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Activity of Ceftazidime-Avibactam Tested against Clinical Isolates of Antimicrobial Resistant *Pseudomonas aeruginosa* from United States Medical Centers (2012-2014)

HS SADER, DJ FARRELL, RK FLAMM, RN JONES
JMI Laboratories, North Liberty, Iowa, USA

Helio S. Sader, MD, PhD
JMI Laboratories
North Liberty, IA, USA
www.jmilabs.com
ph. 319.665.3370
fax 319.665.3371
helio-sader@jmilabs.com

Abstract

Background: Avibactam (AVI) is a non-β-lactam β-lactamase (BL) inhibitor that inhibits ESBLs, KPCs, AmpCs and some OXA enzymes. Ceftazidime (CAZ)-AVI was approved by the USA-FDA for treatment of intra-abdominal and urinary tract infections in 2015, and is under clinical development for treatment of pneumonia.

Methods: 5,643 PSA isolates (one per patient) were consecutively collected in 2012-2014 from 74 USA medical centers (37 states from all 9 census regions) by the INFORM Surveillance Program. CAZ-AVI (AVI at fixed 4 μg/mL) and comparators were tested for susceptibility (S) by CLSI broth microdilution methods. The isolates were predominantly from pneumonia (39.8%) and skin/soft tissue (23.7%).

Results: CAZ-AVI was active against 96.7% of strains at the USA-FDA S breakpoint of ≤8 μg/mL (Table), while S rates for CAZ, cefepime, piperacillin-tazobactam (P/T) and meropenem (MEM) were 83.8, 84.5, 79.9 and 82.3%, respectively. Colistin (COL) and amikacin (AMK) and were active against 99.2 and 97.2% of PSA strains, respectively. High rates of cross-resistance was observed among CAZ, P/T and MEM, whereas CAZ-AVI exhibited good activity against isolates non-S to CAZ (79.6% S), P/T (84.3% S), MEM (84.8%), as well as isolates non-S to CAZ, P/T and MEM (n=610; $MIC_{50/90}$, 8/32 μg/mL; 76.6% S). Multidrug-resistant (MDR) and extensively drug-resistant (XDR) phenotypes were observed in 14.9 and 8.6% of strains, respectively. Among MDR and XDR PSA, 79.8 and 71.5% were CAZ-AVI-S, respectively, while S rates for CAZ, P/T and MEM were ≤21.8% for MDR and ≤9.2% for XDR strains. The most active compounds tested against MDR/XDR strains were COL (98.9/99.0% S), AMK (88.0/83.8% S) and CAZ-AVI (78.9/71.5% S). CAZ-AVI activity remained stable during the study period.

Conclusions: CAZ-AVI exhibited potent *in vitro* activity and spectrum when tested against a large collection (n=5,643) of recent USA PSA clinical strains, and retained activity against isolates non-S to other anti-PSA β-lactams, as well as MDR and XDR strains.

Subset (no.)	MIC_{50}/MIC_{90} in μg/mL (% S)				
	CAZ-AVI	CAZ	P/T	MEM	AMK
All (5,643)	2 / 4 (96.7)	2 / 32 (83.8)	4 / >64 (79.9)	0.5 / 8 (82.3)	2 / 8 (97.2)
CAZ-NS (912)	4 / 16 (79.6)	--	>64 / >64 (7.8)	4 / >8 (44.1)	4 / 16 (90.9)
P/T-NS (1,133)	4 / 16 (84.3)	32 / >32 (25.8)	--	4 / >8 (46.0)	4 / 16 (92.3)
MEM-NS (996)	4 / 16 (84.8)	16 / >32 (48.9)	32 / >64 (38.8)	--	4 / 16 (91.3)
MDR (841)	4 / 16 (79.8)	32 / >32 (21.8)	>64 / >64 (11.1)	8 / >8 (21.2)	4 / 32 (88.0)
XDR (488)	8 / 32 (71.5)	32 / >32 (9.2)	>64 / >64 (3.7)	8 / >8 (6.4)	8 / >32 (83.8)
2012 (1,966)	2 / 4 (96.9)	2 / 32 (83.2)	8 / >64 (78.3)	0.5 / 8 (82.0)	2 / 8 (97.5)
2013 (1,935)	2 / 4 (96.8)	2 / 32 (84.3)	8 / >64 (78.7)	0.5 / 8 (81.9)	2 / 8 (97.3)
2014 (1,742)	2 / 4 (96.3)	2 / 32 (84.0)	4 / 64 (83.0)	0.5 / 8 (83.1)	2 / 8 (96.8)

Introduction

Ceftazidime-avibactam is the combination of the established third-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. In combination with ceftazidime, avibactam restores activity of ceftazidime against a number of clinically relevant β-lactamase-producing Gram-negative pathogens causing serious infections.

Ceftazidime-avibactam has been approved by the United States (US) Food and Drug Administration (FDA) for the treatment of complicated intra-abdominal infections (cIAI), in combination with metronidazole, as well as complicated urinary tract infections (cUTI), including pyelonephritis, in patients with limited or no alternative treatment options. Two phase 3 clinical trials have recently been completed (http://clinicaltrials.gov). Clinical trial NCT01726203 compared ceftazidime-avibactam plus metronidazole versus meropenem for the treatment of cIAI, and clinical trial NCT01644643 compared ceftazidime-avibactam versus best available therapy for the treatment of both cUTI and cIAI caused by ceftazidime-resistant Gram-negative organisms. Ceftazidime-avibactam is also under clinical development for treatment of nosocomial pneumonia (NCT01808092). We evaluated the *in vitro* activity of ceftazidime-avibactam against contemporary (2012-2014) isolates of *Pseudomonas aeruginosa* from US medical centers.

Methods

Bacterial isolates: A total 5,643 *P. aeruginosa* isolates (one per patient episode) were consecutively collected from 74 USA medical centers (37 states from all 9 census regions) between January 2012 and December 2014 as part of the International Network for Optimal Resistance Monitoring (INFORM) program. Only bacterial isolates determined to be significant by local criteria as the reported probable cause of an infection were included in this investigation. Species identification was confirmed when necessary by Matrix-Assisted Laser Desorption Ionization-Time Of Flight mass spectrometry (MALDI-TOF MS) using the Bruker Daltonics MALDI Biotyper (Billerica, Massachusetts, US) by following manufacturer instructions.

Isolates were categorized as multidrug-resistant (MDR), extensively drug-resistant (XDR) and pan drug-resistant (PDR) according to criteria published by Magiorakos *et al.* (2012); i.e. MDR = non-susceptible (NS) to ≥1 agent in ≥3 antimicrobial classes, XDR = NS to ≥1 agent in all but ≤2 antimicrobial classes, and PDR = NS to all antimicrobial classes tested. Class representatives (NS criteria) used in the analysis were 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).

Antimicrobial susceptibility testing: All isolates were tested for susceptibility using the reference broth microdilution method as described by the Clinical and Laboratory Standards Institute (CLSI). Ceftazidime was combined with avibactam at a fixed concentration of 4 μg/mL. Ceftazidime-avibactam breakpoints approved by the US-FDA (≤8/4 μg/mL for susceptible and ≥16/4 μg/mL for resistant) when testing *P. aeruginosa* were applied. Susceptibility interpretations for comparator agents were those found in CLSI document M100-S26, EUCAST breakpoints and/or US-FDA package insert. Quality control (QC) was performed using *Escherichia coli* ATCC 25922 and 35218, *Klebsiella pneumoniae* ATCC 700603 and BAA 1705, and *P. aeruginosa* ATCC 27853.

Results

- The *P. aeruginosa* isolates were predominantly from pneumonia (39.8%) and skin/soft tissue (23.7%; Figure 1).
- Ceftazidime-avibactam inhibited 96.7% of isolates at the US-FDA susceptible breakpoint of ≤8 μg/mL and MIC_{50} and MIC_{90} values were 2 and 4 μg/mL, respectively. Susceptibility rates for ceftazidime ($MIC_{50/90}$, 2/32 μg/mL), cefepime ($MIC_{50/90}$, 2/16 μg/mL), piperacillin-tazobactam ($MIC_{50/90}$, 4/>64 μg/mL) and meropenem ($MIC_{50/90}$, 0.5/8 μg/mL) were 83.8, 84.5, 79.9 and 82.3%, respectively (Tables 1 and 2, and Figures 2 and 3).
- The addition of avibactam to ceftazidime increased the percentage of susceptible *P. aeruginosa* isolates from 83.8% to 96.7% (Table 2 and Figure 3).
- Among non-β-lactam agents, colistin ($MIC_{50/90}$, 1/2 μg/mL and 99.2% susceptible) and amikacin ($MIC_{50/90}$, 2/8 μg/mL and 97.2% susceptible) were the most active compounds (Table 2).
- High rates of cross-resistance were observed for ceftazidime, meropenem and piperacillin-tazobactam. Among piperacillin-tazobactam-non-susceptible isolates, only 46.0 and 25.8% were susceptible to meropenem and ceftazidime, respectively. Furthermore, only 38.8 and 48.9% of meropenem-non-susceptible isolates were susceptible to piperacillin-tazobactam and ceftazidime, respectively (data not shown). In contrast, ceftazidime-avibactam exhibited good activity against isolates non-susceptible to ceftazidime (79.6% susceptible), piperacillin-tazobactam (84.3% susceptible) and meropenem (84.8% susceptible; Tables 1 and 2 and Figure 2).
- Ceftazidime-avibactam was active against 69.8% of *P. aeruginosa* isolates that were non-susceptible to ceftazidime, piperacillin-tazobactam and meropenem (n=474; $MIC_{50/90}$, 8/32 μg/mL; Tables 1 and 2 and Figure 2).
- MDR and XDR phenotypes were observed in 14.9 and 8.6% of isolates, respectively. Among MDR and XDR *P. aeruginosa*, 79.8 and 71.5% were susceptible to ceftazidime-avibactam, respectively; while susceptibility rates for ceftazidime, piperacillin-tazobactam and meropenem were ≤21.8% for MDR and ≤9.2% for XDR strains (Table 2 and Figure 2).
- The most active compounds tested against MDR and XDR strains were colistin (98.9 to 99.0% susceptible), amikacin (83.8 to 88.0% susceptible) and ceftazidime-avibactam (71.5 to 79.8% susceptible; Table 2).

Table 2. Activity of ceftazidime-avibactam and comparator antimicrobial agents when tested against *P. aeruginosa* isolates from USA hospitals.

Antimicrobial Agent/no.	MIC_{50}	MIC_{90}	CLSI[a] %S	CLSI[a] %R
All isolates (5,643)				
Ceftazidime-avibactam	2	4	96.7	3.3[b]
Ceftazidime	2	32	83.8	12.3
Cefepime	2	16	84.5	7.2
Piperacillin-tazobactam	4	>64	79.9	11.2
Meropenem	0.5	8	82.3	11.9
Ciprofloxacin	0.12	>4	77.3	17.7
Gentamicin	≤1	8	88.6	8.0
Amikacin	2	8	97.2	1.6
Colistin	1	2	99.2	<0.1
Non-susceptible to CAZ and MEM and PT (474)				
Ceftazidime-avibactam	8	32	69.8	30.2
Ceftazidime	32	>32	0.0	18.8
Cefepime	>16	>16	13.3	52.3
Meropenem	8	>8	0.0	80.0
Piperacillin-tazobactam	>64	>64	0.0	73.0
Ciprofloxacin	>4	>4	23.6	67.9
Gentamicin	4	>8	54.9	38.2
Amikacin	4	32	88.0	7.2
Colistin	1	2	99.2	0.2
MDR (841)				
Ceftazidime-avibactam	4	16	79.8	20.2[b]
Ceftazidime	32	>32	21.8	61.1
Cefepime	16	>16	25.0	39.1
Meropenem	8	>8	21.2	60.3
Piperacillin-tazobactam	>64	>64	11.1	55.6
Ciprofloxacin	>4	>4	20.2	69.6
Gentamicin	4	>8	51.0	39.8
Amikacin	4	32	88.0	7.5
Colistin	1	2	98.9	0.2
XDR (488)				
Ceftazidime-avibactam	8	32	71.5	28.5[b]
Ceftazidime	32	>32	9.2	73.8
Cefepime	>16	>16	13.7	51.8
Meropenem	8	>8	6.4	76.6
Piperacillin-tazobactam	>64	>64	3.7	68.0
Ciprofloxacin	>4	>4	7.4	83.4
Gentamicin	>8	>8	37.1	53.3
Amikacin	8	>32	83.8	10.2
Colistin	1	2	99.0	0.2

a. Criteria as published by CLSI [2016] and/or US-FDA
b. Breakpoints from US-FDA Package Insert

Abbreviations: CAZ = ceftazidime, MEM = meropenem, PT = piperacillin-tazobactam, MDR = multidrug-resistant and XDR = extensively drug-resistant

Table 1. Summary of ceftazidime-avibactam activity tested against *P. aeruginosa* isolates from United States hospitals (2012-2014).

Organism group/(no. tested)	No. of *P. aeruginosa* isolates (cumulative %) inhibited at ceftazidime-avibactam MIC (μg/mL) of:										
	≤0.25	0.5	1	2	4	8	16	32	>32	MIC_{50}	MIC_{90}
All isolates (5643)	93 (1.6)	298 (6.9)	2128 (44.6)	1800 (76.5)	805 (90.8)	332 (**96.7**)[a]	112 (98.7)	39 (99.4)	36 (100.0)	2	4
CAZ-NS (MIC, ≥16 mg/L) (912)	2 (0.2)	3 (0.5)	56 (6.7)	211 (29.8)	251 (57.3)	203 (**79.6**)	111 (91.8)	39 (96.1)	36 (100.0)	4	16
MEM-NS (MIC, ≥ 8 mg/L) (996)	1 (0.1)	8 (0.9)	82 (9.1)	230 (32.2)	309 (63.3)	215 (**84.8**)	85 (93.4)	33 (96.7)	33 (100.0)	4	16
PT-NS (MIC, ≥ 32 mg/L) (1133)	2 (0.2)	7 (0.8)	77 (7.6)	243 (29.0)	349 (59.8)	277 (**84.3**)	107 (93.7)	38 (97.1)	33 (100.0)	4	16
NS to CAZ and MEM and PT (474)		1 (0.2)	7 (1.7)	60 (14.3)	123 (40.3)	140 (**69.8**)	81 (86.9)	32 (93.7)	30 (100.0)	8	32
MDR (841)	3 (0.4)	5 (1.0)	43 (6.1)	162 (25.3)	243 (54.2)	215 (**79.8**)	98 (91.4)	37 (95.8)	35 (100.0)	4	16
XDR (488)		2 (0.4)	11 (2.7)	67 (16.4)	126 (42.2)	143 (**71.5**)	73 (86.5)	32 (93.0)	34 (100.0)	8	32
PDR (1)									1 (100.0)	--	--

a. Values in bold indicates percentage susceptible by US-FDA criteria.

Abbreviations: CAZ = ceftazidime, MEM = meropenem, PT = piperacillin-tazobactam, NS = non-susceptible, MDR = multidrug-resistant, XDR = extensively drug-resistant, and PDR pan drug-resistant.

Figure 1. Distribution of *P. aeruginosa* isolates by site of infection.

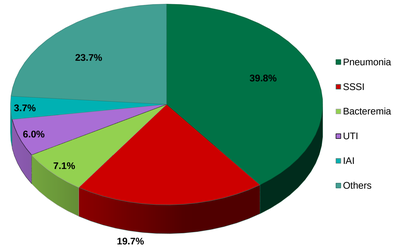
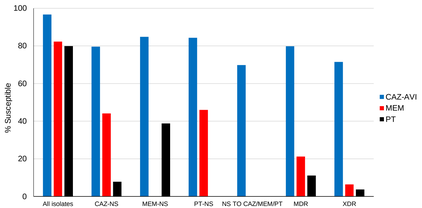
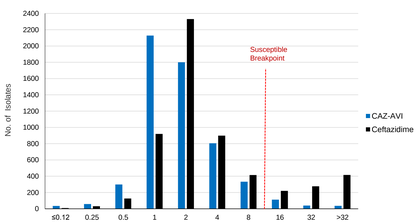


Figure 2. Antimicrobial susceptibility rates of *P. aeruginosa* resistance subsets for ceftazidime-avibactam (CAZ-AVI), meropenem (MEM) and piperacillin-tazobactam (PT).



Abbreviations: CAZ = ceftazidime, NS = non-susceptible; MEM = meropenem, PT = piperacillin-tazobactam, MDR = multidrug-resistant and XDR = extensively drug-resistant

Figure 3. MIC distributions for ceftazidime-avibactam (CAZ-AVI) and ceftazidime when testing 5,643 *P. aeruginosa* isolates from USA hospitals (2012-2014).



Conclusions

- Ceftazidime-avibactam exhibited potent *in vitro* activity and spectrum when tested against a large collection (n=5,643) of recent clinical isolates of *P. aeruginosa* from USA medical centers.
- The addition of avibactam to ceftazidime increased the overall coverage from 83.8% for ceftazidime alone to 96.7% for ceftazidime-avibactam.
- Ceftazidime-avibactam retained activity against isolates non-susceptible to other anti-*P. aeruginosa* β-lactams, as well as MDR and XDR strains.

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