Antimicrobial Activity of Ceftolozane-Tazobactam Tested against Contemporary (2012–2016) *Enterobacteriaceae* and *Pseudomonas aeruginosa* Isolates by US Census Division

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INTRODUCTION

- Ceftolozane-tazobactam (C-T) is a combination of a novel antipseudomonal cephalosporin and a well-described β-lactamase inhibitor
- C-T was approved by the United States (US) Food and Drug Administration in 2014 for complicated urinary tract infections, including acute pyelonephritis, and complicated intra-abdominal infections in combination with metronidazole
  - C-T is currently in clinical trials for the treatment of nosocomial pneumonia, including ventilator-associated pneumonia
- The Program to Assess Ceftolozane-Tazobactam Susceptibility (PACTS) monitors C-T resistance to gram-negative (GN) isolates worldwide
- In this study, the activities of C-T and comparators versus GN isolates from US medical centers in each of the 9 US census divisions were compared

MATERIALS AND METHODS

- A total of 18,856 *Enterobacteriaceae* (ENT) and 4,735 *Pseudomonas aeruginosa* (PSA) isolates were consecutively collected from 32 US hospitals in 2012–2016
  - The 3 most common ENT were *Escherichia coli* (n=7,728), *Klebsiella pneumoniae* (n=3,609), and *Enterobacter cloacae* species complex (n=1,773)
- The most common infection types were pneumonia (n=6,401), urinary tract infections (n=6,163), bloodstream infections (n=4,923), skin and skin structure infections (n=3,745), and intra-abdominal infections (n=2,094)
- Isolates were tested for susceptibility (S) to C-T and comparators by broth microdilution methodology in a central monitoring laboratory
  - Other antibiotics tested included amikacin (AMK), cefepime (CEF), ceftazidime (CAZ), colistin (COL), meropenem (MER), and piperacillin-tazobactam (TZP)
- The following resistant phenotypes were analyzed for ENT: carbapenem-resistant (CRE); extended-spectrum beta-lactamase phenotype screen-positive (ESBL); and ESBL, nonCRE
- For PSA, the following resistant phenotypes were analyzed: MER-nonsusceptible (NS), TZP-NS, CAZ-NS, and TZP/CAZ/MER/FEP-NS (BL-NS)
- CLSI (2017) interpretive criteria were used, and EUCAST (2017) interpretive criteria were used for ENT with COL
- The US divisions are: 1) New England, 2) Middle Atlantic, 3) East North Central, 4) West North Central, 5) South Atlantic, 6) East South Central, 7) West South Central, 8) Mountain, and 9) Pacific

RESULTS

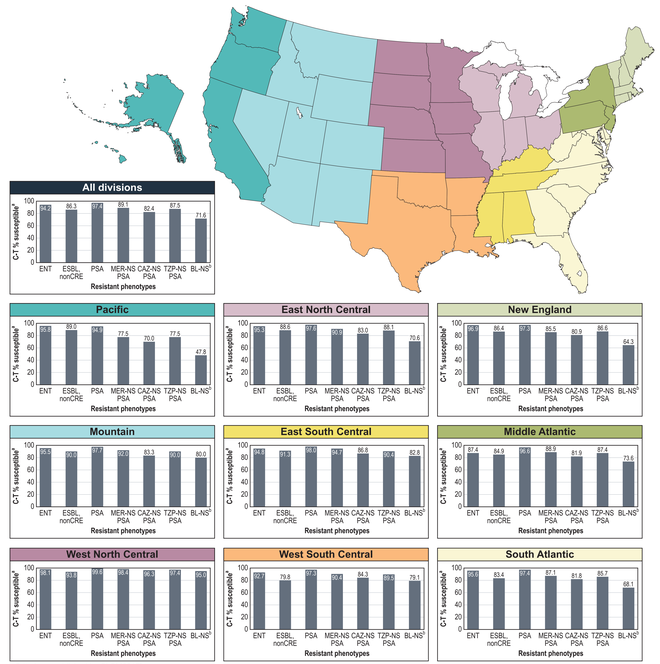
- The percent of C-T susceptibility for resistant phenotypes in each division (DIV) are shown in Figure 1
- The percent of C-T susceptibility for ENT ranged from 98.1% (DIV 4-West North Central) to 87.4% (DIV 2-Middle Atlantic)
  - The percent of C-T susceptibility for ESBL, nonCRE ranged from 93.8% in DIV 4-West North Central to 79.8% in DIV 7-West South Central
- For PSA, the percent of C-T susceptibility ranged from 99.6% in DIV 4-West North Central to 94.9% in DIV 9-Pacific
- Activity of C-T against PSA that were NS to either MER, CAZ, or TZP varied by division and was >80% for all except DIV 9-Pacific
- Activity of C-T against PSA that were NS to all 4 β-lactam comparators (CAZ, FEP, MER, and TZP) varied by division and ranged from 48.7% (DIV 9-Pacific) to 95% (DIV 4-West North Central), with 71.6%S overall
- The C-T MIC distribution and $MIC_{50/90}$ for ENT and PSA with resistant phenotypes overall are shown in Table 1
- For ENT isolates, 94.2% were S to C-T, 91.5% were S to TZP, 98.0% were S to MER, and 98.8% were S to AMK; 1,697 (9.0%) were ESBL, nonCRE and 356 (1.9%) were CRE (Figure 2)
- For PSA isolates, 97.4% were S to C-T, 99.3% were S to COL, 96.9% were S to AMK, and 81.2% were S to MER (Figure 2)

- The percent of C-T and comparator susceptibility by US division when tested against ENT and PSA are shown in Figure 2
  - DIV 2-Middle Atlantic had the lowest susceptibility rates for ENT, particularly for β-lactams while DIV 4-West North Central had the highest susceptibility rates
  - For ENT overall, C-T, AMK, and MER had the highest susceptibility percentages across the US divisions
  - For PSA, the same trend was seen; DIV 2-Middle Atlantic had the lowest susceptibility rates overall and DIV 4-West North Central had the highest susceptibility rates
  - For PSA overall, C-T, AMK, and COL had the highest susceptibility percentages (>94%) across the US divisions

CONCLUSIONS

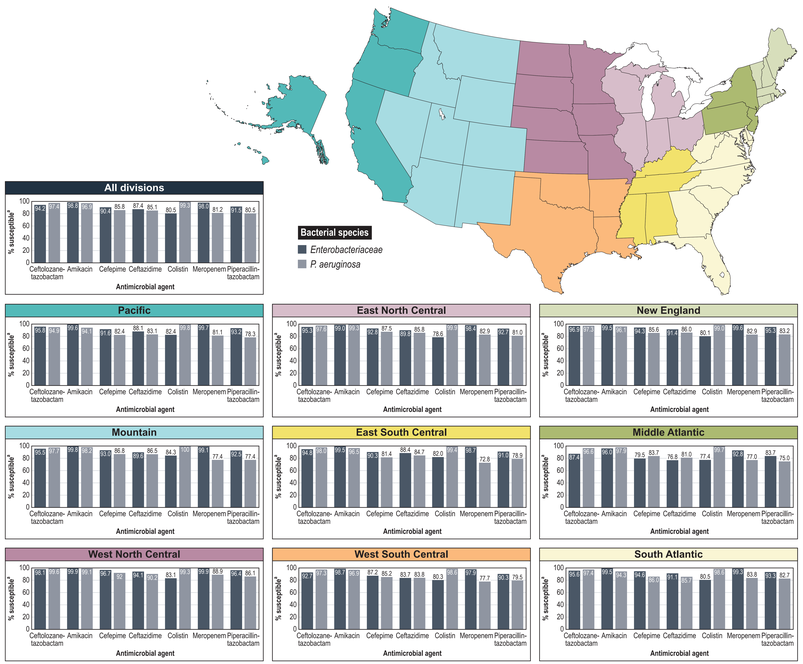
- For both PSA and ENT, the susceptibility percentage varied by division for all agents
  - DIV 2-Middle Atlantic had the lowest susceptibility percentage overall, and DIV 4-West North Central had the highest susceptibility percentage
- Against PSA, COL, C-T, and AMK were the most active antibiotics
  - C-T had activity similar to AMK with ≥94%S for all divisions
- For ENT, AMK, MER, and C-T were the most active agents
  - Overall activity of C-T was very good and ranged from 87–98%S
    - DIV 2-Middle Atlantic was the only division with <90%S
  - AMK was the most active agent with ≥96%S across divisions
  - MER susceptibility was ≥92.8%
- These data indicate that C-T was one of the most active agents tested against ENT and PSA isolates from across the US
  - Against ENT, C-T and MER were the most active β-lactams tested
  - Against PSA, only COL was more active that C-T
  - C-T was the most active β-lactam against PSA in all US divisions
  - C-T maintained activity against PSA that were NS to other beta-lactams

Figure 1. Percent susceptibility for ceftolozane-tazobactam tested against *Enterobacteriaceae*, *P. aeruginosa*, and selected resistant phenotypes (by US census division)



[a] Criteria as published by CLSI [2017]
[b] Isolates resistant to the 4 beta-lactam comparators in this study: CAZ, FEP, MER, and TZP

Figure 2. Percent susceptibility of *Enterobacteriaceae* and *P. aeruginosa* tested against ceftolozane-tazobactam and comparators by US division



[a] Criteria for *Enterobacteriaceae* and *P. aeruginosa* as published by CLSI [2017] and for COL only as published by EUCAST [2017]

Table 1. Antimicrobial activity of ceftolozane-tazobactam tested against the main organisms and organism groups of isolates

Organism / organism group (no. of isolates)	No. of isolates at MIC (mg/L; cumulative %)												MIC_{50}	MIC_{90}
	≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	>		
Pseudomonas aeruginosa (4,735)	0 0.0	3 0.1	7 0.2	32 0.9	475 10.9	2,585 65.5	1,021 87.1	311 93.6	176 97.4	64 98.7	15 99.0	7 99.2	39 100.0	0.5	2
Meropenem-nonsusceptible (889)				0 0.0	11 1.2	224 26.4	302 60.4	152 77.5	103 89.1	43 93.9	12 95.3	6 96.0	36 100.0	1	8
Ceftazidime-nonsusceptible (705)				0 0.0	1 0.1	38 5.5	161 28.4	212 58.4	169 82.4	63 91.3	15 93.5	7 94.5	39 100.0	2	8
Piperacillin-tazobactam-nonsusceptible (923)				0 0.0	4 0.4	109 12.2	293 44.0	233 69.2	169 87.5	69 94.0	14 95.6	4 96.0	37 100.0	2	8
Cefepime-nonsusceptible (671)				0 0.0	2 0.3	21 3.4	163 27.7	203 58.0	164 82.4	61 91.5	15 93.7	4 94.3	38 100.0	2	8
β-lactam-nonsusceptible (303)					0 0.0	2 0.7	42 14.5	80 40.9	93 71.6	40 84.8	11 88.4	2 89.1	33 100.0	4	>32
Enterobacteriaceae (18,856)[a]	2 <0.1	14 0.1	316 1.8	5,377 30.3	7,324 69.1	3,385 87.1	972 92.2	371 94.2	253 95.5	236 96.8	162 97.6	129 98.3	315 100.0	0.25	1
CRE (356)					0 0.0	4 1.1	4 2.2	6 3.9	8 6.2	23 12.6	29 20.8	68 39.9	214 100.0	>32	>32
ESBL, nonCRE (1,697)		0 0.0	4 0.2	109 6.7	434 32.2	517 62.7	255 77.7	145 86.3	73 90.6	48 93.4	32 95.3	21 96.5	59 100.0	0.5	4
E. coli (7,728)	2 <0.1	6 0.1	220 3.0	3,279 45.4	3,149 86.1	716 95.4	172 97.6	77 98.6	35 99.1	24 99.4	14 99.6	14 99.8	19 100.0	0.25	0.5
CRE E. coli (17)								0 0.0	2 11.8	3 29.4	3 47.1	5 76.5	4 100.0	32	>32
ESBL, nonCRE E. coli (1,123)		0 0.0	2 0.2	91 8.3	345 39.0	380 72.8	144 85.7	71 92.0	33 94.9	21 96.8	12 97.9	9 98.7	15 100.0	0.5	2
Klebsiella spp. (4,504)	0 0.0	7 0.2	61 1.5	1,301 30.4	1,754 69.3	655 83.9	238 89.2	85 91.1	40 91.9	41 92.9	43 93.8	62 95.2	217 100.0	0.25	2
CRE *Klebsiella* spp. (264)							0 0.0	3 1.1	1 1.5	14 6.8	23 15.5	50 34.5	173 100.0	>32	>32
ESBL, nonCRE *Klebsiella* spp. (524)		0 0.0	2 0.4	16 3.4	77 18.1	117 40.5	100 59.5	71 73.1	39 80.5	26 85.5	20 89.3	12 91.6	44 100.0	1	32

[a] Organisms include: *Citrobacter amalonaticus* (18), *C. amalonaticus/farmeri* (2), *C. braakii* (32), *C. farmeri* (8), *C. freundii* (383), *C. freundii* species complex (80), *C. koseri* (337), *C. sedlakii* (3), *C. youngae* (14), *Cronobacter sakazakii* (5), *Edwardsiella tarda* (1), *Enterobacter aerogenes* (641), *E. amnigenus* (4), *E. asburiae* (29), *E. cancerogenus* (1), *E. cloacae* (1,381), *E. cloacae* species complex (392), *E. hormaechei* (1), *E. intermedius* (1), *E. kobei* (2), *E. taylorae* (1), *Escherichia coli* (7,728), *E. hermannii* (2), *E. vulneris* (1), *Ewingella americana* (1), gram-negative rods in the family Enterobacteriaceae (1), *Hafnia alvei* (10), *Klebsiella oxytoca* (895), *K. pneumoniae* (3,609), *K. varricola* (19), *Kluyvera ascorbata* (4), *Kosakonia cowanii* (3), *Leclercia adecarboxylata* (2), *Morganella morganii* (486), *Pantoea agglomerans* (11), *P. calida* (2), *P. dispersa* (1), *P. eucrina* (1), *Pluralibacter gergoviae* (8), *Proteus mirabilis* (1,104), *P. penneri* (6), *P. vulgaris* (106), *P. vulgaris* group (25), *Providencia alcalifaciens* (1), *P. rettgeri* (124), *P. stuartii* (128), *Rahnella aquatilis* (1), *Raoultella ornithinolytica* (12), *R. planticola* (6), *Serratia fonticola* (2), *S. liquefaciens* (35), *S. marcescens* (1,137), *S. odorifera* (2), *S. plymuthica* (1), *S. rubidaea* (2), *Shigella sonnei* (1), unspeciated *Cedecea* (1), unspeciated *Citrobacter* (25), unspeciated *Enterobacter* (1), unspeciated *Pantoea* (6), unspeciated *Providencia* (2), unspeciated *Raoultella* (7), unspeciated *Serratia* (1)

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