Global Surveillance: Susceptibility of Ceftolozane-Tazobactam against *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* Isolates Collected from Bloodstream Infections in the United States from 2015–2017

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INTRODUCTION

- Ceftolozane-tazobactam (C-T) is an antibacterial combination of a novel antipseudomonal cephalosporin and a well-established β-lactamase inhibitor
- C-T is approved in over 50 countries, including the United States, to treat complicated urinary tract infections, including acute pyelonephritis, and complicated intra-abdominal infections
- The Program to Assess Ceftolozane-Tazobactam Susceptibility (PACTS) monitors gram-negative (GN) isolates resistant to C-T worldwide
- In the current study, isolates were collected from patients hospitalized with bloodstream infections (BSIs) from 2015–2017 within the United States

MATERIALS AND METHODS

- A total of 3,377 prevalence-based BSI GN isolates were collected during 2015 to 2017 from 32 PACTS hospitals in the United States
  - Isolates were tested for C-T susceptibility by CLSI broth microdilution method in a central monitoring laboratory (JMI Laboratories)
  - Other antibiotics tested included amikacin (AMK), cefepime (FEP), ceftazidime (CAZ), colistin (COL), levofloxacin (LEV), meropenem (MEM), and piperacillin-tazobactam (PIP-TAZ)
- Antibiotic-resistant phenotypes analyzed (CLSI, 2018) for *Escherichia coli* (EC) and *Klebsiella pneumoniae* (KPN) included non-carbapenem-resistant extended-spectrum beta-lactamase (ESBL, non-CR) and multidrug-resistant (MDR)
  - MDR was defined as resistant to at least 3 of the following classes (extended-spectrum cephalosporins, carbapenems, antipseudomonal penicillins + β-lactamase inhibitors, fluoroquinolones, aminoglycosides, gylcylcyclines, and polymyxins)
- Antibiotic-resistant phenotypes analyzed (CLSI, 2018) for *Pseudomonas aeruginosa* (PSA) included CAZ-nonsusceptible (CAZ-NS), FEP-NS, MEM-NS, PIP-TAZ-NS, and NS to all 4 β-lactam comparators tested: CAZ, FEP, MEM, and PIP-TAZ (BL-NS)
- CLSI (2018) C-T breakpoints for *Enterobacteriaceae* (ENT) are ≤2 mg/L susceptible (S), 4 mg/L intermediate (I), and ≥8 mg/L resistant (R); *P. aeruginosa* C-T breakpoints are ≤4 mg/L for S, 8 mg/L for I, and ≥16 mg/L for R
- EUCAST (2018) COL clinical breakpoints (≤2 mg/L for S) were used for ENT

Figure 1 Prevalence of species among gram-negative pathogens from bloodstream infections

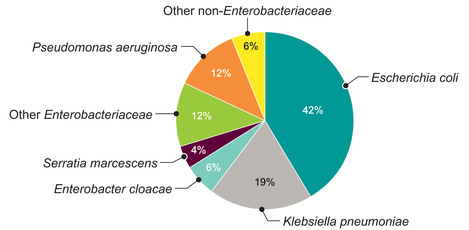


Table 1 Ceftolozane-tazobactam MIC distributions for the most common *Enterobacteriaceae* species

Organism	Number 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	>32
Escherichia coli	3 (0.2)	75 (5.5)	789 (61.0)	390 (88.4)	108 (96.0)	22 (97.5)	9 (98.2)	8 (98.7)	8 (99.3)	6 (99.7)	0 (99.7)	4 (100.0)
Klebsiella pneumoniae	2 (0.3)	13 (2.4)	213 (36.2)	238 (74.0)	97 (89.4)	35 (94.9)	7 (96.0)	5 (96.8)	7 (97.9)	1 (98.1)	2 (98.4)	10 (100.0)
Enterobacter cloacae		4 (1.9)	54 (27.1)	77 (63.1)	24 (74.3)	9 (78.5)	5 (80.8)	19 (89.7)	9 (93.9)	6 (96.7)	0 (96.7)	7 (100.0)
Serratia marcescens			1 (0.7)	18 (12.9)	100 (81.0)	25 (98.0)	1 (98.6)	0 (98.6)	0 (98.6)	0 (98.6)	1 (99.3)	1 (100.0)

[a] The intensity of shading is proportional to the number of tested isolates within each row that displays the indicated MIC value.

RESULTS

- A total of 2,825 ENT and 552 non-enterics were isolated
  - The 5 most common GN species were EC (1,422 isolates), KPN (630), PSA (344), *Enterobacter cloacae* (ECL; 214), and *Serratia marcescens* (SM; 147) (Figure 1)
- Prevalence of ENT and PSA in GN BSIs was 93.8%
  - 97.5% of these GNs had a C-T MIC ≤4 mg/L
- Prevalence of CRE among GN BSIs was low with only 23/2,825 (<1%) isolates observed in this study

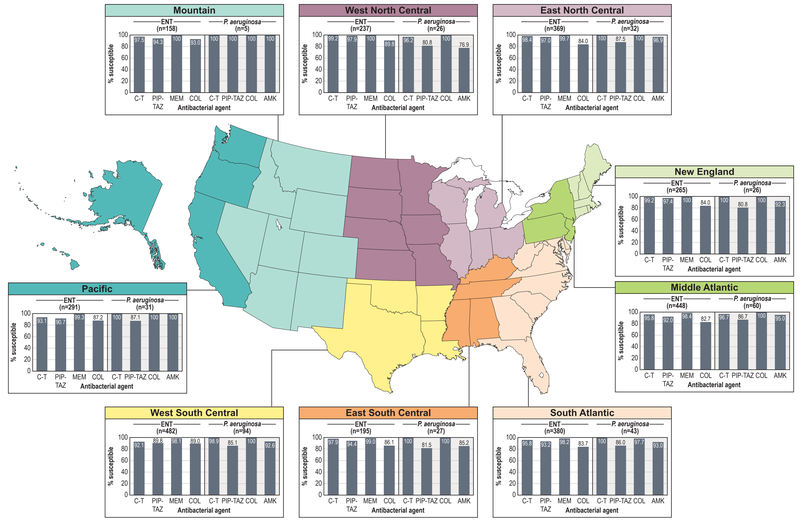
Table 2 MIC distributions of ceftolozane-tazobactam and 4 β-lactams tested against *P. aeruginosa*

Antimicrobial agent	Number and cumulative % of isolates inhibited at MIC (mg/L) of:[a]												MIC_{50}	MIC_{90}
	≤0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	> b		
Ceftolozane-tazobactam		1 (0.3)	63 (18.6)	202 (77.3)	49 (91.6)	17 (96.5)	8 (98.8)	1 (99.1)				3 (100.0)	0.5	1
Cefepime				7 (2.0)	101 (31.4)	115 (64.8)	32 (74.1)	46 (87.5)	29 (95.9)			14 (100.0)	2	16
Ceftazidime				5 (1.5)	95 (29.1)	136 (68.6)	49 (82.8)	16 (87.5)	10 (90.4)	16 (95.1)		17 (100.0)	2	16
Meropenem	16 (4.7)	43 (17.2)	82 (41.0)	71 (61.6)	43 (74.1)	25 (81.4)	24 (88.4)	14 (92.4)	16 (97.1)	8 (99.4)		2 (100.0)	0.5	8
Piperacillin-tazobactam				1 (0.3)		39 (11.6)	183 (64.8)	36 (75.3)	34 (85.2)	10 (88.1)	15 (92.4)	26 (100.0)	4	64

[a] The intensity of shading is proportional to the number of tested isolates within each row that displays the indicated MIC value.
[b] Greater than the highest concentration tested.

- EC and KPN were the most commonly isolated organisms (42% and 18.7% of GN BSI, respectively)
  - 98.2% of EC and 96% of KPN were susceptible to C-T (Table 1)
  - %S was <90% for CAZ, FEP, and LEV
  - MDR among EC and KPN GN BSIs was 8.2% and 7.8%, respectively
- Among PSA isolates, the MIC_{90} value for C-T (1 mg/L) was 8- to 64-fold lower than the other β-lactam comparators (FEP, 16 mg/L; CAZ, 16 mg/L; MEM, 8 mg/L; PIP-TAZ, 64 mg/L; Table 2).
- Susceptibilities of C-T and comparators for the main species and resistant phenotypes are shown in Table 3

Figure 2 Percent susceptibility of C-T and comparator agents against all 2015-2017 BSI GN isolates by US division



- Against ENT, C-T (96.1%S) was more active than other cephalosporins (FEP, 89.5%S; CAZ, 87.1%S; and PIP-TAZ 93.6%S), and only MEM (99.9%S) and AMK (99.6%S) were more active
  - For EC with an ESBL, non-CRE phenotype, C-T was more active (91.6%S) than CAZ (21.9%S), FEP (23.5%S), and PIP-TAZ (85.7%S)
  - Against KPN with an ESBL, non-CRE phenotype, C-T was less active (81.8%S) but still more active than CAZ (19.5%S), FEP (29.9%S), and PIP-TAZ (66.2%S)
- Against PSA, C-T and COL were the most active agents tested (98.8%S and 99.7%S, respectively)
  - C-T was more active than other beta-lactams tested
  - Over 90% of isolates NS to CAZ, FEP, MEM, or PIP-TAZ were S to C-T
  - C-T maintained activity (81.8%S) against 22 isolates resistant to all other beta-lactams tested in this study
- C-T showed some variation in susceptibility among ENT when stratified by US census division, ranging from 92.1%S in the West South Central division to 99.2%S in the New England and West North Central divisions (Figure 2)

Table 3 Susceptibilities and $MIC_{50/90}$ of ceftolozane-tazobactam and comparators tested against main organism groups in this study

Organism/ organism group	n	% susceptible[a] ($MIC_{50/90}$ in mg/L)						
		C-T	FEP	CAZ	MEM	PIP-TAZ	LEV	AMK	COL[b]
Enterobacteriaceae [c]	2,825	96.1 (0.25/0.5)	89.5 (≤0.12/4)	87.1 (0.25/16)	99.0 (0.03/0.06)	93.6 (2/8)	79.2 (0.06/>4)	99.6 (2/4)	86.1 (0.12/>8)
E. coli	1,422	98.2 (0.12/0.5)	86.0 (≤0.12/>16)	85.9 (0.25/16)	99.6 (≤0.015/0.03)	95.5 (2/8)	66.7 (0.06/>4)	99.8 (2/4)	99.8 (0.12/0.25)
MDR	117	80.3 (0.5/8)	10.3 (>16/>16)	12.8 (32/>32)	95.7 (0.03/0.06)	62.4 (8/>64)	1.7 (>4/>4)	97.4 (4/16)	99.1 (0.12/0.25)
ESBL, non-CRE	251	91.6 (0.5/2)	23.5 (>16/>16)	21.9 (16/>32)	100.0 (≤0.015/0.06)	85.7 (4/64)	20.3 (>4/>4)	99.2 (4/8)	99.2 (0.12/0.25)
K. pneumoniae	630	96.0 (0.25/1)	89.8 (≤0.12/4)	88.4 (0.12/16)	97.8 (0.03/0.03)	93.0 (2/16)	91.6 (0.06/1)	98.9 (1/2)	98.9 (0.12/0.25)
MDR	49	57.1 (1/>32)	10.2 (>16/>16)	6.1 (32/>32)	71.4 (0.03/>32)	44.9 (32/>64)	32.7 (>4/>4)	87.8 (2/32)	89.4 (0.12/4)
ESBL, non-CRE	77	81.8 (1/8)	29.9 (16/>16)	19.5 (32/>32)	96.1 (0.03/0.12)	66.2 (16/>64)	58.4 (1/>4)	96.1 (2/8)	94.7 (0.12/0.25)
Enterobacter cloacae	214	80.8 (0.25/8)	90.7 (≤0.12/2)	72.9 (0.25/>32)	98.6 (0.03/0.12)	79.9 (2/64)	95.8 (≤0.03/0.5)	99.5 (1/2)	75.1 (0.12/>8)
Serratia marcescens	147	98.6 (0.5/1)	98.6 (≤0.12/0.25)	98.6 (0.25/0.5)	98.6 (0.06/0.06)	95.2 (2/8)	98.0 (0.12/0.5)	100.0 (2/4)	0.7 (>8/>8)
P. aeruginosa	344	98.8 (0.5/1)	87.5 (2/16)	87.5 (2/16)	81.4 (0.5/8)	85.2 (4/64)	77.9 (0.5/>4)	97.4 (4/8)	99.7 (1/1)
CAZ-NS	43	90.7 (2/4)	27.9 (16/>16)	— (32/>32)	32.6 (8/32)	11.6 (>64/>64)	41.9 (>4/>4)	88.4 (8/>32)	100.0 (1/1)
FEP-NS	43	90.7 (2/4)	— (16/>16)	27.9 (32/>32)	30.2 (8/32)	16.3 (>64/>64)	25.6 (>4/>4)	88.4 (8/>32)	100.0 (1/1)
MEM-NS	64	93.8 (1/4)	53.1 (8/>16)	54.7 (8/>32)	— (8/32)	46.9 (32/>64)	31.2 (>4/>4)	89.1 (8/32)	100.0 (1/1)
PIP-TAZ-NS	51	92.2 (1/4)	29.4 (16/>16)	25.5 (32/>32)	33.3 (8/32)	0.0 (>64/>64)	35.3 (>4/>4)	90.2 (8/16)	100.0 (1/1)
BL-NS [d]	22	81.8 (2/>32)	— (16/>16)	— (32/>32)	— (16/32)	— (>64/>64)	13.6 (>4/>4)	90.9 (8/16)	100.0 (1/1)

[a] CLSI (2018).
[b] EUCAST (2018).
[c] Includes *Citrobacter amalonaticus* (2), *C. amalonaticus/farmeri* (2), *C. braakii* (1), *C. farmeri* (1), *C. freundii* (8), *C. freundii* species complex (10), *C. koseri* (10), *C. youngae* (3), *Cronobacter sakazakii* (2), *Enterobacter aerogenes* (43), *E. asburiae* (1), *E. cloacae* (118), *E. cloacae* species complex (96), *Escherichia coli* (1,422), *E. hermannii* (2), *Ewingella americana* (1), gram-negative rods in the family Enterobacteriaceae (1), *Hafnia alvei* (2), *Klebsiella oxytoca* (109), *K. pneumoniae* (630), *K. varicola* (4), *Kluyvera ascorbata* (1), *Kosakonia cowanii* (1), *Morganella morganii* (30), *Pantoea agglomerans* (9), *P. eucrina* (1), *Pluralibacter gergoviae* (4), *Proteus mirabilis* (133), *P. penneri* (2), *P. vulgaris* group (2), *Providencia stuartii* (7), *Raoultella ornithinolytica* (1), *R. planticola* (2), *Serratia liquefaciens* (5), *S. marcescens* (147), unspeciated *Citrobacter* (2), unspeciated *Pantoea* (5), unspeciated *Raoultella* (5); some species are inherently resistant to COL.
[d] Nonsusceptible to all 4 β-lactam comparators tested: ceftazidime (CAZ), cefepime (FEP), meropenem (MEM), and piperacillin-tazobactam (PIP-TAZ).

CONCLUSIONS

- C-T demonstrated activity against the most prevalent contemporary GN isolates from BSIs in the United States
- C-T demonstrated activity against BSI ENT isolates (96.1%S), EC (98.2%S), KPN (96.0%S), and SM (98.6%S)
  - For ENT, MEM and COL were the most active drugs
  - Against ESBL non-CRE EC, C-T maintained activity (>90.0%S)
- For PSA, C-T demonstrated activity (98.8%S); C-T and COL (99.7%S) were the most potent antibiotics tested
- Against PSA, C-T maintained activity against isolates NS to various beta-lactams, including isolates NS to all other beta-lactams tested in the study
- C-T (≥96%S) was the only beta-lactam that had ≥90%S against EC, KPN, and PSA species
- The results of this study suggest that C-T may be a treatment option for serious GN BSIs

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