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In vitro Antibacterial Activity of Ceftazidime-avibactam Tested against Contemporary *Pseudomonas aeruginosa* Isolates from United States Medical Centers by Census Region

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Revised Abstract

Background: Ceftazidime-avibactam (CAZ-AVI) is a novel β-lactam/non-β-lactam β-lactamase inhibitor combination for the treatment of Gram-negative bacterial infections including those caused by multidrug-resistant (MDR) isolates. The *in vitro* antibacterial activity of CAZ-AVI and comparators was evaluated against a collection of contemporary *P. aeruginosa* (PSA) isolates collected from nine Census regions in the United States (USA).

Methods: 1,743 PSA isolates were collected from 69 medical centers in the USA. MICs of CAZ-AVI and comparators were determined by broth microdilution according to CLSI guidelines. CAZ-AVI activity against MDR PSA subsets was evaluated.

Results: When compared to ceftazidime (CAZ) alone (MIC_{90}=32 µg/mL), CAZ-AVI (MIC_{90}=8 µg/mL, 89.9% inhibited at ≤4 µg/mL) was four-fold more active against 1,743 PSA isolates. Applying breakpoint interpretive criteria (footnote, Table 1), 96.3, 84.0, 83.0, and 83.0%, of PSA isolates were susceptible (S) to CAZ-AVI, CAZ, meropenem (MEM), and piperacillin/tazobactam (P/T), respectively. Against 279 CAZ non-S (NS) isolates, 76.7, 40.1, and 15.4% were S to CAZ-AVI, MEM, and P/T, respectively. Similarly, against 296 MEM-NS isolates, 81.1, 43.6, and 40.5% were S to CAZ-AVI, CAZ, and P/T. Of 144 PSA (8.3%) that were NS to CAZ, MEM, and P/T, 65.3% were S to CAZ-AVI. CAZ-AVI demonstrated the highest % of S isolates in each of the Census regions. The addition of AVI to CAZ increased the % S across regions by 7.9 to 16.3% over CAZ tested alone. Susceptibility was lowest for CAZ (79.1%) and P/T (75.2%) in the East South Central region and for MEM (77.7%) in the Mountain region. Susceptibility to β-lactams was highest (91.6-99.0%) in the West North Central region.

Conclusions: CAZ-AVI demonstrated potent *in vitro* antibacterial activity against PSA, including many isolates NS to CAZ, MEM, and P/T. In each of the nine Census regions, CAZ-AVI had the highest % of S isolates and was more active than the β-lactam comparators commonly used for the treatment of PSA infections.

Introduction

Antimicrobial resistance in Gram-negative bacilli including Enterobacteriaceae and *Pseudomonas aeruginosa* has complicated the treatment of serious nosocomial infections. β-lactam antibacterials which were once highly effective against these Gram-negative pathogens have been compromised by isolates harboring resistance due to the production of β-lactamase enzymes, along with other resistance mechanisms. The spread of β-lactamases is particularly problematic due to the potential for the acquisition of mutations that can broaden their spectrum of hydrolysis, as well as their ability to disseminate.

Ceftazidime-avibactam is the combination of the established 3rd generation cephalosporin ceftazidime, with the novel non-β-lactam β-lactamase inhibitor avibactam. Avibactam inhibits a broad range of serine β-lactamases including Ambler class A (ESBL and KPC), class C (AmpC) and some class D (OXA-48) enzymes. Thus in combination with ceftazidime, avibactam restores activity of ceftazidime against a number of clinically relevant β-lactamase-producing Gram-negative pathogens causing serious infections.

We evaluated the *in vitro* antibacterial activity and susceptibility patterns of ceftazidime-avibactam and comparator compounds against *P. aeruginosa* surveillance isolates obtained in 2014 from a variety of infection types (skin and soft tissue, urinary tract, intraabdominal, and other) from the nine Census regions within the United States (USA).

Methods

Bacterial isolates: A total of 1,743 *P. aeruginosa* isolates collected from 69 medical centers within the nine USA Census regions during 2014 were included in the International Network for Optimal Resistance Monitoring (INFORM) surveillance study.

Susceptibility testing: Broth microdilution susceptibility testing was performed according to Clinical and Laboratory Standards Institute (CLSI) guidelines (CLSI document M07-A10, 2015) using validated dry-form MIC panels produced by Thermo Fisher Scientific (Cleveland, OH, USA).

Susceptibility interpretive criteria for comparator compounds employed CLSI (M100-S25, 2015) and EUCAST (2015) breakpoint criteria, where available. The recently approved, US Food and Drug Administration (FDA) breakpoint interpretative criteria were applied for ceftazidime-avibactam. Quality control (QC) testing was performed according to CLSI (M07-A10, 2015 and M100-S25, 2015) guidelines and included the following bacterial reference strains: *Escherichia coli* ATCC 25922 and 35218, *Klebsiella pneumoniae* ATCC 700603 and *P. aeruginosa* ATCC 27853. All QC results were within published ranges.

Results

- Table 1 summarizes the results of MIC testing of ceftazidime-avibactam and comparator compounds against 1,743 *P. aeruginosa* isolates collected from 69 USA medical centers in the nine Census regions during 2014. Data presented include number of isolates tested, MIC_{50}, MIC_{90} and percentage of isolates categorized by CLSI and EUCAST interpretive criteria.
- Against *P. aeruginosa*, ceftazidime-avibactam activity ($MIC_{50/90}$, 2/8 µg/mL and 96.3% susceptible at ≤8 µg/mL) was enhanced compared to ceftazidime tested alone ($MIC_{50/90}$, 2/32 µg/mL and 84.0% susceptible at ≤8 µg/mL), and was more active than other β-lactam comparators including cefepime, meropenem and piperacillin-tazobactam (86.5, 83.0 and 83.0% susceptible, respectively; Table 1 and Figure 1).
- In each of the nine USA Census regions, *P. aeruginosa* susceptibility rates to ceftazidime-avibactam was greater than ceftazidime alone, cefepime, piperacillin-tazobactam, meropenem, ciprofloxacin, levofloxacin and gentamicin (Table 1).
- Against the 1,743 *P. aeruginosa*, the addition of avibactam to ceftazidime increased the percentage susceptibility across each of the nine USA Census regions by 7.9 to 16.3% over those rates for ceftazidime tested alone (Table 1).
- Susceptibility was lowest for ceftazidime (79.1%) and piperacillin-tazobactam (75.2%) against *P. aeruginosa* in the East South Central region (95.4% susceptible to ceftazidime-avibactam) and for meropenem (77.7%) in the Mountain region (97.0% susceptible to ceftazidime-avibactam; Table 1).
- Ceftazidime-avibactam activity against *P. aeruginosa* was lowest in the Pacific region (91.5% susceptible); however, ceftazidime-avibactam remained more active than the other comparators tested with the exceptions of amikacin and colistin (93.0 and 100.0% susceptible, respectively; Table 1 and Figure 2). Ceftazidime-avibactam activity against *P. aeruginosa* was highest in the New England region (100.0% susceptible).
- *P. aeruginosa* susceptibility to β-lactams was highest (91.6 to 99.0%) in the West North Central region (99.0% susceptible to ceftazidime-avibactam; Table 1 and Figure 2).
- Against 279 ceftazidime non-susceptible *P. aeruginosa* isolates, 76.7, 31.9, 40.1 and 15.4% were susceptible to ceftazidime-avibactam, cefepime, meropenem and piperacillin-tazobactam, respectively (Table 2 and Figure 3).
- Similarly, against 296 meropenem-non-susceptible *P. aeruginosa* isolates, 81.1, 43.6, 46.3 and 40.5% were susceptible to ceftazidime-avibactam, ceftazidime, cefepime and piperacillin-tazobactam, respectively (Table 2 and Figure 3).
- Of the 144 (8.3%) *P. aeruginosa* isolates that were non-susceptible to ceftazidime, meropenem and piperacillin-tazobactam, 94 (65.3%) were susceptible to ceftazidime-avibactam at the US-FDA breakpoint (Figure 3).

Table 1. Activity of ceftazidime-avibactam and comparator antimicrobial agents against contemporary *P. aeruginosa* isolates by USA Census region.

Antimicrobial agent / Region (no. tested)	MIC_{50}	MIC_{90}	CLSI[a] %S	CLSI[a] %I	CLSI[a] %R	EUCAST[a] %S	EUCAST[a] %I	EUCAST[a] %R
All Regions: (1,743)								
Ceftazidime-avibactam	2	8	96.3	-	3.7[b]	-	-	-
Ceftazidime	2	32	84.0	4.5	11.5	84.0	-	16.0
Cefepime	2	16	86.5	8.0	5.5	86.5	-	13.5
Piperacillin-tazobactam	4	64	83.0	8.7	8.3	83.0	-	17.0
Meropenem	0.5	8	83.0	6.1	10.9	83.0	11.6	5.3
Ciprofloxacin	0.12	>4	77.9	4.9	17.2	72.0	5.9	22.1
Levofloxacin	0.5	>4	75.2	6.4	18.5	65.3	9.8	24.8
Gentamicin	≤1	8	88.0	3.7	8.3	88.0	-	12.0
Amikacin	2	8	96.7	1.2	2.1	93.2	3.5	3.3
Colistin	2	2	99.0	1.0	0.0	100.0	-	0.0
Region 1: New England (119)								
Ceftazidime-avibactam	1	4	100.0	-	0.0[b]	-	-	-
Ceftazidime	2	32	84.0	5.9	10.1	84.0	-	16.0
Cefepime	2	16	85.7	12.6	1.7	85.7	-	14.3
Piperacillin-tazobactam	4	64	86.6	8.4	5.0	86.6	-	13.4
Meropenem	0.25	4	85.7	5.0	9.2	85.7	12.6	1.7
Ciprofloxacin	0.12	>4	75.6	5.9	18.5	72.3	3.4	24.4
Levofloxacin	0.5	>4	73.9	6.7	19.3	68.1	5.9	26.1
Gentamicin	≤1	>8	87.4	0.8	11.8	87.4	-	12.6
Amikacin	2	8	97.5	0.8	1.7	93.3	4.2	2.5
Colistin	2	2	99.2	0.8	0.0	100.0	-	0.0
Region 2: Mid-Atlantic (199)								
Ceftazidime-avibactam	2	8	96.0	-	4.0[b]	-	-	-
Ceftazidime	2	32	80.9	7.5	11.6	80.9	-	19.1
Cefepime	2	16	84.9	10.1	5.0	84.9	-	15.1
Piperacillin-tazobactam	8	>64	77.9	11.6	10.6	77.9	-	22.1
Meropenem	0.5	8	79.9	8.5	11.6	79.9	14.6	5.5
Ciprofloxacin	0.12	>4	83.9	2.5	13.6	75.9	8	16.1
Levofloxacin	0.5	>4	79.9	6.0	14.1	69.8	10.1	20.1
Gentamicin	≤1	4	91.0	4.5	4.5	91.0	-	9.0
Amikacin	2	8	99.0	0.0	1.0	96.0	3.0	1.0
Colistin	2	2	100.0	0.0	0.0	100.0	-	0.0
Region 3: East North Central (299)								
Ceftazidime-avibactam	2	4	97.3	-	2.7[b]	-	-	-
Ceftazidime	2	16	88.6	3.0	8.4	88.6	-	11.4
Cefepime	2	16	90.0	6.7	3.3	90.0	-	10.0
Piperacillin-tazobactam	4	32	86.6	7.4	6.0	86.6	-	13.4
Meropenem	0.5	8	83.3	6.4	10.4	83.3	11.4	5.4
Ciprofloxacin	0.12	>4	78.6	5.7	15.7	74.2	4.3	21.4
Levofloxacin	0.5	>4	77.9	4.7	17.4	67.6	10.4	22.1
Gentamicin	≤1	8	88.3	5.4	6.4	88.3	-	11.7
Amikacin	2	8	97.7	0.3	2.0	93.6	4.0	2.3
Colistin	2	2	98.7	1.3	0.0	100.0	-	0.0
Region 4: West North Central (191)								
Ceftazidime-avibactam	1	4	99.0	-	1.0[b]	-	-	-
Ceftazidime	2	8	91.6	3.7	4.7	91.6	-	8.4
Cefepime	2	8	93.7	4.7	1.6	93.7	-	6.3
Piperacillin-tazobactam	4	16	93.2	3.7	3.1	93.2	-	6.8
Meropenem	0.25	2	94.8	1.6	3.7	94.8	2.6	2.6
Ciprofloxacin	0.12	4	85.3	4.2	10.5	80.6	4.7	14.7
Levofloxacin	0.5	>4	83.2	5.2	11.5	73.3	9.9	16.8
Gentamicin	≤1	4	95.3	2.6	2.1	95.3	-	4.7
Amikacin	2	8	99.5	0.5	0.0	97.9	1.6	0.5
Colistin	2	2	99.0	1.0	0.0	100.0	-	0.0
Region 5: South Atlantic (266)								
Ceftazidime-avibactam	2	8	95.1	-	4.9[b]	-	-	-
Ceftazidime	2	32	82.0	5.3	12.8	82.0	-	18.0
Cefepime	4	16	83.5	7.5	9.0	83.5	-	16.5
Piperacillin-tazobactam	4	64	83.1	7.5	9.4	83.1	-	16.9
Meropenem	0.5	8	82.3	5.6	12.0	82.3	12.8	4.9
Ciprofloxacin	0.25	4	77.8	8.3	13.9	71.8	6.0	22.2
Levofloxacin	0.5	>4	74.8	7.9	17.3	62.8	12.0	25.2
Gentamicin	2	>8	85.0	3.8	11.3	85.0	-	15.0
Amikacin	4	16	91.7	3.0	5.3	86.1	5.6	8.3
Colistin	2	2	98.1	1.9	0.0	100.0	-	0.0
Region 6: East South Central (153)								
Ceftazidime-avibactam	2	8	95.4	-	4.6[b]	-	-	-
Ceftazidime	4	32	79.1	4.6	16.3	79.1	-	20.9
Cefepime	2	16	81.0	13.1	5.9	81.0	-	19.0
Piperacillin-tazobactam	4	>64	75.2	9.2	15.7	75.2	-	24.8
Meropenem	0.5	8	78.4	7.2	14.4	78.4	15.7	5.9
Ciprofloxacin	0.12	>4	77.8	3.9	18.3	69.9	7.8	22.2
Levofloxacin	0.5	>4	71.9	9.2	19.0	63.4	8.5	28.1
Gentamicin	≤1	>8	85.6	2.8	12.4	85.6	-	14.4
Amikacin	2	8	98.7	0.7	0.7	95.4	3.3	1.3
Colistin	2	2	98.7	1.3	0.0	100.0	-	0.0
Region 7: West South Central (150)								
Ceftazidime-avibactam	2	4	96.7	-	3.3[b]	-	-	-
Ceftazidime	2	32	82.7	5.3	12.0	82.7	-	17.3
Cefepime	2	16	86.7	8.0	5.3	86.7	-	13.3
Piperacillin-tazobactam	4	64	81.3	10.7	8.0	81.3	-	18.7
Meropenem	0.5	8	80.7	6.7	12.7	80.7	12.7	6.7
Ciprofloxacin	0.25	>4	68.0	4.0	28.0	62.7	5.3	32.0
Levofloxacin	0.5	>4	66.7	4.0	29.3	56.7	10.0	33.3
Gentamicin	≤1	8	88.7	2.0	9.3	88.7	-	11.3
Amikacin	2	8	96.7	2.0	1.3	94.7	2.0	3.3
Colistin	2	2	98.0	2.0	0.0	100.0	-	0.0
Region 8: Mountain (166)								
Ceftazidime-avibactam	2	8	97.0	-	3.0[b]	-	-	-
Ceftazidime	2	32	81.9	4.2	13.9	81.9	-	18.1
Cefepime	2	16	87.3	6.6	6.0	87.3	-	12.7
Piperacillin-tazobactam	4	64	79.5	13.3	7.2	79.5	-	20.5
Meropenem	0.5	8	77.7	9.6	12.7	77.7	15.7	6.6
Ciprofloxacin	0.25	>4	75.3	1.8	22.9	68.1	7.2	24.7
Levofloxacin	0.5	>4	70.5	6.0	23.5	62.7	7.8	29.5
Gentamicin	≤1	8	89.8	4.8	5.4	89.8	-	10.2
Amikacin	2	8	99.4	0.6	0.0	98.2	1.2	0.6
Colistin	2	2	100.0	0.0	0.0	100.0	-	0.0
Region 9: Pacific (200)								
Ceftazidime-avibactam	2	8	91.5	-	8.5[b]	-	-	-
Ceftazidime	2	>32	82.0	2.5	15.5	82.0	-	18.0
Cefepime	2	16	84.0	6.0	10.0	84.0	-	16.0
Piperacillin-tazobactam	4	>64	81.0	8.5	10.5	81.0	-	19.0
Meropenem	0.25	8	83.5	4.5	12.0	83.5	8.5	8.0
Ciprofloxacin	0.25	>4	74.5	6.0	19.5	68.5	6.0	25.5
Levofloxacin	0.5	>4	72.5	8.0	19.5	62.0	10.5	27.5
Gentamicin	2	>8	81.5	5.0	13.5	81.5	-	18.5
Amikacin	2	16	93.0	2.5	4.5	88.0	5.0	7.0
Colistin	1	2	100.0	0.0	0.0	100.0	-	0.0

a. Criteria as published by CLSI [2015] and EUCAST [2015]. b. Breakpoints from FDA product package insert.

Table 2. Activity of ceftazidime-avibactam and comparator agents against two resistant subgroups of *P. aeruginosa*.

Antimicrobial Agent (no. tested)	MIC_{50}	MIC_{90}	CLSI[a] %S	CLSI[a] %I	CLSI[a] %R	EUCAST[a] %S	EUCAST[a] %I	EUCAST[a] %R
Ceftazidime-non-susceptible (279)								
Ceftazidime-avibactam	4	16	76.7	-	23.3[b]	-	-	-
Cefepime	16	>16	31.9	36.2	31.9	31.9	-	68.1
Piperacillin-tazobactam	64	>64	15.4	36.6	48.0	15.4	-	84.6
Meropenem	4	32	40.1	16.1	43.7	40.1	33.3	26.5
Meropenem-non-susceptible (296)								
Ceftazidime-avibactam	4	16	81.1	-	18.9[b]	-	-	-
Ceftazidime	16	>32	43.6	13.5	42.9	43.6	-	56.4
Cefepime	16	>16	46.3	29.4	24.3	46.3	-	53.7
Piperacillin-tazobactam	32	>64	40.5	27.4	32.1	40.5	-	59.5

a. Criteria as published by CLSI [2015] and EUCAST [2015]
b. Breakpoints from FDA product package insert

Figure 2. Ceftazidime-avibactam activity stratified by USA Census Region.

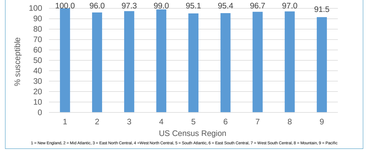


Figure 1. Ceftazidime-avibactam (CAZ-AVI) and ceftazidime (CAZ) MIC distributions for *P. aeruginosa* (n=1,743; USA 2014).

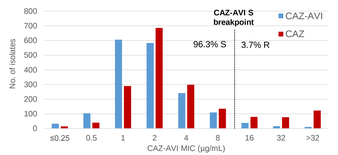
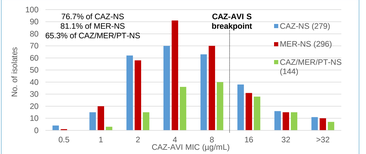


Figure 3. Ceftazidime-avibactam (CAZ-AVI) MIC distribution for resistant subsets of *P. aeruginosa* (USA 2014).



Conclusions

- Ceftazidime-avibactam consistently demonstrated the highest susceptibility rates among the β-lactam compounds commonly utilized for the treatment of serious *P. aeruginosa* infections.
- Ceftazidime-avibactam was the most active β-lactam compound tested against *P. aeruginosa* in each of the nine USA Census regions.
- Avibactam in combination with ceftazidime against *P. aeruginosa* increased the percent susceptibility across each of the nine Census regions by 7.9 to 16.3% over ceftazidime alone and by 4.2 to 19.3% over meropenem.
- Ceftazidime-avibactam demonstrated potent *in vitro* activity against *P. aeruginosa*, including isolates non-susceptible to ceftazidime, meropenem, and piperacillin-tazobactam responsible for serious infections. The results of this surveillance study reinforce clinical data for ceftazidime-avibactam activity against ceftazidime-non-susceptible *P. aeruginosa*.

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