rates varied from 20.5-25.3%, respectively

Conclusions

- The %S varied ≤10% over the 7-year period for the antimicrobials tested
  - A slight trend to lower frequencies of resistant phenotypes was observed for PSA
  - ENT showed a slight increasing trend of resistant phenotypes
- C-T %S remained stable at >87% for both European ENT and PSA for the 7 years of PACTS
- C-T was the most active β-lactam and was second only to colistin against PSA
- C-T was the third most active agent against ENT, after MEM and AMK

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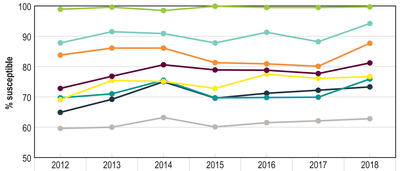
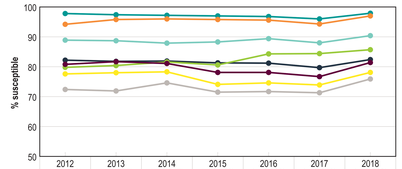
Figure 1 Susceptibility of *P. aeruginosa* to ceftolozane-tazobactam and comparators 2012-2018



	2012 (n=1,200)	2013 (n=1,266)	2014 (n=1,483)	2015 (n=916)	2016 (n=885)	2017 (n=876)	2018 (n=660)
Ceftolozane-tazobactam	87.8	91.5	90.9	87.8	91.3	88.2	94.2
Amikacin	83.8	86.1	86.1	81.3	80.9	80.1	87.7
Cefepime	72.8	76.8	80.6	78.9	78.8	77.7	81.2
Ceftazidime	69.1	75.4	75.1	72.8	77.5	76.1	76.7
Colistin	98.9	99.6	98.5	99.9	99.5	99.5	99.7
Levofloxacin	59.6	60.0	63.2	60.1	61.5	62.1	62.8
Meropenem	69.7	71.0	75.5	69.7	69.8	69.9	75.9
Piperacillin-tazobactam	64.9	69.2	75.0	69.6	71.2	72.2	73.3

EUCAST (2018) breakpoints

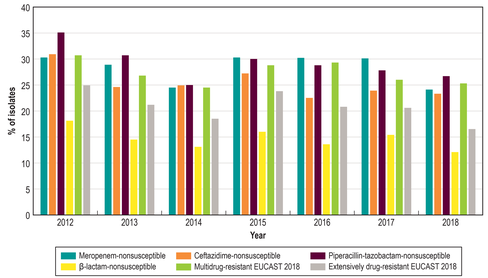
Figure 2 Susceptibility of Enterobacteriaceae to ceftolozane-tazobactam and comparators 2012-2018



	2012 (n=4,518)	2013 (n=4,875)	2014 (n=5,847)	2015 (n=3,373)	2016 (n=3,669)	2017 (n=3,948)	2018 (n=3,322)
Ceftolozane-tazobactam	88.9	88.7	87.9	88.3	89.4	88.0	90.4
Amikacin	94.2	95.8	96.0	95.8	95.6	94.3	97.0
Cefepime	80.8	81.7	81.1	78.1	78.1	76.7	81.4
Ceftazidime	77.6	78.0	78.3	74.1	74.6	73.9	78.1
Colistin	79.8	80.4	81.6	80.6	84.3	84.4	85.7
Levofloxacin	72.4	71.9	74.6	71.5	71.7	71.3	75.9
Meropenem	97.8	97.4	97.2	97.0	96.8	96.0	97.9
Piperacillin-tazobactam	82.2	81.8	81.9	81.3	81.2	79.7	82.4

EUCAST (2018) breakpoints

Figure 3 Frequency of resistant phenotypes of *P. aeruginosa* 2012-2018



β-lactam nonsusceptible: nonsusceptible to meropenem, piperacillin-tazobactam, ceftazidime, and cefepime

Figure 4 Frequency of resistant phenotypes of Enterobacteriaceae 2012-2018

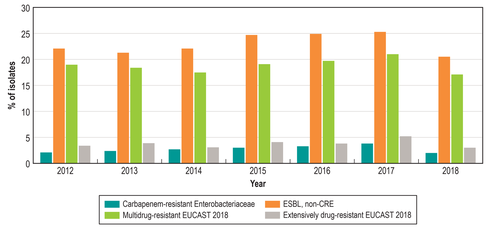


Table 1 Overall MIC frequency distributions of the 3 most common species, *P. aeruginosa*, *E. coli* and *K. pneumoniae*, for C-T and comparators

Organism/organism group (no. of isolates)	No. and cumulative % of isolates inhibited at MIC (mg/L) of:															
	≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	> [a]	MIC_{50}	MIC_{90}
Pseudomonas aeruginosa																
Ceftolozane-tazobactam (7,288)		0	8	34	548	3,683	1,445	553	297	115	66	98		441		
		0	0.1	0.6	8.1	58.6	78.5	86	90.1	91.7	92.6	93.9		100	0.5	4
Amikacin (7,286)					42	163	528	2,417	2,173	790	367	218		588		
					0.6	2.8	10.1	43.2	73.1	83.9	88.9	91.9		100	4	32
Cefepime (7,287)						141	1,111	2,254	1,083	1,090	906			702		
						1.9	17.2	48.1	63	77.9	90.4			100	4	16
Ceftazidime (7,287)					28	111	1,161	2,734	916	474	424	707		732		
					0.4	1.9	17.8	55.4	67.9	74.4	80.3	90		100	2	>32
Colistin (7,286)						1,845	3,345	2,045	39	3				9		
						25.3	71.2	99.3	99.8	99.9				100	1	2
Levofloxacin (7,280)					1,130	2,464	694	562	428					1,828		
				174	17.9	51.8	61.3	69	74.9					100	0.5	>4
Meropenem (7,285)				2.4	1,278	1,227	839	536	532	497				1,033		
			456	887	36	52.8	64.3	71.7	79	85.8				100	0.5	>8
Piperacillin-tazobactam (7,276)			6.3	18.4		140	88	476	2,776	1,053	612	527		1,117		
						1.9	3.1	9.7	47.8	62.3	70.7	78		100	8	>64
Escherichia coli																
Ceftolozane-tazobactam (13,823)	2	5	218	5,450	5,956	1,388	447	157	53	50	35	19		43		
	<0.1	0.1	1.6	41.1	84.1	94.2	97.4	98.6	98.9	99.3	99.6	99.7		100	0.25	0.5
Amikacin (13,784)					5	84	1,793	7,110	3,512	935	257	56		32		
					<0.1	0.6	13.7	65.2	90.7	97.5	99.4	99.8		100	2	4
Cefepime (13,816)						11,041	209	250	253	269	261			1,533		
						79.9	81.4	83.2	85.1	87	88.9			100	≤0.5	>16
Ceftazidime (13,823)	2	32	635	5,399	4,018	866	341	364	348	357	501	477		483		
	<0.1	0.2	4.8	43.9	73	79.2	81.7	84.3	86.8	89.4	93.1	96.5		100	0.25	16
Colistin (13,782)						13,435	242	37	35	28				5		
						97.5	99.2	99.5	99.8	>99.9				100	≤0.5	≤0.5
Levofloxacin (13,804)				8,214	654	744	175	53	364					3,600		
				59.5	64.2	69.6	70.9	71.3	73.9					100	≤0.12	>4
Meropenem (13,822)			13,701	51	27	17	9	3	3	4	3	2		2		
			99.1	99.5	99.7	99.8	99.9	99.9	99.9	99.9	>99.9	>99.9		100	≤0.06	≤0.06
Piperacillin-tazobactam (13,795)						262	2,966	6,352	1,780	816	537	260	225	597		
						1.9	23.4	69.4	82.3	88.3	92.2	94	95.7	100	2	16
Klebsiella pneumoniae																
Ceftolozane-tazobactam (5,784)	1	1	32	861	1,846	933	480	249	207	105	89	133		847		
	<0.1	<0.1	0.6	15.5	47.4	63.5	71.8	76.1	79.7	81.5	83.1	85.4		100	0.5	>32
Amikacin (5,781)					20	433	2,644	1,073	604	221	236	282		268		
					0.3	7.8	53.6	72.1	82.6	86.4	90.5	95.4		100	1	16
Cefepime (5,782)						3,266	96	55	82	115	207			1,961		
						56.5	58.1	59.1	60.5	62.5	66.1			100	≤0.5	>16
Ceftazidime (5,784)	1	25	450	1,428	829	385	156	64	88	193	322	337		1,506		
	<0.1	0.4	8.2	32.9	47.3	53.9	56.6	57.7	59.2	62.6	68.1	74		100	0.5	>32
Colistin (5,736)						4,975	344	49	33	61				274		
						86.7	92.7	93.6	94.2	95.2				100	≤0.5	1
Levofloxacin (5,766)				2,886	144	464	302	122	209					1,639		
				50.1	52.5	60.6	65.8	68	71.6					100	≤0.12	>4
Meropenem (5,779)			4,606	125	59	77	94	70	73	98				577		
			79.7	81.9	82.9	84.2	85.8	87.1	88.3	90				100	≤0.06	8
Piperacillin-tazobactam (5,762)						43	253	1,540	1,122	570	401	244	206	1,383		
						0.7	5.1	31.9	51.3	61.2	68.2	72.4	76	100	4	>64

[a] Greater than the highest concentration tested. Shaded cells are EUCAST v 8.1 susceptible breakpoints (EUCAST 2018).

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