Antimicrobial Activity of Ceftolozane-Tazobactam Tested against Contemporary (2015–2017) Gram-Negative Isolates from Patients with Pneumonia in US Medical Centers

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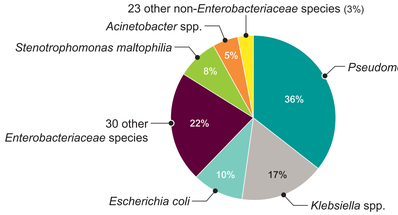
INTRODUCTION

- 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
- A phase 3 clinical trial to assess the safety and efficacy of ceftolozane-tazobactam for the treatment of hospital-acquired bacterial pneumonia (HABP), including ventilator-acquired bacterial pneumonia (VABP), has recently been completed (ClinicalTrials.gov registration no. NCT02070757)
- 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 pneumonia (PIHP) from 2015-2017 within the United States

MATERIALS AND METHODS

- A total of 4,337 prevalence-based PIHP GN isolates were collected during 2015 to 2017 from 30 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 β-lactamase (ESBL, non-CRE) and multidrug-resistant (MDR)
  - MDR was defined as nonsusceptible to at least 3 of the following classes (extended-spectrum cephalosporins, carbapenems, antipseudomonal penicillins + β-lactamase inhibitors, fluoroquinolones, aminoglycosides, glycylcyclines, and polymyxins)
- Antibiotic-resistant phenotypes analyzed (CLSI, 2018) for *Pseudomonas aeruginosa* (PSA) included nonsusceptible to all β-lactam comparators tested (BL-NS) and nonsusceptible to any individual β-lactam comparator tested (CAZ-NS, FEP-NS, MEM-NS, and PIP-TAZ-NS)

Figure 1 Prevalence of species among gram-negative isolates from pneumonia in hospitalized patients



- 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); PSA 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

RESULTS

- A total of 4,337 GN organisms were isolated, including 1,528 PSA and 2,102 ENT isolates: KPN, 562; and EC, 434 (Figure 1)
- Prevalence of ENT and PSA in GN PIHP infections was 83.7%
  - 94.8% of these GNs had a C-T MIC ≤4mg/L
- Prevalence of CRE among GN PIHP infections was low with only 83/2,102 (3.9%) isolates observed in this study
- KPN and EC were the most commonly isolated ENT organisms (13.0% and 10.0% of GN PIHP infections, respectively)
  - 96.5% of EC and 88.6% of KPN were susceptible to C-T (Table 1)
  - %S was <86% for CAZ, FEP, and LEV
  - MDR among EC and KPN GN BSIs was 13.8% and 17.3%, respectively
- Among PSA isolates, the MIC_{90} value for C-T (2 mg/L) was 8- to >32-fold lower than the other β-lactam comparators (FEP, 16 mg/L; CAZ, 32 mg/L; MEM, 16 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

Table 1 Ceftolozane-tazobactam MIC distributions for the most common gram-negative species causing PIHP

Organism (no. of isolates)	Number and cumulative % of isolates inhibited at MIC (mg/L) of:[a]												MIC_{50}	MIC_{90}
	≤0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	>32		
All GN PIHP isolates (4,337)	56 (1.3)	48 (2.4)	606 (16.4)	871 (36.5)	1263 (65.6)	506 (77.2)	198 (81.8)	161 (85.5)	111 (88.1)	103 (90.5)	84 (92.4)	330 (100.0)	0.5	16
Pseudomonas aeruginosa (1,528)	1 (0.1)	5 (0.4)	18 (1.6)	214 (15.6)	779 (66.6)	325 (87.8)	96 (94.1)	52 (97.5)	13 (98.4)	7 (98.8)	2 (99.0)	16 (100.0)	0.5	2
Klebsiella pneumoniae (562)	0 (0.0)	5 (0.9)	158 (29.0)	189 (62.6)	80 (76.9)	52 (86.1)	14 (88.6)	9 (90.2)	7 (91.5)	11 (93.4)	4 (94.1)	33 (100.0)	0.25	4
Escherichia coli (434)	0 (0.0)	10 (2.3)	201 (48.6)	132 (79.0)	56 (91.9)	18 (96.1)	2 (96.5)	6 (97.9)	3 (98.6)	2 (99.1)	1 (99.3)	3 (100.0)	0.25	0.5

[a] The intensity of shading is proportional to the number of tested isolates within each row that displays the indicated MIC value.
Abbreviation: PIHP, pneumonia in hospitalized patient.

Table 2 MIC distributions of ceftolozane-tazobactam and 4 β-lactams 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	6 (0.4)	18 (1.6)	214 (15.6)	779 (66.6)	325 (87.8)	96 (94.1)	52 (97.5)	13 (98.4)	7 (98.8)	2 (99.0)		16 (100.0)	0.5	2
Cefepime				65 (4.3)	240 (20)	432 (48.3)	256 (65)	283 (83.6)	169 (94.6)			82 (100.0)	4	16
Ceftazidime			14 (0.9)	51 (4.3)	339 (26.4)	535 (61.5)	211 (75.3)	112 (82.6)	76 (87.6)	81 (92.9)		109 (100.0)	2	32
Meropenem	159 (10.4)	136 (19.3)	309 (39.5)	255 (56.2)	191 (68.7)	112 (76.0)	99 (82.5)	105 (89.4)	92 (95.4)	54 (99.0)		16 (100.0)	0.5	16
Piperacillin-tazobactam				99 (6.5)	49 (9.7)	99 (16.2)	581 (54.2)	207 (67.7)	152 (77.7)	95 (83.9)	78 (89.0)	168 (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.

- Against ENT, C-T (90.3%S) was more active than other cephalosporins (FEP 84.9%S; CAZ 80.0%S) and PIP-TAZ (85.8%S), only MEM (95.9%S) and AMK (98.5%S) were more active
  - For EC with an ESBL, non-CRE phenotype, C-T was more active (91.0%S) than CAZ (26.1%S), FEP (18.7%S), and PIP-TAZ (85.0%S)
  - Against KPN with an ESBL, non-CRE phenotype, C-T was slightly less active (79.8%S) but still more active than CAZ (20.2%S), FEP (32.7%S), and PIP-TAZ (60.6%S)
- Along with COL, C-T was one of the most active antimicrobial agents against PSA PIHP isolates across most US census divisions (Figure 2)
  - C-T was more active than other β-lactams tested
  - Over 85% of isolates nonsusceptible to CAZ, FEP, MEM, or PIP-TAZ were susceptible to C-T
  - C-T maintained activity (73.3%S) against 116 isolates resistant to all other β-lactams tested in this study
- C-T showed some variation in susceptibility for EC and KPN when stratified by US census division, ranging from 78.3%S in the Middle Atlantic division to 100.0%S in the East South Central and Mountain divisions (Figure 2)

CONCLUSIONS

- C-T demonstrated activity against the most prevalent contemporary GN isolates from PIHP in the United States
- C-T demonstrated activity against PIHP ENT isolates (90.3%S); EC (96.5%S) and KPN (88.6%S)
  - Against ESBL non-CRE EC, C-T maintained activity
- C-T and COL were the only agents tested that had >95%S for EC and PSA pathogens in PIHP
- Against PSA, C-T and COL were the most active agents tested (97.5%S and 99.9%S, respectively)
- 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 was the only β-lactam that had >88%S against all 3 species: EC, KPN, and PSA
- The results of this study suggest that C-T may be a treatment option for serious GN infections causing PIHP

Figure 2 Percent susceptibility of C-T and comparator agents against the 3 most prevalent gram-negative species, *P. aeruginosa*, *K. pneumoniae*, and *E. coli*, from pneumonia in hospitalized patient isolates by US census division

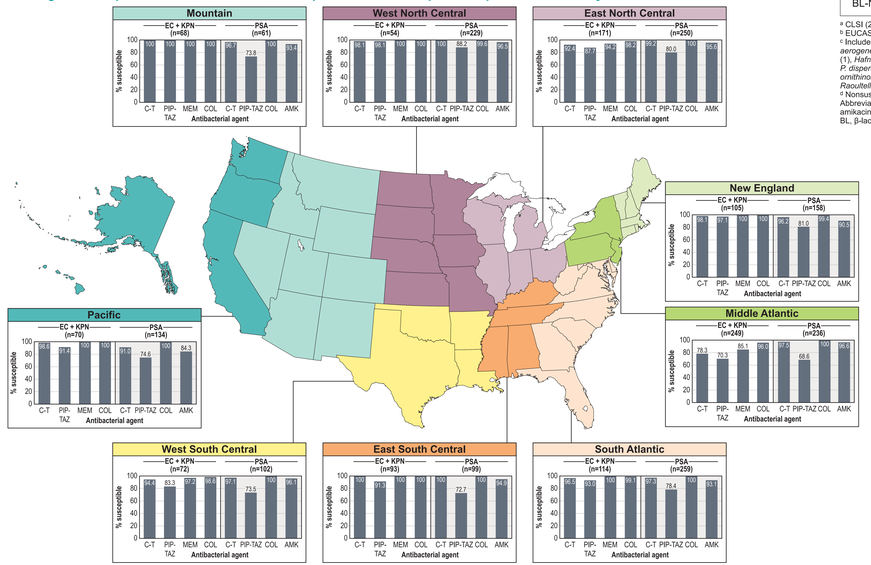


Table 3 Susceptibilities and $MIC_{50/90}$ of ceftolozane-tazobactam and comparators tested against main organism groups in this study

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]	2,102	90.3 (0.25/2)	84.9 (≤0.12/16)	80.0 (0.25/>32)	95.9 (0.03/0.06)	85.8 (2/64)	82.1 (0.06/>4)	98.5 (2/4)	77.6 (0.12/>8)
E. coli	434	96.5 (0.25/0.5)	74.2 (≤0.12/>16)	76.5 (0.25/>32)	99.3 (≤0.015/0.03)	90.5 (2/16)	55.4 (0.5/>4)	99.1 (2/8)	99.5 (0.12/0.25)
MDR	60	76.7 (0.5/8)	10.0 (>16/>16)	11.7 (32/>32)	95.0 (0.03/0.12)	61.0 (16/>64)	3.3 (>4/>4)	95.0 (4/16)	98.3 (0.12/0.25)
ESBL, non-CRE	134	91.0 (0.5/2)	18.7 (>16/>16)	26.1 (32/>32)	100.0 (0.03/0.03)	85.0 (8/64)	16.4 (>4/>4)	97.8 (4/16)	99.3 (0.12/0.25)
K. pneumoniae	562	88.6 (0.25/4)	80.1 (≤0.12/>16)	77.6 (0.25/>32)	91.8 (0.03/0.06)	83.6 (4/>64)	85.6 (0.06/>4)	96.4 (1/4)	97.7 (0.12/0.25)
MDR	97	38.1 (8/>32)	6.2 (>16/>16)	4.1 (>32/>32)	52.6 (0.12/32)	26.8 (>64/>64)	26.8 (>4/>4)	79.4 (4/32)	89.7 (0.12/4)
ESBL, non-CRE	104	79.8 (1/8)	32.7 (16/>16)	20.2 (32/>32)	95.2 (0.03/0.06)	60.6 (16/>64)	62.5 (1/>4)	96.2 (1/8)	97.1 (0.12/0.25)
P. aeruginosa	1528	97.5 (0.5/2)	83.6 (4/16)	82.6 (2/32)	76.0 (0.5/16)	77.7 (4/>64)	71.7 (1/>4)	93.8 (4/16)	99.9 (≤0.5/1)
CAZ-NS	266	85.7 (2/8)	30.8 (16/>16)	— (32/>32)	39.1 (8/32)	6.4 (>64/>64)	42.1 (4/>4)	81.2 (8/>32)	99.6 (≤0.5/1)
FEP-NS	251	86.1 (2/8)	— (16/>16)	26.7 (32/>32)	35.1 (8/32)	19.9 (>64/>64)	33.1 (>4/>4)	79.3 (8/>32)	99.6 (≤0.5/1)
MEM-NS	366	90.7 (1/4)	55.5 (8/>16)	55.7 (8/>32)	— (8/32)	44.3 (32/>64)	30.6 (>4/>4)	85.8 (8/32)	99.7 (≤0.5/1)
PIP-TAZ-NS	341	89.1 (1/8)	40.9 (16/>16)	27 (32/>32)	40.2 (8/32)	— (64/>64)	42.2 (4/>4)	85.9 (4/32)	99.4 (≤0.5/1)
BL-NS [d]	116	73.3 (4/>32)	— (16/>16)	— (>32/>32)	— (16/32)	— (>64/>64)	20.7 (>4/>4)	69.8 (8/>32)	99.1 (≤0.5/1)

[a] CLSI (2018).
[b] EUCAST (2018).
[c] Includes *Citrobacter amalonaticus/farmeri* (1), *C. freundii* (11), *C. freundii* species complex (21), *C. koseri* (34), *Cronobacter sakazakii* (1), *Enterobacter aerogenes* (152), *E. asburiae* (5), *E. cloacae* (141), *E. cloacae* species complex (138), *E. kobei* (1), *E. taylorae* (1), *Escherichia coli* (434), *Ewingella americana* (1), *Hafnia alvei* (6), *Klebsiella oxytoca* (156), *K. pneumoniae* (562), *K. variicola* (4), *Kosakonia cowanii* (1), *Morganella morganii* (14), *Pantoea agglomerans* (3), *P. dispersa* (1), *Pluralibacter gergoviae* (1), *Proteus mirabilis* (96), *P. vulgaris* group (3), *Providencia rettgeri* (8), *P. stuartii* (15), *Rahnella aquatilis* (2), *Raoultella ornithinolytica* (6), *R. planticola* (1), *Serratia liquefaciens* (8), *S. marcescens* (267), unspecified *Cedecea* (1), unspecified *Pantoea* (3), unspecified *Raoultella* (3); some species are inherently resistant to COL.
[d] Nonsusceptible to all 4 β-lactam comparators tested: CAZ, FEP, MEM, and PIP-TAZ.
Abbreviations: C-T, ceftolozane-tazobactam; FEP, cefepime; CAZ, ceftazidime; MEM, meropenem; PIP-TAZ, piperacillin-tazobctam; LEV, levofloxacin; AMK, amikacin; COL, colistin; MDR, multidrug-resistant; ESBL, extended-spectrum β-lactamase; CRE, carbapenem-resistant *Enterobacteriaceae*; NS, nonsusceptible; BL, β-lactam.

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