Presented at IDWeek 2016
October 26-30, 2016
New Orleans, LA, USA

Ceftolozane/Tazobactam Activity Tested Against Bacterial Bloodstream Isolates From Multiple Infection Sources

Shortridge D; Duncan LR; Sader HS; Flamm RK; Castanheira M

JMI Laboratories, North Liberty, Iowa, USA

Dee Shortridge, PhD
JMI Laboratories
345 Beaver Kreek Centre, Ste A
North Liberty, IA 52317, USA
319-665-3370
dee-shortridge@jmilabs.com

INTRODUCTION

- Ceftolozane is a novel oxyimino-aminothiazolyl cephalosporin with potent activity against Enterobacteriaceae (similar to other oxyimino-aminothiazolyl cephalosporins) and has demonstrated greater activity than ceftazidime against *Pseudomonas aeruginosa*
  - Ceftolozane maintains its stability against many *P. aeruginosa* resistance mechanisms, including AmpC hyperproduction and efflux mechanisms
  - Furthermore, ceftolozane is little affected by porin deficiency
  - As with other oxyimino-aminothiazolyl cephalosporins, however, the activity of ceftolozane is compromised in bacteria producing extended-spectrum β-lactamases (ESBLs), stably derepressed AmpC β-lactamases, and carbapenemases
- Tazobactam, a penicillanic acid sulfone, is a well-established β-lactamase inhibitor that extends the spectrum of β-lactam agents
- Ceftolozane/tazobactam is approved by the US Food and Drug Administration for the treatment of patients with complicated intra-abdominal infections and complicated urinary tract infections, including pyelonephritis
- In US hospitals, bloodstream infections account for 10% of hospital-acquired infections; 44% of bloodstream infections are caused by Gram-negative pathogens and 15-30% of Gram-negative bloodstream infections are caused by multidrug-resistant strains (*P. aeruginosa, Klebsiella pneumoniae,* and *Escherichia coli*) (Magill et al, 2014)
  - Empiric and targeted therapies to treat infections caused by these organisms are becoming increasingly limited in efficacy
- We evaluated the activity of ceftolozane/tazobactam and comparators against *P. aeruginosa* and Enterobacteriaceae bloodstream infection isolates stratified by primary infection site (if known)

MATERIALS AND METHODS

- 1475 *P. aeruginosa* and 11,588 Enterobacteriaceae clinical isolates from patients with bloodstream infections were collected in North America, Europe, and Asia-Western Pacific from 2011 to 2015 by the Program to Assess Ceftolozane/Tazobactam Susceptibility (PACTS)
- Isolates were from documented infections, and only 1 isolate per patient-infection episode was included
- Minimum inhibitory concentration (MIC) values were determined for ceftolozane/tazobactam (tazobactam at fixed 4 µg/mL) and comparators using the reference Clinical and Laboratory Standards Institute (CLSI) broth microdilution method (M07-A10)
  - Quality control (QC) ranges and interpretive criteria for comparator compounds used the CLSI M100-S26 guidelines
  - QC strains included *E. coli* ATCC 25922 and NCTC 13353, *K. pneumoniae* ATCC 700603, and *P. aeruginosa* ATCC 27853; all QC results were within published ranges

RESULTS

- Among the bloodstream infection isolates with a known primary infection site, urinary tract (UT) was the most common (n = 2483; 19.0%) followed by gastrointestinal (GI) tract/bowel (n = 1030; 7.9%) (**Table 1**)

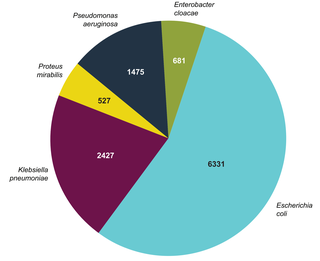
Table 1. Percentage of susceptible isolates for ceftolozane/tazobactam and comparators for bloodstream isolates by primary infection site (PACTS,† 2011-2015)

Species/Group (no.)	% Susceptible (CLSI)				
Primary Infection Site/Source‡	C/T	P/T	FEP	MEM	CAZ
P. aeruginosa (1475)	90.6	75.0	81.3	75.8	77.5
GI tract/bowel (60)	88.3	73.3	85.0	80.0	75.0
IV line (147)	90.5	71.4	81.5	81.0	77.6
LRT (162)	84.0	65.4	73.5	63.6	69.1
SSS (170)	80.6	63.5	71.2	67.1	67.6
UT (133)	94.0	78.8	82.0	80.5	79.7
Other/unknown (803)	93.8	79.5	84.7	78.2	81.1
Enterobacteriaceae (11,588)	93.3	89.0	85.1	97.4	84.0
GI tract/bowel (970)	92.5	88.2	86.2	97.8	83.7
IV line (660)	88.5	82.5	78.9	96.2	77.1
LRT (479)	84.6	81.6	72.4	94.8	71.0
SSS (762)	92.8	89.8	84.1	97.4	84.0
UT (2350)	95.7	91.4	87.8	98.5	87.8
Other/unknown (6367)	93.7	89.3	85.6	97.3	84.3

CAZ = ceftazidime; CLSI = Clinical and Laboratory Standards Institute; C/T = ceftolozane/tazobactam; FEP = cefepime; GI = gastrointestinal; IV = intravenous; LRT = lower respiratory tract; MEM = meropenem; PACTS = Program to Assess Ceftolozane/Tazobactam Susceptibility; P/T = piperacillin/tazobactam; SSS = skin and skin structure; UT = urinary tract.
†PACTS includes North America, Europe, and Asia-Western Pacific.
‡Primary infection site of blood culture isolate as indicated by laboratory.

- *E. coli* was the most common Gram-negative isolate from bloodstream infections (n = 6331; 48.5%); *K. pneumoniae* (n = 2427; 18.6%) and *P. aeruginosa* (n = 1475; 11.3%) were the second and third most common (**Figure 1** and **Table 1**)
- Ceftolozane/tazobactam inhibited 90.6% of all *P. aeruginosa* and 93.3% of all Enterobacteriaceae bloodstream infection isolates (CLSI breakpoints) (**Table 1**)
  - *P. aeruginosa* susceptibility to ceftolozane/tazobactam was 96.3% in North America, 86.0% in Europe, and 96.0% in Asia-Western Pacific
  - Enterobacteriaceae susceptibility to ceftolozane/tazobactam was 95.2% in North America, 91.4% in Europe, and 99.2% in Asia-Western Pacific
- Ceftolozane/tazobactam susceptibility ranged from 80.6% (skin and skin structure [SSS]) to 94.0% (UT) against *P. aeruginosa* bloodstream infection isolates derived from various identified infection sites
  - Ceftolozane/tazobactam activity was markedly superior to that of meropenem overall (90.6% vs 75.8% susceptibility for all *P. aeruginosa* isolates) and against each of the isolate subsets

Figure 1. Top 5 pathogens from bloodstream infection cultures collected from 2011 to 2015 as part of PACTS.



PACTS = Program to Assess Ceftolozane/Tazobactam Susceptibility.

- Ceftolozane/tazobactam was also very active against Enterobacteriaceae bloodstream isolates derived from various sites of infection (% susceptible range, 84.6% lower respiratory tract [LRT] to 95.7% UT)
  - The only 2 primary infection sites for which Enterobacteriaceae isolates exhibited susceptibility <90% were intravenous line (88.5% susceptible) and LRT (84.6% susceptible), and these constituted only 9.8% of all Enterobacteriaceae isolates
- **Table 2** shows the 50% minimum inhibitory concentration (MIC_{50}), 90% minimum inhibitory concentration (MIC_{90}), and susceptibility rates (CLSI 2016 breakpoints) for ceftolozane/tazobactam and comparators against *P. aeruginosa* and Enterobacteriaceae
  - For *P. aeruginosa*, ceftolozane/tazobactam and meropenem have the lowest MIC_{50} (0.5 µg/mL). Ceftolozane/tazobactam also has the lowest MIC_{90} (4 µg/mL) and the highest percentage susceptible (90.6%)
  - For Enterobacteriaceae, ceftolozane/tazobactam has a lower MIC_{90} (1 µg/mL) than all comparators except meropenem (≤0.06 µg/mL)

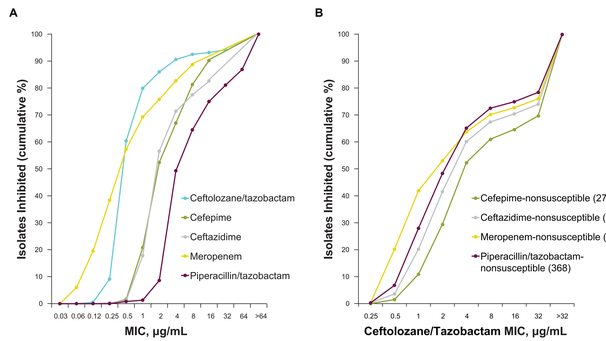
Table 2. Activity of ceftolozane/tazobactam and comparator antimicrobial agents when tested against 1475 isolates of *Pseudomonas aeruginosa* and 11,588 isolates of Enterobacteriaceae from bloodstream infections (PACTS, 2011-2015)

	MIC, µg/mL			CLSI†		
Antimicrobial Agent	MIC_{50}	MIC_{90}	Range	%S	%I	%R
P. aeruginosa						
Ceftolozane/tazobactam	0.5	4	0.12–>32	90.6	1.9	7.5
Cefepime	2	16	≤0.5–>16	81.3	8.9	9.8
Ceftazidime	2	>16	≤0.25–>16	77.5	5.0	17.5
Meropenem	0.5	>8	≤0.06–>8	75.8	6.9	17.3
Piperacillin/tazobactam	8	>64	≤0.5–>64	75.0	11.9	13.1
Enterobacteriaceae‡						
Ceftolozane/tazobactam	0.25	1	0.03–>32	93.3	1.3	5.5
Cefepime	≤0.5	>16	≤0.5–>16	85.1	2.8§	12.2
Ceftazidime	0.25	>16	≤0.12–>16	84.0	2.1	14.0
Meropenem	≤0.06	≤0.06	≤0.06–>8	97.4	0.2	2.4
Piperacillin/tazobactam	2	32	≤0.5–>64	89.0	4.2	6.9

CLSI = Clinical and Laboratory Standards Institute; MIC_{50} = 50% minimum inhibitory concentration; MIC_{90} = 90% minimum inhibitory concentration; PACTS = Program to Assess Ceftolozane/Tazobactam Susceptibility; S = susceptible; I = intermediate; R = resistant.
†Criteria as published by CLSI (2016).
‡Organisms include *Citrobacter amalonaticus* (4), *C. braakii* (9), *C. farmeri* (1), *C. freundii* (88), *C. freundii sp. complex* (7), *C. koseri* (87), *C. youngae* (3), *Cronobacter sakazakii* (1), *Enterobacter aerogenes* (216), *E. asburiae* (15), *E. cloacae* (681), *E. cloacae* sp. complex (60), *E. cowanii* (1), *E. gergoviae* (2), *E. intermedius* (2), *Escherichia coli* (6331), *E. hermannii* (2), Group B *Salmonella enterica* (2), *Hafnia alvei* (7), *Klebsiella oxytoca* (414), *K. pneumoniae* (2427), *K. variicola* (7), *Kluyvera ascorbata* (1), *Leclercia adecarboxylata* (1), *Morganella morganii* (144), *Pantoea agglomerans* (9), *P. eucrina* (1), *Proteus mirabilis* (527), *P. penneri* (1), *P. vulgaris* (26), *Providencia rettgeri* (17), *P. stuartii* (29), *Raoultella ornithinolytica* (1), *R. planticola* (6), *Salmonella enterica* subsp. *enterica* serovar enteritidis (3), *S. enterica* subsp. *enterica* serovar typhi (2), *S. enterica* subsp. *enterica* serovar typhimurium (2), *Serratia fonticola* (1), *S. liquefaciens* (15), *S. marcescens* (390), *S. plymuthica* (1), unspecified *Citrobacter* (5), unspecified *Enterobacter* (9), unspecified *Klebsiella* (5), unspecified *Morganella* (1), unspecified *Pantoea* (1), unspecified *Proteus* (7), unspecified *Providencia* (1), unspecified *Raoultella* (2), unspecified *Salmonella* (12), and unspecified *Serratia* (1).
§Intermediate interpreted as susceptible-dose dependent.

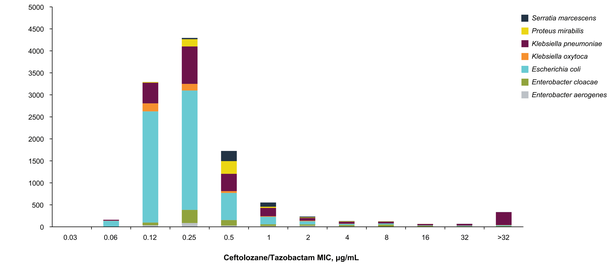
- **Figures 2** and **3** show the ceftolozane/tazobactam MIC distributions for the most common species isolated from bloodstream infections
  - **Figure 2A** shows the ceftolozane/tazobactam MIC distribution of *P. aeruginosa* (n = 1475) with an MIC_{50} of 0.5 and an MIC_{90} of 4 µg/mL; MIC distributions for comparator agents are also shown. **Figure 2B** shows the ceftolozane/tazobactam MIC distributions of *P. aeruginosa* isolates nonsusceptible to comparator agents
  - **Figure 3** shows the ceftolozane/tazobactam MIC distributions of the most common Enterobacteriaceae (n = 10,986), with an overall MIC_{50} of 0.25 µg/mL and an overall MIC_{90} of 1 µg/mL

Figure 2. Cumulative MIC distribution of *P. aeruginosa* bloodstream infection isolates collected from 2011 to 2015 as part of PACTS. (A) Ceftolozane/tazobactam and comparator agents† against all *P. aeruginosa*. (B) Ceftolozane/tazobactam against *P. aeruginosa* isolates nonsusceptible to other agents.‡



MIC = minimum inhibitory concentration; PACTS = Program to Assess Ceftolozane/Tazobactam Susceptibility.
†Ceftolozane/tazobactam range 0.12 to >32; cefepime range ≤0.5 to >16; ceftazidime range ≤0.25 to >16; meropenem range ≤0.06 to >8; piperacillin/tazobactam range ≤0.5 to >64.
‡Breakpoints used for nonsusceptibility were ≥ the intermediate CLSI breakpoint for each comparator: cefepime ≥16; ceftazidime ≥16; meropenem ≥4; piperacillin/tazobactam ≥32.

Figure 3. Ceftolozane/tazobactam MIC distribution of most common bloodstream infection species of Enterobacteriaceae collected from 2011 to 2015 as part of PACTS.

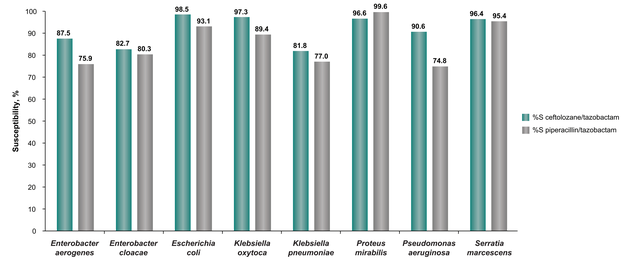


MIC = minimum inhibitory concentration; PACTS = Program to Assess Ceftolozane/Tazobactam Susceptibility.

- Notably, ceftolozane/tazobactam was more active than piperacillin/tazobactam and cefepime against the overall Enterobacteriaceae isolate set (93.3% vs 89.0% vs 85.1% susceptible) and against the isolate subsets from each site of infection (**Table 1**)

- **Figure 4** shows the susceptibility rate for ceftolozane/tazobactam (and piperacillin/tazobactam) of the most common bloodstream infection isolates, using CLSI breakpoints, ranging from 81.8% for *K. pneumoniae* to 98.5% for *E. coli*
  - Ceftolozane/tazobactam was more active than piperacillin/tazobactam for all species except *Proteus mirabilis*

Figure 4. Percentage susceptibility to ceftolozane/tazobactam and piperacillin/tazobactam of the most common bloodstream isolates collected from 2011 to 2015 as part of PACTS.



PACTS = Program to Assess Ceftolozane/Tazobactam Susceptibility; S = susceptible.

CONCLUSIONS

- Ceftolozane/tazobactam was active against a large worldwide collection of *P. aeruginosa* (90.6% susceptible, CLSI) and Enterobacteriaceae (93.3% susceptible, CLSI) bloodstream infection isolates, regardless of primary infection site, collected from 2011 to 2015 as part of PACTS
- Among the antimicrobials tested here, ceftolozane/tazobactam was the most active β-lactam against *P. aeruginosa* and, except for the carbapenems, was also the most active β-lactam against Enterobacteriaceae
- Ceftolozane/tazobactam had very good activity against most common bloodstream isolates; in North America, *P. aeruginosa* isolates were 96.3% susceptible, and Enterobacteriaceae were 95.2% susceptible
- Ceftolozane/tazobactam may represent a valuable treatment option for bloodstream infections caused by Gram-negative pathogens

REFERENCES

Anderson DJ, Moehring RW, Sloane R, et al. Bloodstream infections in community hospitals in the 21st century: a multicenter cohort study. *PLoS One.* 2014;9:e91713.

Clinical and Laboratory Standards Institute. M07-A10. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard tenth edition. Wayne, PA: CLSI; 2015.

Clinical and Laboratory Standards Institute. M100-S26. Performance standards for antimicrobial susceptibility testing: 26th informational supplement. Wayne, PA: CLSI; 2016.

Craig WA, Andes DR. In vivo activities of ceftolozane, a new cephalosporin, with and without tazobactam against *Pseudomonas aeruginosa* and Enterobacteriaceae, including strains with extended-spectrum beta-lactamases, in the thighs of neutropenic mice. *Antimicrob Agents Chemother.* 2013;57:1577-1582.

European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters. Version 6.0, January 2016. http://www.eucast.org/clinical_breakpoints. Accessed September 23, 2016.

Farrell DJ, Flamm RK, Sader HS, Jones RN. Antimicrobial activity of ceftolozane-tazobactam tested against Enterobacteriaceae and *Pseudomonas aeruginosa* with various resistance patterns isolated in U.S. hospitals (2011-2012). *Antimicrob Agents Chemother.* 2013;57:6305-6310.

Magill SS, Edwards JR, Bamber W, et al. Multistate point-prevalence survey of health care-associated infections. *N Engl J Med.* 2014;370:1198-1208.

Sader HS, Farrell DJ, Castanheira M, Flamm RK, Jones RN. Antimicrobial activity of ceftolozane/tazobactam tested against *Pseudomonas aeruginosa* and Enterobacteriaceae with various resistance patterns isolated in European hospitals (2011-12). *J Antimicrob Chemother.* 2014;69:2713-2722.

Sievert DM, Ricks P, Edwards JR, et al. Antimicrobial-resistant pathogens associated with healthcare-associated infections: summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2009-2010. *Infect Control Hosp Epidemiol.* 2013;34:1-14.

Skalweit MJ. Profile of ceftolozane/tazobactam and its potential in the treatment of complicated intra-abdominal infections. *Drug Des Dev Ther.* 2015;9:2919-2925.

ACKNOWLEDGMENTS

Funding for this research was provided by Merck & Co., Inc., Kenilworth, NJ, USA. Editorial assistance was provided by Sally Mitchell, PhD (ApotheCom, Yardley, PA, USA). This assistance was funded by Merck & Co., Inc., Kenilworth, NJ, USA.

http://tinyurl.com/jla6t8c