Poster # 246

Frequency of Occurrence and Antimicrobial Susceptibility of Gram-negative Organisms Isolated From Healthcare-Associated (HCA) Urinary Tract Infections (UTI) in the United States: Results from the Program to Assess Ceftolozane/Tazobactam Susceptibility (PACTS)

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ABSTRACT

BACKGROUND: HCA-UTI is the most frequent HCA infection and is responsible for significant patient morbidity and mortality. Ceftolozane/tazobactam (TOL/TAZ) is under clinical development for the treatment of nosocomial pneumonia, complicated intra-abdominal infections, and complicated UTIs. We evaluated the activity of TOL/TAZ and comparators tested against Gram-negative (GN) organisms causing HCA-UTI in United States (USA) hospitals.

METHODS: In 2013, a total of 1451 unique patient organisms were consecutively collected from USA medical centers from patients with HCA-UTI. Susceptibility (S) testing was performed for TOL/TAZ (TAZ at fixed 4 µg/mL) and comparators by reference CLSI broth microdilution methods.

RESULTS: The most frequently isolated pathogens were *Escherichia coli* (EC; 52.2%), *Klebsiella* spp. (KSP; 14.1%), indole-positive *Proteus* spp. (IPP; 7.2%), *Enterobacter* spp. (ESP; 6.6%), and *Pseudomonas aeruginosa* (PSA; 6.2%). EC and KSP ESBL-phenotype rates were 12.1 and 17.6%, respectively. TOL/TAZ inhibited 97.4% of 1355 Enterobacteriaceae ($MIC_{50/90}$, 0.25/1 µg/mL) and 72.9% of 107 (7.9%) multidrug-resistant (MDR) strains, 99.9% of all EC and 99.6% of ESBL-phenotype EC, and 90.2% of all KSP and 44.4% of ESBL-phenotype (75.0% of meropenem [MEM]-S-ESBL) KSP at ≤8 µg/mL. Susceptibility (S) rates for levofloxacin (LVX) and gentamicin (GEN) were 73.4% and 89.6% for EC, 86.2% and 87.7% for KSP, 75.0% and 85.6% for IPP, and 92.7% and 94.8% for ESP, respectively. TOL/TAZ ($MIC_{50/90}$, 0.5/8 µg/mL; 92.7% at ≤8 µg/mL) demonstrated greater activity than ceftazidime (CAZ; $MIC_{50/90}$, 0.5/>32 µg/mL; 76.0% S) and piperacillin/TAZ (PIP/TAZ) ($MIC_{50/90}$, 4/>64 µg/mL; 78.9% S) when tested against ESP. TOL/TAZ ($MIC_{50/90}$, 0.25/1 µg/mL; 99.0% at ≤8 µg/mL) demonstrated greater potency than CAZ ($MIC_{50/90}$, 0.12/8 µg/mL; 88.3% S) and PIP/TAZ ($MIC_{50/90}$, 4/>64 µg/mL; 99.0% S) when tested against IPP. TOL/TAZ inhibited 98.9% of PSA ($MIC_{50/90}$, 0.5/1 µg/mL) and 10/11 (90.9%) of MDR strains at ≤8 µg/mL. PSA had S rates to MEM (83.0%), CAZ (90.0%), PIP/TAZ (83.3%), LVX (75.6%), and GEN (90.0%).

Organism (No. Tested)	No. of isolates (Cumulative %) Inhibited at TOL/TAZ MIC (µg/mL) ≤0.25	0.5	1	2	4	8	16	≥32
Enterobacteriaceae (1355)	962 (71.0)	248 (89.3)	63 (94.0)	16 (95.1)	17 (96.4)	14 (97.4)	10 (98.2)	25 (100.0)
MDR (107)	12 (11.2)	31 (40.2)	16 (55.1)	6 (60.8)	6 (66.4)	7 (72.9)	7 (79.4)	22 (100.0)
E. coli (758)	642 (84.7)	82 (95.5)	23 (98.6)	4 (99.1)	3 (99.5)	1 (99.6)	1 (99.7)	2 (100.0)
ESBL-phenotype (92)	25 (27.2)	37 (67.4)	20 (89.1)	3 (92.4)	3 (95.7)	1 (96.7)	1 (97.8)	2 (100.0)
Klebsiella spp. (204)	135 (66.2)	36 (83.8)	8 (87.8)	2 (88.7)	1 (89.2)	2 (90.2)	3 (91.7)	17 (100.0)
ESBL-phenotype (36)	4 (11.1)	5 (25.0)	2 (30.6)	2 (36.1)	1 (38.9)	2 (44.4)	3 (52.8)	17 (100.0)
MEM-S-ESBL (20)	4 (20.0)	5 (45.0)	2 (55.0)	2 (65.0)	1 (70.0)	1 (75.0)	2 (85.0)	2 (100.0)
Indole (+) *Proteus* spp. (104)	57 (54.8)	33 (86.5)	7 (93.3)	4 (97.1)	1 (98.1)	1 (99.0)	0 (99.0)	1 (100.0)
Enterobacter spp. (96)	44 (45.8)	20 (66.7)	8 (75.0)	2 (77.1)	8 (85.4)	7 (92.7)	3 (95.8)	4 (100.0)
P. aeruginosa (90)	6 (6.7)	52 (64.4)	23 (90.0)	6 (96.7)	2 (98.9)	0 (98.9)	0 (98.9)	1 (100.0)
MDR (11)	0 (0.0)	1 (9.1)	5 (54.6)	2 (72.7)	2 (90.9)	0 (90.9)	0 (90.9)	1 (100.0)

CONCLUSIONS: TOL/TAZ demonstrated potent activity against contemporary (2013) GN bacilli, including many ESBL-phenotype and MDR strains, and may represent a valuable treatment option for HCA-UTI in the USA.

INTRODUCTION

- Urinary tract infections (UTIs) are among the most frequent healthcare-associated (HCA) infections. *Escherichia coli* is the most common UTI pathogen observed in both the community and healthcare settings. In recurrent UTI, and especially when structural abnormalities of the urinary tract are present, the relative frequency of *Klebsiella* spp., *Proteus* spp., *Pseudomonas* spp., and *Enterobacter* spp. increases. Antimicrobial-resistant isolates are common in these complicated UTIs (cUTIs) in which instrumentation and repeat courses of antimicrobial therapy are frequently used.
- Antimicrobial-resistant strains that produce extended-spectrum β-lactamases (ESBLs) are prevalent among Enterobacteriaceae, predominantly *E. coli* and *Klebsiella* spp., and have become endemic in many hospitals. *Pseudomonas aeruginosa* also represents a major cause of UTI, and often demonstrates decreased susceptibility to various antimicrobial agents.

INTRODUCTION (cont'd)

- Ceftolozane/tazobactam is a novel antibacterial with activity against *P. aeruginosa*, including multidrug-resistant (MDR) strains, and other common Gram-negative pathogens including most ESBL-producing Enterobacteriaceae.
- In the Phase 3 clinical trial ASPECT-cUTI (Assessment of the Safety Profile and Efficacy of Ceftolozane/Tazobactam in Complicated Urinary Tract Infections), ceftolozane/tazobactam met its primary endpoint of noninferior efficacy and was superior to high-dose, extended-duration levofloxacin in the primary and key secondary endpoints in patients with cUTI including pyelonephritis.
- In this study, we evaluated the activity of ceftolozane/tazobactam and comparator agents tested against Gram-negative organisms causing HCA-UTI in patients from United States (USA) hospitals during 2013.

MATERIALS AND METHODS

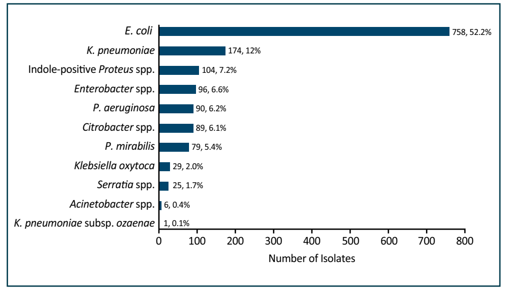
- The organism collection included only Gram-negative bacilli collected from hospitalized patients with a diagnosis of UTI. In 2013, a total of 1451 unique patient organisms were consecutively collected from 29 USA medical centers from patients with HCA-UTI. Species identification was performed at the participant medical centers and confirmed at the monitoring laboratory (JMI Laboratories, North Liberty, IA, USA) using the VITEK 2 System (bioMérieux, Hazelwood, MO, USA) or MALDI-TOF (Bruker Daltonics Inc., Billerica, MA, USA), when necessary. Only 1 strain per patient infection episode was included in this surveillance study.
- Isolates were tested for susceptibility to multiple antimicrobial agents at a reference laboratory (JMI Laboratories) by standardized broth microdilution methods as described by the Clinical and Laboratory Standards Institute (CLSI) M07-A9 document. Minimum inhibitory concentration (MIC) results were interpreted according to CLSI criteria in M100-S24, as well as European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoint tables. *E. coli* and *Klebsiella* spp. isolates with MIC of ≥2 µg/mL for ceftazidime or ceftriaxone or aztreonam were categorized as ESBL-phenotype.
- To better evaluate the activities of ceftolozane/tazobactam against *K. pneumoniae* and *Enterobacter*, strains were stratified by susceptibility pattern to ceftazidime and meropenem. MDR, extensively drug-resistant (XDR), and pandrug-resistant (PDR) bacteria were classified as such as per recently recommended guidelines by Magiorakos et al using antimicrobial class representative agents and CLSI susceptibility MIC breakpoints. Classifications were based on the following recommended parameters: MDR = non-susceptible to ≥3 antimicrobial classes; XDR = susceptible to ≤2 antimicrobial classes; PDR = non-susceptible to all antimicrobial classes.

RESULTS

- Overall, *E. coli* was the most frequent (52.2%) HCA-UTI pathogen isolated, followed by *Klebsiella pneumoniae* (12.0%), indole-positive *Proteus* spp. (7.2%), *Enterobacter* spp. (6.6%), *P. aeruginosa* (6.2%), *Citrobacter* spp. (6.1%), and *Proteus mirabilis* (5.4%; **Figure 1**).
- Ceftolozane/tazobactam demonstrated good activity (MIC required to inhibit the growth of 50%/90% of organisms [$MIC_{50/90}$], 0.25/1 µg/mL) against the 1355 Enterobacteriaceae, inhibited 96.4% and 97.4% of isolates at MIC values of 4 and 8 µg/mL, respectively, and retained activity against many of the 107 (7.9%) isolates that were MDR ($MIC_{50/90}$, 1/>32 µg/mL), but not against most of the XDR isolates (**Table 1**).

RESULTS (cont'd)

Figure 1. Prevalence of HCA-UTI Gram-negative Pathogens Isolated in USA and EU Hospitals During 2013 (n, % of Total)



- Ceftolozane/tazobactam was active ($MIC_{50/90}$, 0.25/0.5 µg/mL) against all *E. coli* and 92 (12.1%) isolates with an ESBL-phenotype ($MIC_{50/90}$, 0.5/2 µg/mL; **Table 1**). Meropenem was the most active ($MIC_{50/90}$, ≤0.06/≤0.06 µg/mL) agent overall against *E. coli* (**Table 2**). Against all 758 *E. coli* tested, CLSI criteria susceptibility ranged from 73.4% for levofloxacin to 99.7% for meropenem (**Table 2**).
- Ceftolozane/tazobactam was active ($MIC_{50/90}$, 0.25/8 µg/mL) against most strains of 204 *Klebsiella* spp. isolated (**Table 1**). Ceftolozane/tazobactam potency was high against 140 non-ESBL-phenotype *K. pneumoniae* ($MIC_{50/90}$, 0.25/0.5 µg/mL) compared with low activity ($MIC_{50/90}$, 16/>32 µg/mL) against ESBL-phenotype *K. pneumoniae*. However, ceftolozane/tazobactam demonstrated higher activity ($MIC_{50/90}$, 1/>32 µg/mL) against most meropenem-susceptible ESBL-phenotype *K. pneumoniae* (**Table 1**). Against all 204 *Klebsiella* spp. tested, CLSI criteria susceptibility ranged from 82.8% for ceftriaxone to 92.2% for meropenem (**Table 2**).
- Ceftolozane/tazobactam also demonstrated good activity against other prevalent Enterobacteriaceae: *Enterobacter* spp. ($MIC_{50/90}$, 0.5/8 µg/mL), indole-positive *Proteus* spp. ($MIC_{50/90}$, 0.25/1 µg/mL), *Citrobacter* spp. ($MIC_{50/90}$, 0.25/4 µg/mL), *P. mirabilis* ($MIC_{50/90}$, 0.5/0.5 µg/mL), and *Serratia* spp. ($MIC_{50/90}$, 0.5/1 µg/mL; **Table 1**).
- Overall, ceftolozane/tazobactam was the most active agent tested ($MIC_{50/90}$, 0.5/1 µg/mL; **Table 2**) against 90 *P. aeruginosa*, demonstrating at least 4-fold greater activity than ceftazidime ($MIC_{50/90}$, 2/8 µg/mL) and cefepime ($MIC_{50/90}$, 2/16 µg/mL), at least 8-fold greater activity than aztreonam ($MIC_{50/90}$, 4/>16 µg/mL) and piperacillin/tazobactam ($MIC_{50/90}$, 4/64 µg/mL), and up to 8-fold greater activity than meropenem ($MIC_{50/90}$, 0.5/8 µg/mL; **Table 2**). Susceptibility rates (CLSI criteria) for β-lactam agents tested ranged from 74.4% for aztreonam to 90.0% for ceftazidime (**Table 2**). All isolates were susceptible to colistin (100.0% susceptible) and most to amikacin (98.9% susceptible), with levofloxacin susceptibility being the lowest active non–β-lactam agent tested (75.6%; **Table 2**).
- Ceftolozane/tazobactam retained potency against most MDR ($MIC_{50/90}$, 1/4 µg/mL; 90.9% inhibited at ≤4 µg/mL; n=11) and XDR (87.5% inhibited at ≤4 µg/mL; n=8) strains of *P. aeruginosa* (**Table 1**).
- Ceftolozane/tazobactam had limited activity against the 6 isolates of *Acinetobacter* spp. tested (**Table 1**).

Table 1. Cumulative MIC Distributions of Ceftolozane/Tazobactam Tested Against HCA-UTI Gram-negative Pathogens Isolated in USA Hospitals During 2013

Organism	N	Number of Isolates (Cumulative %) Inhibited at Ceftolozane/Tazobactam MIC (µg/mL) ≤12	0.25	0.5	1	2	4	8	16	32	>32	MIC_{50}	MIC_{90}
Enterobacteriaceae (all)	1355	352 (26.9)	**598 (71.0)**	248 (89.3)	63 (94.0)	16 (95.1)	17 (96.4)	14 (97.4)	10 (98.2)	9 (98.8)	16 (100.0)	0.25	1
MDR	107	0 (0.0)	12 (11.2)	31 (40.2)	**16 (55.1)**	6 (60.8)	6 (66.4)	7 (72.9)	7 (79.4)	8 (86.9)	14 (100.0)	1	>32
XDR	18	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	2 (16.7)	0 (16.7)	1 (22.2)	2 (33.3)	**4 (55.6)**	8 (100.0)	32	>32
E. coli	758	273 (37.1)	**361 (84.7)**	82 (95.5)	23 (98.6)	4 (99.1)	3 (99.5)	1 (99.6)	1 (99.7)	1 (99.9)	1 (100.0)	0.25	0.5
non-ESBL-phenotype	666	269 (41.6)	**340 (92.6)**	45 (99.4)	3 (99.9)	1 (100.0)	-	-	-	-	-	0.25	0.25
ESBL-phenotype	92	4 (4.4)	21 (27.2)	**37 (67.4)**	20 (89.1)	3 (92.4)	3 (95.7)	1 (96.7)	1 (97.8)	1 (98.9)	1 (100.0)	0.5	2
Klebsiella spp.	204	53 (27.5)	**79 (66.2)**	36 (83.8)	8 (87.8)	2 (88.7)	1 (89.2)	2 (90.2)	3 (91.7)	7 (95.1)	10 (100.0)	0.25	8
K. pneumoniae	174	41 (24.7)	**69 (64.4)**	31 (82.2)	7 (86.2)	2 (87.4)	1 (87.9)	2 (89.1)	3 (90.8)	6 (94.3)	10 (100.0)	0.25	16
non-ESBL-phenotype	140	41 (30.7)	**65 (77.1)**	26 (95.7)	6 (100.0)	-	-	-	-	-	-	0.25	0.5
ESBL-phenotype	34	0 (0.0)	4 (11.8)	5 (26.5)	1 (29.4)	2 (35.3)	1 (38.2)	2 (44.1)	**3 (52.9)**	6 (70.6)	10 (100.0)	16	>32
ESBL (MEM-S)	19	0 (0.0)	4 (21.1)	5 (47.4)	**1 (52.6)**	2 (63.2)	1 (68.4)	1 (73.7)	2 (84.2)	1 (89.5)	2 (100.0)	1	>32
MEM-S	159	41 (27.0)	**69 (70.4)**	31 (89.9)	7 (94.3)	2 (95.6)	1 (96.2)	1 (96.9)	2 (98.1)	1 (98.7)	2 (100.0)	0.25	1
MEM-NS	15	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.7)	1 (13.3)	5 (46.7)	**8 (100.0)**	>32	>32
Enterobacter spp.	96	4 (4.2)	40 (45.8)	**20 (66.7)**	8 (75.0)	2 (77.1)	8 (85.4)	7 (92.7)	3 (95.8)	1 (96.9)	3 (100.0)	0.5	8
CAZ-S	73	4 (5.5)	**40 (60.3)**	20 (87.7)	6 (95.9)	1 (97.3)	1 (98.6)	1 (100)	-	-	-	0.25	1
CAZ-NS	23	0 (0.0)	0 (0.0)	0 (0.0)	2 (8.7)	1 (13.0)	7 (43.5)	**6 (69.6)**	3 (82.6)	1 (87.0)	3 (100.0)	8	>32
Citrobacter spp.	89	14 (15.7)	**48 (69.7)**	12 (83.2)	3 (86.5)	1 (87.6)	4 (92.1)	3 (95.5)	3 (98.9)	0 (98.9)	1 (100.0)	0.25	4
P. mirabilis	79	1 (1.3)	19 (25.3)	**53 (92.4)**	5 (98.7)	1 (100.0)	-	-	-	-	-	0.5	0.5
Indole-positive *Proteus* spp.	104	6 (6.7)	**50 (54.8)**	33 (86.5)	7 (93.3)	4 (97.1)	1 (98.1)	1 (99.0)	0 (99.0)	0 (99.0)	1 (100.0)	0.25	1
Serratia spp.	25	1 (4.0)	1 (8.0)	**12 (56.0)**	9 (92.0)	2 (100.0)	-	-	-	-	-	0.5	1
P. aeruginosa	90	0 (0.0)	6 (6.7)	**52 (64.4)**	23 (90.0)	6 (96.7)	2 (98.9)	0 (98.9)	0 (98.9)	0 (98.9)	1 (100.0)	0.5	1
MDR	11	0 (0.0)	0 (0.0)	1 (9.1)	**5 (54.6)**	2 (72.7)	2 (90.9)	0 (90.9)	0 (90.9)	0 (90.9)	1 (100.0)	1	4
XDR	8	0 (0.0)	0 (0.0)	0 (0.0)	**4 (50.0)**	2 (75.0)	1 (87.5)	0 (87.5)	0 (87.5)	0 (87.5)	1 (100.0)	1	-
Acinetobacter spp.	6	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (16.7)	1 (33.3)	**1 (50.0)**	1 (66.7)	2 (100.0)	16	-

Bolded values represent MIC_{50}; underlined values represent MIC_{90}. CAZ-NS = ceftazidime-non-susceptible; CAZ-S = ceftazidime-susceptible; MEM-NS = meropenem-non-susceptible; MEM-S = meropenem-susceptible.

Table 2. Antimicrobial Activity of Ceftolozane/Tazobactam and Various Comparator Agents Tested Against HCA-UTI Pathogens Collected in the USA During 2013

Organism Subset (No. Tested)/ Antimicrobial Agent	MIC (µg/mL) 50%	90%	Range	%S/%I/%R CLSI[a]	EUCAST[a]
E. coli (758)					
Ceftolozane/tazobactam	0.25	0.5	≤0.015 – >32	-[b]/-/-	-/-/-
Ceftriaxone	≤0.06	>8	≤0.06 – >8	88.8/0.1/11.1	88.0/0.1/11.1
Ceftazidime	0.12	2	≤0.015 – >32	91.6/1.5/6.9	89.3/2.3/8.4
Cefepime	≤0.5	4	≤0.5 – >16	90.0/1.5/8.5	89.2/1.3/9.5
Meropenem	≤0.06	≤0.06	≤0.06 – 4	99.7/0.2/0.1	99.9/0.1/0.0
Aztreonam	≤0.12	4	≤0.12 – >16	90.5/0.5/9.0	88.3/2.2/9.5
Piperacillin/tazobactam	2	4	≤0.5 – >64	97.1/2.1/0.8	95.9/1.2/2.9
Levofloxacin	≤0.12	>4	≤0.12 – >4	73.4/0.8/25.8	73.3/0.1/26.6
Gentamicin	≤1	>8	≤1 – >8	89.6/0.2/10.2	89.2/0.4/10.4
Colistin	0.5	0.5	≤0.12 – 8	-/-/-	99.3/0.0/0.7
Klebsiella spp. (204)[c]					
Ceftolozane/tazobactam	0.25	8	0.06 – >32	-/-/-	-/-/-
Ceftriaxone	≤0.06	>8	≤0.06 – >8	82.8/0.5/16.7	82.8/0.5/16.7
Ceftazidime	0.12	32	0.03 – >32	83.8/2.0/14.2	83.3/0.5/16.2
Cefepime	≤0.5	>16	≤0.5 – >16	83.8/2.5/13.7	83.3/1.5/15.2
Meropenem	≤0.06	≤0.06	≤0.06 – >8	92.2/0.0/7.8	92.2/0.9/6.9
Aztreonam	≤0.12	>16	≤0.12 – >16	83.3/0.0/16.7	82.4/0.9/16.7
Piperacillin/tazobactam	4	>64	≤0.5 – >64	86.3/1.9/11.8	82.4/3.9/13.7
Levofloxacin	≤0.12	>4	≤0.12 – >4	86.2/1.0/12.8	84.2/2.0/13.8
Gentamicin	≤1	>8	≤1 – >8	87.7/0.5/11.8	87.3/0.4/12.3
Colistin	0.5	0.5	0.25 – >8	-/-/-	97.0/0.0/3.0
K. pneumoniae (174)					
Ceftolozane/tazobactam	0.25	16	0.06 – >32	-/-/-	-/-/-
Ceftriaxone	≤0.06	>8	≤0.06 – >8	81.0/0.6/18.4	81.0/0.6/18.4
Ceftazidime	0.12	>32	0.03 – >32	81.6/2.3/16.1	81.0/0.6/18.4
Cefepime	≤0.5	>16	≤0.5 – >16	81.6/2.9/15.5	81.0/1.8/17.2
Meropenem	≤0.06	≤0.06	≤0.06 – >8	91.4/0.0/8.6	91.4/0.6/8.0
Aztreonam	≤0.12	>16	≤0.12 – >16	81.6/0.0/18.4	80.5/1.1/18.4
Piperacillin/tazobactam	4	>64	≤0.5 – >64	85.6/2.3/12.1	81.0/4.6/14.4
Levofloxacin	≤0.12	>4	≤0.12 – >4	83.8/1.2/15.0	82.1/1.7/16.2
Gentamicin	≤1	>8	≤1 – >8	86.2/0.6/13.2	85.6/0.6/13.8
Colistin	0.5	1	0.25 – >8	-/-/-	96.5/0.0/3.5
Enterobacter spp. (96)[d]					
Ceftolozane/tazobactam	0.5	8	0.12 – >32	-/-/-	-/-/-
Ceftriaxone	0.25	>8	≤0.06 – >8	66.3/7.4/26.3	66.3/7.4/26.3
Ceftazidime	0.5	>32	0.12 – >32	76.0/0.0/24.0	69.8/6.2/24.0
Cefepime	≤0.5	2	≤0.5 – >16	90.6/4.2/5.2	87.5/6.2/6.3
Meropenem	≤0.06	0.12	≤0.06 – 4	99.0/0.0/1.0	99.0/1.0/0.0
Aztreonam	≤0.12	>16	≤0.12 – >16	73.1/2.2/24.7	72.0/1.1/26.9
Piperacillin/tazobactam	4	>64	1 – >64	78.9/10.6/10.5	74.7/4.2/21.1
Levofloxacin	≤0.12	2	≤0.12 – >4	92.7/0.0/7.3	89.6/3.1/7.3
Gentamicin	≤1	≤1	≤1 – >8	94.8/0.0/5.2	94.8/0.0/5.2
Colistin	0.5	>8	0.25 – >8	-/-/-	86.0/0.0/14.0
Citrobacter spp. (89)[e]					
Ceftolozane/tazobactam	0.25	4	0.12 – >32	-/-/-	-/-/-
Ceftriaxone	≤0.06	>8	≤0.06 – >8	80.7/1.1/18.2	80.7/1.1/18.2
Ceftazidime	0.25	>32	0.06 – >32	82.0/1.1/16.9	80.9/1.1/18.0
Cefepime	≤0.5	1	≤0.5 – 8	97.7/2.2/0.0	94.3/4.6/1.1
Meropenem	≤0.06	≤0.06	≤0.06 – ≤0.06	100.0/0.0/0.0	100.0/0.0/0.0
Aztreonam	≤0.12	>16	≤0.12 – >16	80.9/2.2/16.9	80.9/0.0/19.1
Piperacillin/tazobactam	4	32	≤0.5 – >64	86.4/6.8/6.8	81.8/4.6/13.6
Levofloxacin	≤0.12	2	≤0.12 – >4	94.4/2.2/3.4	89.9/4.5/5.6
Gentamicin	≤1	≤1	≤1 – >8	94.4/0.0/5.6	94.4/0.0/5.6
Colistin	0.5	1	≤0.12 – 2	-/-/-	100.0/0.0/0.0
P. mirabilis (79)					
Ceftolozane/tazobactam	0.5	0.5	0.12 – 2	-/-/-	-/-/-
Ceftriaxone	≤0.06	≤0.06	≤0.06 – >8	94.9/0.0/5.1	94.9/0.0/5.1
Ceftazidime	0.06	0.12	≤0.015 – 4	100.0/0.0/0.0	96.2/3.8/0.0
Cefepime	≤0.5	≤0.5	≤0.5 – >16	94.9/0.0/5.1	94.9/0.0/5.1
Meropenem	≤0.06	≤0.06	≤0.06 – 0.12	100.0/0.0/0.0	100.0/0.0/0.0
Aztreonam	≤0.12	≤0.12	≤0.12 – 2	100.0/0.0/0.0	98.7/1.3/0.0
Piperacillin/tazobactam	≤0.5	1	≤0.5 – 2	100.0/0.0/0.0	100.0/0.0/0.0
Levofloxacin	≤0.12	>4	≤0.12 – >4	69.6/6.3/24.1	63.3/6.3/30.4
Gentamicin	≤1	>8	≤1 – >8	84.6/3.9/11.5	82.1/2.5/15.4
Colistin	>8	>8	>8 – >8	-/-/-	0.0/0.0/100.0
Indole-positive *Proteus* spp. (104)[f]					
Ceftolozane/tazobactam	0.25	1	0.06 – >32	-/-/-	-/-/-
Ceftriaxone	≤0.06	2	≤0.06 – >8	87.4/4.8/7.8	87.4/4.8/7.8
Ceftazidime	0.12	8	0.03 – >32	88.3/3.9/7.8	81.6/6.7/11.7
Cefepime	≤0.5	≤0.5	≤0.5 – 16	99.0/0.0/1.0	99.0/0.0/1.0
Meropenem	≤0.06	0.12	≤0.06 – 0.5	100.0/0.0/0.0	100.0/0.0/0.0
Aztreonam	≤0.12	0.25	≤0.12 – >16	97.0/0.0/3.0	96.0/1.0/3.0
Piperacillin/tazobactam	≤0.5	4	≤0.5 – >64	99.0/0.0/1.0	97.1/1.9/1.0
Levofloxacin	≤0.12	>4	≤0.12 – >4	75.0/3.8/21.2	72.1/2.9/25.0
Gentamicin	≤1	>8	≤1 – >8	85.6/1.9/12.5	77.9/7.7/14.4
Colistin	>8	>8	8 – >8	-/-/-	0.0/0.0/100.0
Serratia spp. (25)[g]					
Ceftolozane/tazobactam	0.5	1	0.12 – 2	-/-/-	-/-/-
Ceftriaxone	0.25	2	≤0.06 – 4	84.0/8.0/8.0	84.0/8.0/8.0
Ceftazidime	0.25	0.5	0.03 – 2	100.0/0.0/0.0	96.0/4.0/0.0
Cefepime	≤0.5	≤0.5	≤0.5 – 1	100.0/0.0/0.0	100.0/0.0/0.0
Meropenem	≤0.06	0.12	≤0.06 – 0.25	100.0/0.0/0.0	100.0/0.0/0.0
Aztreonam	≤0.12	0.5	≤0.12 – 1	100.0/0.0/0.0	100.0/0.0/0.0
Piperacillin/tazobactam	2	4	1 – 16	100.0/0.0/0.0	96.0/4.0/0.0
Levofloxacin	0.25	2	≤0.12 – >4	92.0/0.0/8.0	84.0/8.0/8.0
Gentamicin	≤1	2	≤1 – >8	96.0/0.0/4.0	96.0/0.0/4.0
Colistin	>8	>8	0.5 – >8	-/-/-	12.0/0.0/88.0
P. aeruginosa (90)					
Ceftolozane/tazobactam	0.5	1	0.25 – >32	-/-/-	-/-/-
Ceftazidime	2	8	0.25 – >32	90.0/3.3/6.7	90.0/0.0/10.0
Cefepime	2	16	≤0.5 – >16	85.6/8.8/5.6	85.6/0.0/14.4
Meropenem	0.5	8	≤0.06 – >8	83.0/4.5/12.5	83.0/111.3/5.7
Aztreonam	4	>16	0.25 – >16	74.4/8.9/16.7	1.1/82.2/16.7
Piperacillin/tazobactam	4	64	1 – >64	83.3/8.9/7.8	83.3/0.0/16.7
Levofloxacin	0.5	>4	≤0.12 – >4	75.6/1.1/23.3	71.1/4.5/24.4
Gentamicin	≤1	4	≤1 – >8	90.0/2.2/7.8	90.0/0.0/10.0
Amikacin	2	4	≤0.25 – 32	98.9/1.1/0.0	96.7/2.2/1.1
Colistin	1	2	0.5 – 2	100.0/0.0/0.0	100.0/0.0/0.0

[a] Criteria as published by the CLSI [2013] and EUCAST [2013].
[b] breakpoints not available.
[c] Includes *K. oxytoca* (29 strains), *K. pneumoniae* subsp. *ozaenae* (1 strain), *K. pneumoniae* (174 strains).
[d] Includes *E. aerogenes* (32 strains), *E. asburiae* (1 strain), *E. cloacae* (61 strains), *E. hormaechei* (1 strain), *E. gergoviae* (1 strain).
[e] Includes *C. amalonaticus* (2 strains), *C. freundii* (57 strains), *C. koseri* (28 strains), *C. youngae* (2 strains).
[f] Includes *Morganella morganii* (59 strains), *P. vulgaris* (13 strains), *Providencia rettgeri* (17 strains), *Providencia stuartii* (15 strains).
[g] Includes *S. fonticola* (1 strain), *S. marcescens* (24 strains).
I = intermediate; R = resistant; S = susceptible.

CONCLUSIONS

- *E. coli* was the predominant Gram-negative pathogen (52.2% of isolates) isolated from hospitalized patients in 2013 with UTIs in this USA study, followed by *K. pneumoniae* (12.0%), indole-positive *Proteus* spp. (7.2%), *Enterobacter* spp. (6.6%), and *P. aeruginosa* (6.2%).
- Ceftolozane/tazobactam demonstrated potent activity against contemporary Enterobacteriaceae, including activity against most meropenem-susceptible ESBL-phenotype strains and many MDR strains, and potent activity against contemporary *P. aeruginosa* including coverage of most MDR and XDR strains.
- Ceftolozane/tazobactam could be a valuable treatment option for HCA-UTI in the USA, especially for MDR pathogens.

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ACKNOWLEDGMENTS

This study was funded by research grants from Cubist Pharmaceuticals (Lexington, MA, USA). Editorial and layout support for this poster was provided by PAREXEL and funded by Cubist Pharmaceuticals.