Susceptibility Trends of Ceftolozane-Tazobactam and Comparators When Tested against US 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
- C-T was recently approved by the FDA for the treatment of hospital-acquired bacterial pneumonia, including ventilator-associated bacterial pneumonia
- The Program to Assess Ceftolozane-Tazobactam Susceptibility (PACTS) monitors C-T resistance worldwide
- We analyzed resistance trends in the United States over the 7 years of PACTS for gram-negative (GN) isolates collected in 35 US medical centers

Materials and Methods

- In 2012–2018, 35,514 GN isolates, including 26,707 *Enterobacteriaceae* (ENT) and 6,583 PSA isolates, were tested for susceptibility (S) by the CLSI broth microdilution method at JMI Laboratories
- Infection types were bloodstream (BSI), patients hospitalized with pneumonia (PHP), skin and skin structure (SSSI), complicated intra-abdominal (cIAI), and complicated urinary tract (cUTI)
- Antimicrobials tested included C-T, amikacin (AMK), colistin (COL), cefepime (FEP), ceftazidime (CAZ), levofloxacin (LEV), meropenem (MEM), and piperacillin-tazobactam (PIP-TAZ)
- Phenotypes identified were:
  - Carbapenem-resistant ENT (CRE),
  - ENT screen-positive for ESBL that are non-CRE (ESBL)
  - CAZ nonsusceptible, MEM nonsusceptible, FEP nonsusceptible, PIP-TAZ nonsusceptible, and nonsusceptible to all 4 β-lactam (BL) 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 or fewer antimicrobial classes
- CLSI (2019) interpretive criteria were used, except for ENT with COL, which used EUCAST (2019)

Results

- The most common infection type caused by a GN pathogen was PHP (10,406) followed by UTI (8,683), BSI (7,565), SSSI (5,595), and IAI (3,000) (Figure 1)

Table 1 Overall antimicrobial activity of ceftolozane-tazobactam, amikacin, cefepime, ceftazidime, colistin, levofloxacin, meropenem, and piperacillin-tazobactam tested against the main organisms and organism groups

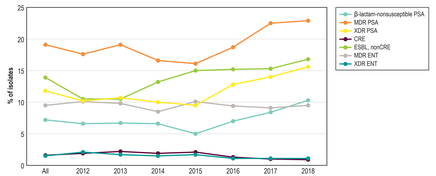
Organism/organism group (no. of isolates)	No. and cumulative % of isolates inhibited at MIC (mg/L) of[a]														
	≤0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	>[a]	MIC$_{50}$	MIC$_{90}$
Pseudomonas aeruginosa															
Ceftolozane-tazobactam (6,583)	4 0.1	12 0.2	43 0.9	588 9.8	3,576 64.2	1,479 86.6	456 93.5	240 97.2	86 98.5	26 98.9	13 99.1		60 100	0.5	2
Amikacin (6,583)				58 0.9	180 3.6	481 10.9	2,143 43.5	2,192 76.8	965 91.4	312 96.2	102 97.7		150 100	4	8
Cefepime (6,580)					220 3.3	1,105 20.1	2,129 52.5	1,024 68.1	1,078 84.4	634 94.1			390 100	2	16
Ceftazidime (6,583)				52 0.8	149 3.1	1,298 22.8	2,572 61.8	979 76.7	483 84	283 88.3	306 93		461 100	2	32
Colistin (6,583)					2,191 33.3	2,795 75.7	1,560 99.4	31 99.9	0 99.9				6 100	1	2
Levofloxacin (6,579)			268 4.1	1,048 20	2,333 55.5	693 66	608 75.2	472 82.4					1,157 100	0.5	>4
Meropenem (6,575)		544 8.3	844 21.1	1,399 42.4	1,274 61.8	748 73.1	438 79.8	385 85.7	415 92				528 100	0.5	8
Piperacillin-tazobactam (6,580)					260 4	131 5.9	460 12.9	2,669 53.5	1,048 69.4	668 79.6	373 85.2	264 89.3	707 100	4	>64
Enterobacteriaceae															
Ceftolozane-tazobactam (26,707)	19 0.2	374 1.5	7,574 29.8	10,539 69.3	4,850 87.5	1,402 92.7	509 94.6	344 95.9	322 97.1	215 97.9	167 98.5		392 100	0.25	1
Amikacin (26,658)				51 0.2	1,119 4.4	8,670 36.9	10,920 77.9	4,429 94.5	950 98.1	248 99	200 99.7		71 100	2	4
Cefepime (26,698)					23,239 87	444 88.7	392 90.2	331 91.4	309 92.6	316 93.8			1,667 100	≤0.5	2
Ceftazidime (26,705)	573 2.2	3,198 14.1	8,625 46.4	6,828 72	2,504 81.4	809 84.4	428 86	343 87.3	387 88.7	639 91.1	770 94		1,601 100	0.25	16
Colistin[b] (26,542)					20,569 77.5	789 80.5	116 80.9	68 81.2	88 81.5				4,912 100	≤0.5	>8
Levofloxacin (26,680)			18,280 68.5	1,357 73.6	1,204 78.1	578 80.3	356 81.6	464 83.4					4,441 100	≤0.12	>4
Meropenem (26,705)		25,212 94.4	799 97.4	134 97.9	58 98.1	41 98.3	65 98.6	79 98.9	73 99.1				244 100	≤0.06	≤0.06
Piperacillin-tazobactam (26,675)					2,658 10	4,674 27.5	10,518 66.9	4,297 83	1,488 88.6	868 91.9	460 93.6	449 95.3	1,263 100	2	16

[a] CLSI, 2019.
[b] EUCAST, 2019.
Green is susceptible.
Yellow is intermediate or susceptible dose dependent (cefepime).
Red is resistant.

- The top 5 GN species from the infection types are shown in Figure 1
  - *Escherichia coli* was the most common species among BSI, IAI, and UTI
  - PSA was the most common pathogen in PHP and SSSI
- C-T and comparator MIC distributions for PSA and ENT are shown in Table 1
- Overall, the %S of C-T vs. 1,258 MDR PSA was 86.6% and was 81.8% against 777 XDR
  - Against MDR and XDR PSA, AMK had 84.5% and 80.4% S, respectively
  - COL %S for MDR was 98.9% and for XDR was 98.5%
- Frequencies of the resistant phenotypes are shown in Figure 2
  - During the period, the MDR ENT rate varied from 8.5% to 10.1% and the XDR remained flat
  - The CRE and ESBL, non-CRE rates varied from 0.9% to 2.2% and 10.5% to 16.8%, respectively
  - The PSA MDR rate increased from 16.1% to 22.9%
  - The PSA XDR rate increased from 9.5% to 15.6%
  - The BL-NS PSA rate doubled from 5.0% in 2015 to 10.3% in 2018
- Over the period, the most active drugs were
  - For PSA: C-T (96.4–98.8%S), AMK (93.8–98.0%S), and COL (98.4%–100.0%) (Figure 3)

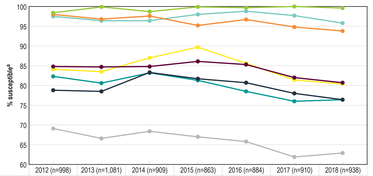
Figure 1 Top 5 gram-negative isolates by infection type

Figure 2 Change in percent of resistant phenotypes for *P. aeruginosa* and *Enterobacteriaceae* over the 7-year period



PSA, *P. aeruginosa*; MDR, multidrug-resistant; XDR, extensively drug-resistant; CRE, carbapenem-resistant *Enterobacteriaceae*; ESBL, extended-spectrum β-lactamase; ENT, *Enterobacteriaceae*

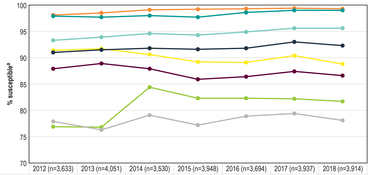
Figure 3 Susceptibility of *P. aeruginosa* by year



	2012 (n=998)	2013 (n=1,081)	2014 (n=909)	2015 (n=863)	2016 (n=884)	2017 (n=910)	2018 (n=938)
Ceftolozane-tazobactam	97.5	96.4	96.4	98.0	98.8	97.7	95.8
Amikacin	98.0	96.8	97.6	95.2	96.7	94.8	93.8
Cefepime	84.1	83.5	87.0	89.7	85.6	81.4	80.4
Ceftazidime	84.8	84.7	84.8	86.1	85.3	82.0	80.7
Colistin	98.4	99.9	98.7	99.9	99.7	100.0	99.6
Levofloxacin	69.1	66.6	68.4	67.0	65.8	61.9	62.9
Meropenem	82.3	80.6	83.2	81.3	78.5	76.0	76.4
Piperacillin-tazobactam	78.8	78.5	83.3	81.7	80.7	78.0	76.4

[a] CLSI, 2019.

Figure 4 Susceptibility of *Enterobacteriaceae* by year



	2012 (n=3,633)	2013 (n=4,051)	2014 (n=3,530)	2015 (n=3,948)	2016 (n=3,694)	2017 (n=3,937)	2018 (n=3,914)
Ceftolozane-tazobactam	93.3	93.9	94.6	94.3	94.9	95.6	95.6
Amikacin	98.1	98.5	99.1	99.2	99.3	99.4	99.3
Cefepime	91.4	91.7	90.6	89.2	89.1	90.4	88.8
Ceftazidime	87.9	88.9	87.9	85.9	86.4	87.4	86.6
Colistin[b]	76.9	76.8	84.4	82.3	82.3	82.2	81.7
Levofloxacin	77.9	76.3	79.1	77.2	78.9	79.4	78.1
Meropenem	97.9	97.7	98.0	97.7	98.6	99.0	99.0
Piperacillin-tazobactam	91.0	91.5	91.8	91.6	91.8	93.0	92.3

[a] CLSI (2019).
[b] EUCAST (2019).

- PSA %S trended lower over time for LEV and β-lactams FEP, CAZ, MEM, and PIP-TAZ
- For ENT, AMK (98.1–99.4%S), MEM (97.7–99.0%S), and C-T (93.3–95.6%S) were the most active (Figure 4)
  - No trends were observed for %S for ENT

Conclusions

- The %S for the agents tested varied <10% over the 7-year period
- The frequency of resistant phenotypes in PSA increased, with % of MDR, XDR, and BL-NS highest in 2018
- CRE, MDR, and XDR enterics remained steady, while ESBL, non-CRE increased 6.3%
- Over the study period, C-T %S remained stable at >93.0% for ENT and >95.0% for PSA
- Against all PSA, C-T had similar %S to AMK and COL
  - Against MDR and XDR PSA, C-T was more active than AMK.
- Against ENT, C-T was the second most active β-lactam after MEM

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