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Antimicrobial Activity of Ceftolozane/Tazobactam and Comparator Agents Tested Against *Pseudomonas aeruginosa* Isolates From United States Medical Centers (2013)

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AMENDED ABSTRACT

BACKGROUND: Ceftolozane/tazobactam (TOL/TAZ) is a novel antibacterial with activity against *P. aeruginosa* (PSA) and most ESBL-producing Enterobacteriaceae. TOL/TAZ is currently under review by the FDA. Studies in VAP/HAP are ongoing.

METHODS: 1081 PSA isolates were consecutively collected in 2013 from 30 USA medical centers by the Program to Assess Ceftolozane/Tazobactam Susceptibility (PACTS). Susceptibility (S) testing was performed by CLSI broth microdilution methods (TOL/TAZ at a fixed 4 µg/mL of TAZ).

RESULTS: TOL/TAZ ($MIC_{50/90}$, 0.5/2 µg/mL) was 4- to 16-fold more active than ceftazidime (CAZ; $MIC_{50/90}$, 2/32 µg/mL; 84.7% S) and inhibited 98.2 and 96.4% of isolates at MIC of ≤8 and ≤4 µg/mL, respectively (Table summarizes the activities of anti-PSA agents). The highest TOL/TAZ MIC among CAZ-S strains was 8 µg/mL (99.3% inhibited at ≤2 µg/mL). TOL/TAZ inhibited 88.5% of CAZ non-S ($MIC_{50/90}$, 2/16 µg/mL) and 92.8% of meropenem (MEM) non-S ($MIC_{50/90}$, 1/8 µg/mL) PSA at ≤8 µg/mL. Among PSA strains non-S to both CAZ and MEM (85 strains), TOL/TAZ ($MIC_{50/90}$, 4/>32 µg/mL) inhibited 82.4% at ≤8 µg/mL. TOL/TAZ was also active against strains non-S to MEM, CAZ, and piperacillin/tazobactam (P/T; 84.2% inhibited at ≤8 µg/mL). At MIC ≤8 µg/mL, TOL/TAZ inhibited 89.2 and 93.7% of PSA non-S to gentamicin (GEN) and ciprofloxacin (CIP), respectively. Among PSA strains non-S to both GEN and CIP (85 strains), TOL/TAZ inhibited 87.1% at ≤8 µg/mL. Further, 82.7% (43/52) of strains non-S to CIP, GEN, and MEM had TOL/TAZ MIC of ≤8 µg/mL. Overall, the most active agents were TOL/TAZ ($MIC_{50/90}$, 0.5/2 µg/mL), colistin ($MIC_{50/90}$, 1/2 µg/mL; 99.9% S), and amikacin ($MIC_{50/90}$, 2/8 µg/mL; 96.8% S). S rates for CAZ (84.7%), cefepime (83.5%), P/T (78.5%), MEM (80.6%), doripenem (84.2%), CIP (76.6%), and GEN (88.9%) were lower than TOL/TAZ at ≤8 (98.2%) or ≤4 µg/mL (96.4%).

CONCLUSIONS: TOL/TAZ exhibited potent activity against recent USA clinical PSA and provided greater coverage than β-lactams currently available for treatment of *P. aeruginosa* infections.

Antimicrobial agent	MIC (µg/mL) 50%	90%	%S[a]	%R[a]
Ceftolozane/tazobactam	0.5	2	98.2[b]	--
Ceftazidime	2	32	84.7	11.4
Cefepime	2	16	83.5	7.2
Piperacillin/tazobactam	8	>64	78.5	11.9
Meropenem	0.5	8	80.6	13.0
Doripenem	0.5	4	84.2	7.1
Ciprofloxacin	0.12	>4	76.6	17.5
Gentamicin	≤1	8	88.9	8.4
Amikacin	2	8	96.8	2.1
Colistin	1	2	99.9	0.1

[a]According to CLSI criteria; [b]% inhibited at ≤8 µg/mL.

INTRODUCTION

- Ceftolozane is a novel oxyimino-aminothiazolyl cephalosporin with potent activity against Enterobacteriaceae (similar to other oxyimino-aminothiazolyl cephalosporins) and has demonstrated greater activity (as 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, ceftolozane's activity is compromised in bacteria-producing extended-spectrum β-lactamases (ESBLs), stably derepressed AmpC β-lactamases, and carbapenemases.

INTRODUCTION (cont'd)

- 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.
- Over the past decade, nosocomial infections caused by *P. aeruginosa* and Enterobacteriaceae in intensive care units worldwide have been increasing in prevalence, along with antimicrobial resistance; and there have been associated increases in morbidity and mortality.
- Empirical and targeted therapies to treat infections with these organisms are becoming increasingly limited.
- In Phase 3 trials
  - Ceftolozane/tazobactam demonstrated superior clinical efficacy to high-dose levofloxacin for the treatment of patients with complicated lower urinary tract infection/pyelonephritis.
  - Ceftolozane/tazobactam plus metronidazole was as efficacious as meropenem in patients with complicated intra-abdominal infection.
- A Phase 3 trial comparing ceftolozane/tazobactam with meropenem in ventilated nosocomial pneumonia is ongoing.
- In the present study, we evaluated the potency of ceftolozane/tazobactam and comparator drugs tested against a large, contemporary (2013) collection of clinically derived *P. aeruginosa* obtained from patients in United States (USA) hospitals.

MATERIALS AND METHODS

Sampling Sites and Organisms

- A total of 1081 *P. aeruginosa* isolates were consecutively collected in 2013 from 30 medical centers located across all 9 USA census regions by the Program to Assess Ceftolozane/Tazobactam Susceptibility (PACTS).
- All organisms were isolated from documented infections and only 1 strain per patient-infection episode was included in the surveillance collection.
- The isolates were derived primarily from: bloodstream infections; skin and skin-structure infections; pneumonia aspirates; and urinary tract infections; and intra-abdominal infections from hospitalized patients according to a common surveillance design.

Antimicrobial Susceptibility Testing

- Minimum inhibitory concentration (MIC) values were determined using the reference Clinical and Laboratory Standards Institute (CLSI) broth microdilution method (M07-A9). Quality control ranges and interpretive criteria for comparator compounds used the CLSI M100-S24 guidelines. The ESBL phenotype was defined as a MIC of ≥2 µg/mL for ceftazidime or ceftriaxone or aztreonam.
- To better evaluate the activities of ceftolozane/tazobactam against *P. aeruginosa*, strains were stratified by susceptibility pattern to ceftazidime and meropenem. Multidrug-resistant (MDR), extensively drug-resistant (XDR), and pandrug-resistant (PDR) bacteria were classified as such per recently recommended guidelines by Magiorakos et al (2012), using the following antimicrobial class representative agents and CLSI susceptibility MIC breakpoints: ceftazidime (≥16 µg/mL), meropenem (≥4 µg/mL), piperacillin/tazobactam (≥32/4 µg/mL), levofloxacin (≥4 µg/mL), gentamicin (≥8 µg/mL), and colistin (≥4 µg/mL).
- Classifications were based on the following recommended parameters: MDR = nonsusceptible to representative agent in ≥3 antimicrobial classes; XDR = nonsusceptible to representative agent in all but ≤2 antimicrobial classes; PDR = nonsusceptible to all antimicrobial classes.

RESULTS

Table 1. Cumulative MIC Distributions of Ceftolozane/Tazobactam Against 1081 *P. aeruginosa* Isolates, by Resistance Phenotype

Organism (n)	No. of Isolates (Cumulative %) Inhibited at Ceftolozane/Tazobactam MIC (µg/mL) 0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	>32	MIC_{50}	MIC_{90}
All *P. aeruginosa* (1081)	2 (0.2)	1 (0.3)	6 (0.8)	43 (4.8)	593 (59.7)	263 (84.0)	94 (92.7)	40 (96.4)	20 (98.2)	6 (98.8)	1 (98.9)	12 (100.0)	0.5	2
MDR (157)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	13 (8.3)	40 (33.8)	49 (65.0)	26 (81.5)	11 (88.5)	5 (91.7)	1 (92.4)	12 (100.0)	2	16
XDR (84)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.4)	11 (15.5)	28 (48.8)	16 (67.9)	11 (81.0)	5 (86.9)	0 (86.9)	11 (100.0)	4	>32
CAZ-S (916)	2 (0.2)	1 (0.3)	6 (1.0)	43 (5.7)	586 (69.7)	240 (95.9)	32 (99.3)	5 (99.9)	1 (100.0)	--	--	--	0.5	1
CAZ-NS (165)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	7 (4.2)	23 (18.2)	62 (55.8)	35 (77.0)	19 (88.5)	6 (92.1)	1 (92.7)	12 (100.0)	2	16
MEM-S (865)	2 (0.2)	1 (0.3)	6 (1.0)	43 (6.0)	538 (68.2)	192 (90.4)	56 (96.9)	14 (98.5)	9 (99.5)	2 (99.8)	1 (99.9)	1 (100.0)	0.5	1
MEM-NS (208)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	49 (23.6)	69 (56.7)	38 (75.0)	26 (87.5)	11 (92.8)	4 (94.7)	0 (94.7)	11 (100.0)	1	8
CAZ- and MEM-NS (85)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.4)	6 (9.4)	27 (41.2)	24 (69.4)	11 (82.4)	4 (87.1)	0 (87.1)	11 (100.0)	4	>32
P/T-S (848)	2 (0.2)	1 (0.4)	6 (1.1)	43 (6.1)	574 (73.8)	193 (96.6)	21 (99.1)	4 (99.5)	1 (99.7)	0 (99.7)	1 (99.8)	2 (100.0)	0.5	1
P/T-NS (232)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	19 (8.2)	69 (37.9)	73 (69.4)	36 (84.9)	19 (93.1)	6 (95.7)	0 (95.7)	10 (100.0)	2	8
CAZ-, MEM-, and P/T-NS (82)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)	6 (8.5)	27 (41.5)	24 (70.7)	11 (84.2)	4 (89.0)	0 (89.0)	9 (100.0)	4	>32
Cefepime-S (902)	2 (0.2)	1 (0.3)	6 (1.0)	43 (5.8)	587 (70.8)	229 (96.2)	29 (99.5)	2 (99.7)	2 (99.9)	0 (99.9)	1 (100.0)	-	0.5	1
Cefepime-NS (178)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (2.8)	34 (21.9)	65 (58.4)	38 (79.8)	18 (89.9)	6 (93.3)	0 (93.3)	12 (100.0)	2	16
Levofloxacin-S (814)	2 (0.3)	1 (0.4)	5 (1.0)	39 (5.8)	527 (70.5)	163 (90.5)	42 (95.7)	21 (98.3)	11 (99.6)	2 (99.9)	0 (99.9)	1 (100.0)	0.5	1
Levofloxacin-NS (267)	0 (0.0)	0 (0.0)	1 (0.4)	4 (1.9)	66 (26.6)	100 (64.1)	52 (83.5)	19 (90.6)	9 (94.0)	4 (95.5)	1 (95.9)	11 (100.0)	1	4
Gentamicin-S (960)	2 (0.2)	1 (0.3)	6 (0.9)	41 (5.2)	572 (64.8)	226 (88.3)	64 (95.0)	29 (98.0)	13 (99.4)	4 (99.8)	0 (99.8)	2 (100.0)	0.5	2
Gentamicin-NS (120)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.7)	21 (19.2)	36 (49.2)	30 (74.2)	11 (83.3)	7 (89.2)	2 (90.8)	1 (91.7)	10 (100.0)	2	16

CAZ-NS, ceftazidime-nonsusceptible; CAZ-S, ceftazidime-susceptible; MEM, meropenem; P/T, piperacillin/tazobactam.

- Ceftolozane/tazobactam was the most potent agent ($MIC_{50/90}$, 0.5/2 µg/mL) tested against 1081 *P. aeruginosa*, inhibiting 98.2% of isolates at a MIC of ≤8 µg/mL (**Table 1**).
- Ceftolozane/tazobactam was 4-fold more active than ceftazidime ($MIC_{50/90}$, 2/32 µg/mL; 84.7% susceptible) and cefepime ($MIC_{50/90}$, 2/16 µg/mL; 83.5% susceptible), 16-fold more active than piperacillin/tazobactam ($MIC_{50/90}$, 8/>64 µg/mL; 78.5% susceptible), and slightly more potent than meropenem ($MIC_{50/90}$, 0.5/8 µg/mL; 80.6% susceptible) and doripenem ($MIC_{50/90}$, 0.5/4 µg/mL; 84.2% susceptible; **Table 2**).
- After colistin ($MIC_{50/90}$, 1/2 µg/mL, 99.9% susceptible), ceftolozane/tazobactam was the most active agent ($MIC_{50/90}$, 2/16 µg/mL; 88.5% inhibited at MIC ≤8 µg/mL) tested against 157 MDR *P. aeruginosa*, with resistance for all other agents ranging from 10.2% for amikacin to 70.1% for levofloxacin (**Table 2**).
- Similarly, against 84 XDR strains, ceftolozane/tazobactam retained good activity ($MIC_{50/90}$, 4/>32 µg/mL; 81.0% inhibited at MIC ≤8 µg/mL) while resistance to other agents ranged from 15.5% for amikacin to 82.1% for levofloxacin (**Table 2**). All XDR strains remained susceptible to colistin (100.0% susceptible), while in contrast, high levels of resistance to ceftazidime (71.4% resistant), doripenem (57.1% resistant), and meropenem (78.6% resistant) were observed (**Table 2**).
- No PDR *P. aeruginosa* strains were detected.
- Ceftolozane/tazobactam had good activity against many ceftazidime-nonsusceptible ($MIC_{50/90}$, 2/16 µg/mL; 88.5% inhibited at MIC ≤8 µg/mL), meropenem-nonsusceptible ($MIC_{50/90}$, 1/8 µg/mL; 92.8% inhibited at MIC ≤8 µg/mL), piperacillin/tazobactam-nonsusceptible ($MIC_{50/90}$, 2/8 µg/mL, 93.1% inhibited at MIC ≤8 µg/mL), cefepime-nonsusceptible ($MIC_{50/90}$, 2/16 µg/mL; 89.9% inhibited at MIC ≤8 µg/mL), levofloxacin-nonsusceptible ($MIC_{50/90}$, 1/4 µg/mL; 94.0% inhibited at MIC ≤8 µg/mL), and gentamicin-nonsusceptible ($MIC_{50/90}$, 2/16 µg/mL; 89.2% inhibited at MIC ≤8 µg/mL isolates (**Table 1**).
- Ceftolozane/tazobactam also had good activity against many isolates with combined ceftazidime- and meropenem-nonsusceptibility ($MIC_{50/90}$, 4/>32 µg/mL; 82.4% inhibited at MIC ≤8 µg/mL) and combined ceftazidime- and meropenem- and piperacillin/tazobactam-nonsusceptibility ($MIC_{50/90}$, 4/>32 µg/mL; 84.2% inhibited at MIC ≤8 µg/mL; **Table 1**).

Table 2. Antimicrobial Activity of Ceftolozane/Tazobactam and Various Comparator Agents Against *P. aeruginosa* Collected in the USA During 2013

Antimicrobial Agent/Organism (No. Tested)	MIC_{50}	MIC_{90}	%Susceptible[a]	%Resistant[a]
All isolates (1081)				
Ceftolozane/tazobactam	0.5	2	-[b]	-
Ceftazidime	2	32	84.7	11.4
Cefepime	2	16	83.5	7.2
Meropenem	0.5	8	80.6	13.0
Doripenem	0.5	4	84.2	7.1
Piperacillin/tazobactam	8	>64	78.5	11.9
Aztreonam	4	>16	71.5	18.4
Ciprofloxacin	0.12	>4	76.6	17.5
Levofloxacin	0.5	>4	75.3	18.7
Amikacin	2	8	96.8	2.1
Gentamicin	≤1	8	88.9	8.4
Colistin	1	2	99.9	0.1
MDR (157)				
Ceftolozane/tazobactam	2	16	-	-
Ceftazidime	32	>32	31.9	33.8
Cefepime	16	>16	28.7	36.9
Meropenem	8	>8	17.8	61.8
Doripenem	4	>8	28.9	41.7
Piperacillin/tazobactam	>64	>64	12.7	52.9
Aztreonam	>16	>16	14.0	66.9
Ciprofloxacin	>4	>4	22.9	63.1
Levofloxacin	>4	>4	16.6	70.1
Amikacin	8	>32	84.7	10.2
Gentamicin	4	>8	51.0	41.4
Colistin	1	2	99.4	0.6
XDR (84)				
Ceftolozane/tazobactam	4	>32	-	-
Ceftazidime	32	>32	14.3	71.4
Cefepime	>16	>16	11.9	56.0
Meropenem	8	>8	7.1	78.6
Doripenem	8	>8	15.5	57.1
Piperacillin/tazobactam	>64	>64	2.4	73.8
Aztreonam	>16	>16	1.2	77.4
Ciprofloxacin	>4	>4	9.5	76.2
Levofloxacin	>4	>4	4.8	82.1
Amikacin	8	>32	77.4	15.5
Gentamicin	>8	>8	39.3	52.4
Colistin	1	2	100.0	0.0

[a]According to CLSI interpretive criteria. [b]No published interpretive criteria.

CONCLUSIONS

- In 2013, ceftolozane/tazobactam demonstrated continued high potency against contemporary *P. aeruginosa* isolates consecutively collected from 30 medical centers located across all 9 USA census regions.
- Ceftolozane/tazobactam retained clear activity against many MDR, XDR, ceftazidime-nonsusceptible, meropenem-nonsusceptible, piperacillin/tazobactam-nonsusceptible, and combined ceftazidime-, piperacillin/tazobactam-, and meropenem-nonsusceptible strains.
- These in vitro data support the further clinical development of ceftolozane/tazobactam.

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