Activity of Ceftolozane-Tazobactam and Comparators When Tested against Bacterial Surveillance Isolates Collected from Pediatric Patients in the US during 2012–2016 as Part of a Global Surveillance Program

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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 was approved by the US Food and Drug Administration in 2014 and by the European Medicine Agency in 2015 to treat complicated urinary tract infections, including acute pyelonephritis, and complicated intra-abdominal infections in adults
  - Pediatric treatment trials are planned for urinary tract infections and complicated intra-abdominal infections
- The Program to Assess Ceftolozane-Tazobactam Susceptibility (PACTS) monitors C-T resistance to gram-negative (GN) isolates worldwide

MATERIALS AND METHODS

- A total of 4,121 GN isolates were collected during 2012–2016 from pediatric patients (<18 years old) in 31 US hospitals
  - Isolates were tested for C-T susceptibility (S) by CLSI broth microdilution method in a central monitoring laboratory (JMI Laboratories)
  - Other antibiotics tested were amikacin (AMK), cefepime (FEP), ceftazidime (CAZ), colistin (COL), levofloxacin (LVX), meropenem (MER), and piperacillin-tazobactam (TZP)
- Antibiotic-resistant phenotypes identified using CLSI (2017) clinical breakpoints included: carbapenem-resistant *Enterobacteriaceae* (CRE), non-CRE extended-spectrum beta-lactamase screen positive (ESBL, non-CRE), ceftazidime-nonsusceptible (CAZ-NS), and meropenem-NS (MER-NS)
- CLSI (2017) C-T breakpoints for *Enterobacteriaceae* (ENT) are ≤2.0 mg/L susceptible (S), 4.0 mg/L intermediate (I), and ≥8.0 mg/L resistant (R); *P. aeruginosa* C-T breakpoints are ≤4.0 mg/L for S, 8.0 mg/L for I, and ≥16.0 mg/L for R
- EUCAST (2017) C-T breakpoints for ENT are ≤1.0 mg/L for S and >1.0 mg/L R; *Pseudomonas spp.* C-T breakpoints are ≤4.0 mg/L for S and >4mg/L for R
- EUCAST (2017) COL clinical breakpoints were used for ENT

RESULTS

- The most common infection type caused by gram-negative bacteria in hospitalized pediatric patients was pneumonia (n=1,488) followed by urinary tract infection (n=1,143) and bloodstream infection (n=767) (Table 1)
- A total of 2,969 ENT and 1,152 non-enterics were isolated
  - The 5 most common species were *Escherichia coli* (EC: 1,311), *Pseudomonas aeruginosa* (PSA: 823 isolates), *Klebsiella pneumoniae* (KPN: 429), *Enterobacter cloacae* complex (ECC: 360), and *Serratia marcescens* (SM: 264) (Figure 1)
- MIC distributions of C-T for the most common enteric species are shown in Figure 2
- MIC distributions of C-T, CAZ, MER, and TZP when tested against PSA are shown in Figure 3

Figure 1. Five most common gram-negative pathogens from pediatric infections

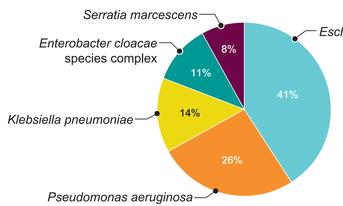

Table 1. Most common infections caused by gram-negative pathogens in hospitalized pediatric patients

Infection type	Enteric	Non-enteric	Total GN
Pneumonia in hospitalized patients	736	752	1,488
Urinary tract infection	1,089	54	1,143
Bloodstream infection	628	139	767
Skin and skin structure infection	271	140	411
Intra-abdominal infection	189	56	245
Other	56	11	67

- Susceptibilities of C-T and comparators for the main species and resistant phenotypes are shown in Table 2
  - Against ENT, C-T (96.1%S) was more active than other cephalosporins (FEP 95.2%S; CAZ 91.0%S) and TZP (94.0%S), only MER (99.7%S) and AMK (99.8%S) were more active
    - For EC with the ESBL non-CRE phenotype, C-T had excellent activity (92.4%S) and was more active than CAZ (32.8%S), FEP (35.3%S), and TZP (84.0%S)
    - Against KPN with an ESBL non-CRE phenotype, C-T was slightly less active (86.4%S)
      - Only 7 isolates were CRE
  - Against PSA, C-T was the most active agent tested (99.5%S) and was similar to COL (99.3%S)
    - C-T was more active than other beta-lactams tested
    - Over 90% of isolates nonsusceptible to CAZ, FEP, MER, or TZP were susceptible to C-T
    - C-T maintained very good activity (83%S) against 12 isolates resistant to all other beta-lactams tested in this study

Figure 2. Ceftolozane-tazobactam MIC distributions for most common enteric species

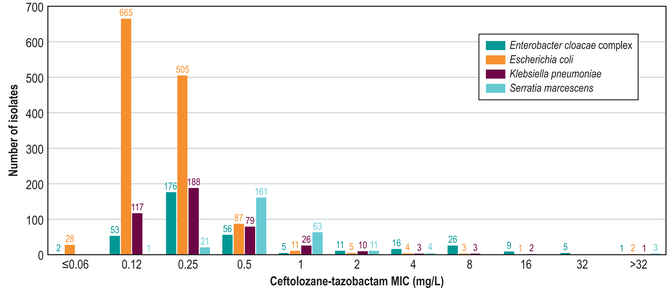

Figure 3. MIC distributions of 4 β-lactams for *P. aeruginosa*

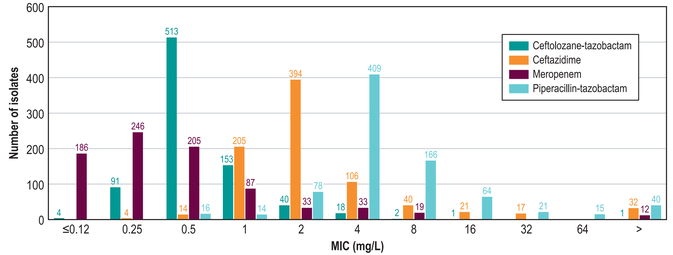

Table 2. Susceptibilities and MIC $_{50/90}$ of ceftolozane-tazobactam and comparators tested against main organism groups in this study

Organism / organism group		% susceptible[a] (MIC$_{50/90}$ mg/L)							
	N	C-T	FEP	CAZ	MER	TZP	LVX	AMK	COL[b]
Enterobacteriaceae[c]	2,969	96.1 (0.25/0.5)	95.2 (≤0.5/≤0.5)	91.0 (0.12/2)	99.7 (≤0.06/≤0.06)	94.0 (2/8)	92.9 (≤0.12/0.5)	99.8 (2/4)	81.9 (≤0.5/>8)[d]
E. coli	1,311	99.2 (0.12/0.25)	94.0 (≤0.5/≤0.5)	93.8 (0.12/0.5)	99.8 (≤0.06/≤0.06)	96.9 (2/4)	86.2 (≤0.12/>4)	99.7 (2/4)	99.8 (≤0.5/≤0.5)
ESBL, non-CRE	119	92.4 (0.5/2)	35.3 (16/>16)	32.8 (16/>32)	99.2 (≤0.06/≤0.06)	84.0 (4/64)	37.0 (>4/>4)	97.5 (2/8)	100.0 (≤0.5/≤0.5)
K. pneumoniae	429	97.9 (0.25/1)	92.3 (≤0.5/≤0.5)	90.9 (0.12/2)	98.8 (≤0.06/≤0.06)	95.3 (4/16)	98.1 (≤0.12/0.5)	99.8 (1/2)	98.8 (≤0.5/≤0.5)
ESBL, non-CRE	44	86.4 (0.5/4)	36.4 (8/>16)	20.5 (16/>32)	97.7 (≤0.06/≤0.06)	70.5 (8/>64)	88.6 (0.25/4)	100.0 (2/8)	95.5 (≤0.5/≤0.5)
Enterobacter cloacae complex	360	84.2 (0.25/8)	95.3 (≤0.5/2)	77.5 (0.25/>32)	99.7 (≤0.06/≤0.06)	82.7 (2/64)	100.0 (≤0.12/≤0.12)	100.0 (1/2)	77.1 (≤0.5/8)
Serratia marcescens	264	97.3 (0.5/1)	98.1 (≤0.5/≤0.5)	97.0 (0.25/0.5)	100.0 (≤0.06/≤0.06)	97.0 (2/4)	97.7 (≤0.12/0.5)	99.6 (2/4)	N/A (>8/>8)
P. aeruginosa	823	99.5 (0.5/1)	94.2 (2/8)	92.7 (2/8)	92.2 (0.25/2)	90.8 (4/16)	90.4 (0.5/2)	97.1 (4/8)	99.3 (1/2)
CAZ-NS	60	93.3 (2/4)	36.7 (16/>16)	0.0 (32/>32)	63.3 (1/>8)	15.0 (>64/>64)	71.7 (2/>4)	86.7 (4/32)	96.7 (1/2)
FEP-NS	49	91.7 (2/8)	0.0 (16/>16)	20.4 (32/>32)	61.2 (1/>8)	14.3 (>64/>64)	59.2 (2/>4)	85.7 (4>32)	95.9 (1/2)
MER-NS	64	95.3 (1/4)	71.9 (8/16)	65.6 (4>32)	0.0 (4/>8)	64.1 (16>64)	56.2 (2/>4)	89.1 (4/32)	96.9 (1/2)
TZP-NS	76	96.1 (2/4)	46.1 (16/>16)	32.9 (16/>32)	69.7 (1/8)	0.0 (>64/>64)	69.7 (2/>4)	89.5 (4/32)	98.7 (1/2)
BL-NS[e]	12	83.3 (4/8)	0.0 (16/>16)	0.0 (>32/>32)	0.0 (8/32)	0.0 (>64/>64)	33.3 (4/>4)	66.7 (8/>32)	100.0 (1/2)

[a] CLSI (2017)
[b] EUCAST (2017)
[c] Includes species that are inherently resistant to COL
[d] Organisms include: *Citrobacter amalonaticus* (3), *C. braakii* (10), *C. farmeri* (2), *C. freundii* (54), *C. freundii* species complex (12), *C. koseri* (24), *C. youngae* (4), *Enterobacter aerogenes* (88), *E. asburiae* (14), *E. cloacae* (259), *E. cloacae* species complex (101), *E. intermedius* (1), *Escherichia coli* (1,311), *E. hermannii* (1), *E. vulneris* (1), gram-negative rods in the family Enterobacteriaceae (1), *Hafnia alvei* (1), *Klebsiella oxytoca* (178), *K. pneumoniae*(429), *K. varicola* (2), *Kluyvera ascorbata* (2), *Kosakonia cowanii* (2), *Leclercia adecarboxylata* (1), *Morganella morganii* (50), *Pantoea agglomerans* (5), *P. dispersa* (1), *Pluralibacter gergoviae* (3), *Proteus mirabilis* (98), *P. vulgaris* (11), *Providencia rettgeri* (13), *P. stuartii* (3), *Raoultella ornithinolytica* (3), *R. planticola* (1), *Serratia liquefaciens* (5), *S. marcescens* (264), *Shigella sonnei* (1), unspeciated *Citrobacter* (1), unspeciated *Enterobacter* (1), unspeciated *Pantoea* (5), unspeciated *Raoultella* (2), unspeciated *Serratia* (1)
[e] Nonsusceptible to 4 beta-lactam comparators tested: CAZ, FEP, MER, and TZP

CONCLUSIONS

- C-T demonstrated excellent activity against pediatric ENT isolates (96.1%S), EC (99.2%S), and KPN (97.9%S)
  - For ENT, MER and COL were the most active drugs
  - Against ESBL non-CRE EC, C-T had excellent activity
- For PSA, C-T demonstrated potent activity (99.5%S) and was the most potent antibiotic tested with activity similar to COL (99.3%S)
- Against PSA, C-T maintained activity against isolates nonsusceptible to various beta-lactams, including isolates nonsusceptible to all other beta-lactams tested in the study
- The results of this study suggest that C-T may be a valuable treatment for serious infections in pediatric patients
- Pediatric treatment trials for complicated intra-abdominal infection and complicated urinary tract infection, including pyelonephritis are planned

Acknowledgements

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