Antimicrobial Activity of Ceftolozane/Tazobactam Tested Against Enterobacteriaceae, *Pseudomonas aeruginosa*, and *Streptococcus pneumoniae* From USA and European Hospitals (2014)

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ABSTRACT

Background: Ceftolozane/tazobactam (TOL/TAZ) is an antipseudomonal cephalosporin with a β-lactamase inhibitor currently in clinical development in patients with ventilated nosocomial bacterial pneumonia, and recently approved for complicated intra-abdominal infections (cIAI; in combination with metronidazole) and complicated urinary tract infections (cUTI), including pyelonephritis, in the United States (USA).

Methods: Enterobacteriaceae (ENT), *P. aeruginosa* (PSA), and *S. pneumoniae* (SPN), consecutively collected from various infection sources from USA and European (EU) hospitals in 2014, were tested for susceptibility (S) by CLSI broth microdilution methods (TOL/TAZ at a fixed 4 μg/mL of TAZ). US-FDA breakpoints for S were applied (≤2 μg/mL for ENT; ≤4 μg/mL for PSA).

Results: In USA and EU, TOL/TAZ was active ($MIC_{50/90}$, USA 0.25/1, EU 0.25/2 μg/mL) against ENT with S rates of 94.6% (USA) and 91.4% (EU). Extended-spectrum β-lactamases (ESBL) phenotype *Escherichia coli* (EC) represented 15.0% (241/1603) and 18.9% (480/2536) of USA and EU EC isolates, respectively, and 87.6/89.2% (USA/EU) of isolates were S to TOL/TAZ. ESBL phenotype *Klebsiella pneumoniae* (KPN) represented 18.4% (128/695) and 41.7% (503/1207) of USA and EU KPN isolates, respectively, and 48.4/44.3% (USA/EU) of isolates were S to TOL/TAZ, rising to 75.0/61.5% S in meropenem (MEM)-S ESBL phenotype KPN. TOL/TAZ was active ($MIC_{50/90}$, USA 0.5/2, EU 0.25/4 μg/mL) against PSA with S rates of 96.4% (USA) and 90.9% (EU). Ceftazidime (CAZ) non-S PSA were 15.2/24.9% in USA/EU and TOL/TAZ % S was 76.1/65.9%. MEM non-S PSA were 16.8/24.5% in USA/EU and TOL/TAZ % S was 81.1/65.4%. TOL/TAZ in vitro activity, as with other β-lactams, varied according to SPN susceptibility to penicillin (PEN).

Conclusions: TOL/TAZ demonstrated good activity against ENT (including most ESBL strains), PSA (including CAZ- and MEM-resistant strains), and PEN-S SPN isolated from patients in USA and EU hospitals during 2014 (**Table 1**).

INTRODUCTION

- Ceftolozane is a novel oxyimino-aminothiazolyl cephalosporin with potent activity against Enterobacteriaceae (similar to other oxyimino-aminothiazolyl cephalosporins), and it has demonstrated greater activity (compared with ceftazidime) against *Pseudomonas aeruginosa*. Ceftolozane has stability against many *P. aeruginosa* resistance mechanisms, including AmpC hyperproduction and efflux mechanisms; furthermore, ceftolozane is little affected by porin deficiency. However, as with other oxyimino-aminothiazolyl cephalosporins, the activity of ceftolozane is compromised in bacteria that produce 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 a novel antibacterial with activity against *P. aeruginosa*, including drug-resistant strains, and other common Gram-negative pathogens, including most ESBL-producing Enterobacteriaceae
- During the past decade, the prevalence of nosocomial infections caused by *P. aeruginosa* and Enterobacteriaceae in intensive care units worldwide has increased, as has antimicrobial resistance, with resultant associated increases in morbidity and mortality rates. Empiric and targeted therapies to treat infections with these organisms are becoming increasingly limited
- Ceftolozane/tazobactam is in clinical development for treatment in ventilator-dependent patients with nosocomial bacterial pneumonia and was recently approved in the United States for the treatment of complicated intra-abdominal infection (cIAI; in combination with metronidazole) and complicated urinary tract infection (cUTI), including pyelonephritis
- In the current study, we evaluate the potency of ceftolozane/tazobactam and comparator drugs tested against a large, contemporary (2014) collection of clinically derived Enterobacteriaceae, *P. aeruginosa*, and *Streptococcus pneumoniae* obtained from patients in European and US hospitals

METHODS

Sampling Sites and Organisms

- Enterobacteriaceae, *P. aeruginosa*, and *S. pneumoniae* isolates were consecutively collected in 2014 from 41 medical centers in Europe, Turkey, and Israel and from 29 medical centers located across the 9 US census regions by the Program to Assess Ceftolozane/Tazobactam Susceptibility (PACTS)
- For Europe, the following countries (number of medical centers) participated: Austria (1), Belgium (1), Czech Republic (1), Denmark (1), Finland (1), France (4), Germany (5), Greece (1), Ireland (2), Israel (1), Italy (4), Netherlands (1), Norway (1), Poland (1), Portugal (1), Russia (3), Spain (3), Sweden (2), Switzerland (1), Turkey (2), United Kingdom (3), and Ukraine (1)
- For the United States, the following states (number of medical centers) participated: Arkansas (1), California (1), Colorado (1), Florida (2), Georgia (1), Iowa (1), Indiana (1), Kentucky (2), Massachusetts (2), Michigan (1), Missouri (1), Nebraska (1), New Jersey (1), New York (3), Ohio (1), Texas (3), Utah (1), Virginia (1), Vermont (1), Washington (2), and Wisconsin (1)
- All organisms were isolated from documented infections and only 1 strain per patient-infection episode was included in the surveillance collection

Antimicrobial Susceptibility Testing

- Minimum inhibitory concentration (MIC) values were determined using the reference Clinical and Laboratory Standards Institute (CLSI) broth microdilution method (M07-A10). Quality control ranges and interpretive criteria for comparator compounds used the CLSI M100-S25 and European Committee on Antimicrobial Susceptibility Testing (EUCAST) v5.0 (2015) guidelines. The ESBL phenotype was defined as an MIC ≥2 μg/mL for ceftazidime, ceftriaxone, or aztreonam

RESULTS

- In the United States and Europe, ceftolozane/tazobactam was active ($MIC_{50/90}$: United States: 0.25/1; Europe: 0.25/2 μg/mL; **Table 1**) against Enterobacteriaceae with US Food and Drug Administration (FDA) breakpoint susceptibility rates of 94.6% (United States; **Table 2**) and 91.4% (Europe; **Table 3**). Meropenem ($MIC_{50/90}$: United States: ≤0.015/0.06; Europe: ≤0.015/0.06 μg/mL) was the most active agent tested against Enterobacteriaceae, followed by tigecycline and then ceftolozane/tazobactam (**Tables 2** and **3**)
- ESBL phenotype *E. coli* represented 15.0% (241/1603) and 18.9% (480/2536) of *E. coli* isolates from patients from the United States and from Europe, respectively, and 87.6%/89.2% (United States/Europe) of these isolates were susceptible to ceftolozane/tazobactam. ESBL phenotype *Klebsiella pneumoniae* represented 18.4% (128/695) and 41.7% (503/1207) of *K. pneumoniae* isolates from patients from the United States and Europe, respectively, and 48.4%/44.3% (United States/Europe) of isolates were susceptible to ceftolozane/tazobactam, increasing to 75.0%/61.5% susceptible in meropenem-susceptible ESBL phenotype *K. pneumoniae* (**Table 1**)
- Ceftolozane/tazobactam ($MIC_{50/90}$: United States: 0.5/2; Europe: 0.25/4 μg/mL; **Table 1**) was the most active agent tested against *P. aeruginosa,* with susceptibility rates of 96.4% (United States; **Table 2**) and 90.9% (Europe; **Table 3**). Ceftazidime-nonsusceptible *P. aeruginosa* was 15.2%/24.9% in the United States/Europe and against these strains, ceftolozane/tazobactam susceptibility rates were 76.1%/65.9%. Meropenem-nonsusceptible *P. aeruginosa* were 16.8%/24.5% in the United States/Europe and against these strains, ceftolozane/tazobactam susceptibility rates were 81.1%/65.4%
- Ceftolozane/tazobactam in vitro activity ($MIC_{50/90}$: United States: 0.12/8; Europe: 0.12/2 μg/mL; **Table 1**), as with other β-lactams, varied according to *S. pneumoniae* susceptibility to penicillin (**Tables 2** and **3**)

Table 1. Activity and Cumulative Percentage Distribution of Ceftolozane/Tazobactam Tested Against Bacterial Isolates From Hospitalized Patients (2014)

Organism (n)	Cumulative Percentage Inhibited at Ceftolozane/Tazobactam MIC (μg/mL) of:								$MIC_{50/90}$ (μg/mL)
	≤0.25	0.5	1	2	4	8	16	32	
Enterobacteriaceae (all isolates)									
United States (3530)	65.4	85.3	92.0	94.6[a]	95.7	96.8	97.8	98.4	0.25/1
Europe (5847)	59.1	80.3	87.9	91.4	93.3	94.8	95.9	96.6	0.25/2
E. coli (all)									
United States (1603)	82.5	93.8	96.4	98.1	98.5	98.9	99.3	99.8	0.25/0.5
Europe (2536)	81.6	93.1	96.5	98.0	98.5	99.0	99.3	99.6	0.25/0.5
E. coli (ESBL)									
United States (241)	27.4	63.1	77.2	87.6	90.0	93.0	95.0	98.3	0.5/4
Europe (480)	31.5	66.0	81.9	89.2	92.1	94.8	96.5	97.7	0.5/4
K. pneumoniae (all isolates)									
United States (696)	64.8	81.3	88.2	90.5	91.4	92.1	93.1	94.4	0.25/2
Europe (1208)	47.1	65.7	73.1	76.8	80.3	82.4	84.2	86.4	0.5/>32
K. pneumoniae (ESBL)									
United States (129)	16.3	27.1	39.5	48.8	53.5	57.4	62.8	69.8	4/>32
Europe (503)	8.0	24.5	36.8	44.3	52.7	57.7	62.0	67.4	4/>32
K. pneumoniae (ESBL/MEM-S)									
United States (81)	25.9	43.2	63.0	75.3	82.7	88.9	93.8	97.5	1/16
Europe (356)	11.2	34.6	51.1	61.5	73.0	80.1	84.8	87.4	1/>32
Enterobacter spp.									
United States (459)	53.6	72.1	80.4	85.2	90.2	94.3	98.3	98.7	0.25/4
Europe (671)	46.8	64.5	74.2	83.0	88.2	93.1	96.7	97.9	0.5/8
P. aeruginosa (all isolates)									
United States (909)	6.5	60.5	85.7	92.5	96.4	98.4	98.7	99.1	0.5/2
Europe (1483)	4.2	54.4	76.3	85.9	90.9	93.3	94.4	96.0	0.5/4
P. aeruginosa (CAZ-NS)									
United States (138)	0.0	1.5	23.2	50.7	76.1	89.1	91.3	94.2	2/16
Europe (369)	0.0	1.6	18.4	47.4	65.9	73.7	78.3	84.6	4/>32
P. aeruginosa (MEM-NS)									
United States (153)	0.7	13.7	45.1	67.3	81.1	90.2	92.2	94.8	2/8
Europe (364)	0.6	11.8	33.0	52.5	65.4	73.1	77.8	84.3	2/>32
S. pneumoniae									
United States (46)	63.0	65.2	76.1	78.3	89.1	93.5	100.0		0.12/8
Europe (110)	82.7	84.6	86.4	90.0	94.6	97.3	100.0		0.12/2

CAZ-NS = ceftazidime nonsusceptible; ESBL = extended-spectrum β-lactamase; FDA = US Food and Drug Administration; MEM-NS = meropenem nonsusceptible; MEM-S = meropenem susceptible.
[a]Percentages susceptible by FDA breakpoint are underlined (no breakpoints available for *S. pneumoniae*).

Table 2. Activity of Ceftolozane/Tazobactam and Comparator Antimicrobial Agents When Tested Against Bacterial Isolates From Hospitalized Patients (United States, 2014)

Organisms (No. tested)/Antimicrobial Agent	MIC (μg/mL)		%S/%I/%R	
	MIC_{50}	MIC_{90}	CLSI[a]	EUCAST[b]
Enterobacteriaceae (3530)[b]				
Ceftolozane/tazobactam[c]	0.25	1	94.6/1.1/4.3	–[d]/–/–
Ceftazidime	≤0.12	16	87.9/1.7/10.4	85.4/2.5/12.1
Cefepime	≤0.5	2	90.6/2.9/6.5	88.8/3.1/8.1
Ceftriaxone	≤0.06	>8	84.1/0.7/15.2	84.1/0.7/15.2
Piperacillin/tazobactam	2	16	91.8/3.4/4.8	88.7/3.1/8.2
Meropenem	≤0.015	0.06	98.0/0.4/1.6	98.4/0.6/1.0
Levofloxacin	≤0.12	>4	81.8/1.1/17.1	80.9/0.9/18.2
Gentamicin	≤1	>8	89.0/0.9/10.1	87.8/1.2/11.0
Tigecycline[e]	0.12	0.5	99.4/0.6/0.0	96.5/2.9/0.6
Colistin	≤0.5	>8	–/–/–	84.4/0.0/15.6
P. aeruginosa (909)				
Ceftolozane/tazobactam[c]	0.5	2	96.4/1.9/1.7	–/–/–
Ceftazidime	2	>16	84.8/4.0/11.2	84.8/0.0/15.2
Cefepime	2	16	87.0/7.2/5.8	87.0/0.0/13.0
Meropenem	0.5	8	83.2/5.6/11.2	83.2/11.4/5.4
Piperacillin/tazobactam	4	64	83.3/8.2/8.5	83.3/0.0/16.7
Levofloxacin	0.5	>4	77.1/5.6/17.3	68.4/8.7/22.9
Gentamicin	≤1	8	89.0/2.9/8.1	89.0/0.0/11.0
Amikacin	2	8	97.6/0.7/1.7	93.7/3.9/2.4
Colistin	2	2	98.7/1.3/0.0	100.0/0.0/0.0
S. pneumoniae (46)				
Ceftolozane/tazobactam	0.12	8	–/–/–	–/–/–
Amoxicillin/clavulanate	≤1	2	91.3/0.0/8.7	–/–/–
Penicillin[e]	≤0.06	2	65.2/23.9/10.9	65.2/–/–
Penicillin[f]	≤0.06	2	91.3/6.5/2.2	65.2/26.1/8.7
Ceftriaxone[g]	≤0.06	1	91.3/8.7/0.0	82.6/17.4/0.0
Imipenem	≤0.12	0.25	89.1/4.4/0.0	100.0/0.0/0.0
Erythromycin	≤0.12	>16	56.5/0.0/43.5	56.5/0.0/43.5
Levofloxacin	1	1	100.0/0.0/0.0	100.0/0.0/0.0
Tetracycline	≤0.5	>8	80.4/2.2/17.4	80.4/2.2/17.4
Tigecycline[e]	0.03	0.06	100.0/–/–	–/–/–
Trimethoprim/sulfamethoxazole	≤0.5	4	76.1/8.7/15.2	80.4/4.4/15.2
Linezolid	1	1	100.0/–/–	100.0/0.0/0.0
Vancomycin	0.25	0.25	100.0/–/–	100.0/0.0/0.0

CLSI = Clinical and Laboratory Standards Institute; FDA = US Food and Drug Administration; I = intermediate; R = resistant; S = susceptible.
[a]Criteria as published by CLSI (2015) and EUCAST (2015).
[b]Includes: *Citrobacter amalonaticus* (6 strains), *Citrobacter braakii* (5 strains), *Citrobacter freundii* (43 strains), *Citrobacter farmeri* (3 strains), *Citrobacter freundii* species complex (13 strains), *Citrobacter koseri* (33 strains), *Citrobacter youngae* (2 strains), *Enterobacter aerogenes* (110 strains), *Enterobacter amnigenus* (1 strain), *Enterobacter asburiae* (8 strains), *Escherichia coli* (1603 strains), *Enterobacter cloacae* (272 strains), *Enterobacter cloacae* species complex (66 strains), *Enterobacter gergoviae* (1 strain), *Cronobacter sakazakii* (1 strain), *Klebsiella varricola* (9 strains), *Klebsiella oxytoca* (194 strains), *Klebsiella pneumoniae* (696 strains), *Morganella morganii* (41 strains), *Proteus mirabilis* (207 strains), *Proteus vulgaris* (9 strains), *Providencia rettgeri* (10 strains), *Providencia stuartii* (6 strains), *Serratia liquefaciens* (9 strains), *Serratia marcescens* (179 strains), *Serratia odorifera* (2 strains), *Serratia plymuthica* (1 strain).
[c]In the absence of CLSI breakpoint, FDA breakpoints were applied when available (Zerbaxa Product Insert, 2014).
[d]– = no breakpoint available for interpretation.
[e]In the absence of CLSI breakpoint, FDA breakpoints were applied when available (Tygacil Product Insert, 2012).
[f]Oral penicillin V breakpoints used.
[g]CLSI parenteral (nonmeningitis) and EUCAST "infections other than meningitis" breakpoints used.

Table 3. Activity of Ceftolozane/Tazobactam and Comparator Antimicrobial Agents When Tested Against Bacterial Isolates From Hospitalized Patients (Europe, 2014)

Organisms (No. tested)/Antimicrobial Agent	MIC (μg/mL)		%S/%I/%R	
	MIC_{50}	MIC_{90}	CLSI[a]	EUCAST[b]
Enterobacteriaceae (5847)[b]				
Ceftolozane/tazobactam[c]	0.25	2	91.5/1.8/6.7	–[d]/–/–
Ceftazidime	0.25	>16	82.3/3.0/14.7	78.3/4.0/17.7
Cefepime	≤0.5	>16	83.4/3.3/13.3	81.1/3.9/15.0
Ceftriaxone	0.12	>8	75.6/1.5/22.9	75.6/1.5/22.9
Piperacillin/tazobactam	2	64	86.1/5.1/8.8	81.9/4.2/13.9
Meropenem	≤0.015	0.06	97.0/0.2/2.8	97.2/1.0/1.8
Levofloxacin	≤0.12	>4	79.2/2.3/18.5	77.6/1.6/20.8
Gentamicin	≤1	>8	87.1/0.6/12.3	85.9/1.2/12.9
Tigecycline[e]	0.12	0.5	99.4/0.6/0.0	96.5/2.9/0.6
Colistin	≤0.5	>8	–/–/–	81.6/0.0/18.4
P. aeruginosa (1483)				
Ceftolozane/tazobactam[c]	0.5	4	90.9/2.4/6.7	–/–/–
Ceftazidime	2	>16	75.1/6.4/18.5	75.1/0.0/24.9
Cefepime	2	16	80.6/11.6/7.8	80.6/0.0/19.4
Meropenem	0.5	16	75.5/7.6/16.9	75.5/14.2/10.3
Piperacillin/tazobactam	4	>64	75.0/12.4/12.6	75.0/0.0/25.0
Levofloxacin	0.5	>4	71.1/6.9/22.0	63.2/7.9/28.9
Gentamicin	≤1	>8	82.1/3.3/14.6	82.1/0.0/17.9
Amikacin	2	16	91.9/3.7/4.4	86.1/5.8/8.1
Colistin	2	2	98.5/1.5/0.0	100.0/0.0/0.0
S. pneumoniae (110)				
Ceftolozane/tazobactam	0.12	2	–/–/–	–/–/–
Amoxicillin/clavulanate	≤1	≤1	95.5/0.0/4.5	–/–/–
Penicillin[e]	≤0.06	0.5	83.6/10.0/6.4	83.6/–/–
Penicillin[f]	≤0.06	0.5	95.5/4.5/0.0	83.6/11.8/4.6
Ceftriaxone[g]	≤0.06	0.25	94.5/5.5/0.0	92.7/7.3/0.0
Imipenem	≤0.12	≤0.12	92.7/7.3/0.0	100.0/0.0/0.0
Erythromycin	≤0.12	>16	85.3/0.0/14.7	85.3/0.0/14.7
Levofloxacin	1	1	99.1/0.0/0.9	99.1/0.0/0.9
Tetracycline	≤0.5	8	86.4/0.9/12.7	86.4/0.9/12.7
Tigecycline[e]	0.03	0.03	100.0/–/–	–/–/–
Trimethoprim/sulfamethoxazole	≤0.5	>4	78.2/5.4/16.4	83.6/0.0/16.4
Linezolid	1	1	100.0/–/–	100.0/0.0/0.0
Vancomycin	0.25	0.25	100.0/–/–	100.0/0.0/0.0

CLSI = Clinical and Laboratory Standards Institute; FDA = US Food and Drug Administration; I = intermediate; R = resistant; S = susceptible.
[a]Criteria as published by CLSI (2015) and EUCAST (2015).
[b]Includes: *Citrobacter amalonaticus* (5 strains), *Citrobacter braakii* (19 strains), *Citrobacter freundii* (84 strains), *Citrobacter freundii* species complex (23 strains), *Citrobacter koseri* (95 strains), *Citrobacter youngae* (1 strain), *Enterobacter aerogenes* (152 strains), *Enterobacter amnigenus* (3 strains), *Enterobacter asburiae* (11 strains), *Escherichia coli* (2536 strains), *Enterobacter cloacae* (423 strains), *Enterobacter cloacae* species complex (77 strains), *Enterobacter cancerogenus* (1 strain), *Enterobacter kobei* (3 strains), *Cronobacter sakazakii* (1 strain), *Klebsiella varricola* (6 strains), *Klebsiella oxytoca* (297 strains), *Klebsiella pneumoniae* (1208 strains), *Morganella morganii* (130 strains), *Proteus mirabilis* (359 strains), *Proteus vulgaris* (66 strains), *Providencia rettgeri* (14 strains), *Providencia stuartii* (28 strains), *Serratia fonticola* (1 strain), *Serratia liquefaciens* (25 strains), *Serratia marcescens* (275 strains), *Serratia rubidaea* (1 strain), *Serratia odorifera* (2 strains), *Serratia plymuthica* (1 strain).
[c]In the absence of CLSI breakpoint, FDA breakpoints were applied when available (Zerbaxa Product Insert, 2014).
[d]– = no breakpoint available for interpretation.
[e]In the absence of CLSI breakpoint, FDA breakpoints were applied when available (Tygacil Product Insert, 2012).
[f]Oral penicillin V breakpoints were used.
[g]CLSI parenteral (nonmeningitis) and EUCAST "infections other than meningitis" breakpoints used.

CONCLUSIONS

- Ceftolozane/tazobactam showed greater potency than ceftriaxone and currently available anti-*P. aeruginosa* cephalosporins (ceftazidime and cefepime) and piperacillin/tazobactam when tested against Enterobacteriaceae strains, including ESBL (meropenem-susceptible), from US and European hospitals during 2014
- In 2014, ceftolozane/tazobactam showed continued high potency against contemporary *P. aeruginosa* isolates consecutively collected from patients in 70 medical centers located across the 9 US census regions and from 22 countries across the European region (including Turkey and Israel)
- Ceftolozane/tazobactam in vitro activity, as with other β-lactams, varied according to *S. pneumoniae* susceptibility to penicillin
- Ceftolozane/tazobactam might represent a valuable treatment option for Gram-negative infections, including those caused by various resistant organisms. These in vitro data support the further clinical development of ceftolozane/tazobactam

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