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Ceftazidime-Avibactam Activity when Tested against Gram-negative Bacteria Isolated from Patients With Pneumonia, Including Ventilator-Associated Pneumonia (VAP), Hospitalized in United States Medical Centers (2011-2015)

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Amended Abstract

Background: Ceftazidime-avibactam (CAZ-AVI) consists of CAZ combined with the β-lactamase (BL) inhibitor AVI, a non-β-lactam inhibitor that inhibits Ambler classes A (eg, ESBL and KPC), C and some D enzymes.

Methods: 11,185 Gram-negative (GN) organisms (1/patient) were collected from 76 USA medical centers during 2011-2015 from patients hospitalized with pneumonia (PHP), including VAP (n=1,097). Susceptibility (S) testing was performed for CAZ-AVI (AVI at fixed 4 µg/mL) and comparators by reference broth microdilution methods. Enterobacteriaceae (ENT) with an ESBL-phenotype were evaluated for the presence of genes encoding ESBLs, KPC, NDM and transferable AmpC enzymes using a microarray-based assay.

Results: An ESBL-phenotype was observed among 19.2, 19.2 and 12.2% of *E. coli* (EC), *Klebsiella* spp. (KSP) and *P. mirabilis* (PM), respectively. CAZ-AVI inhibited 99.9% of all ENT at the S breakpoint of ≤8 µg/mL, and was highly active against KSP, including ESBL-phenotype (n=433; $MIC_{50/90}$, 0.25/1 µg/mL; 99.5% S), carbapenem-resistant (R) ENT (CRE, n=189; $MIC_{50/90}$, 0.5/2 µg/mL; 98.0% S), multidrug-R ENT (n=674; $MIC_{50/90}$, 0.5/2 µg/mL; 98.8% S) and extensively drug-R ENT (n=156; $MIC_{50/90}$, 0.5/2 µg/mL; 98.1% S). Only 59.8% of ESBL-phenotype *K. pneumoniae* were meropenem (MEM)-S. Among *E. cloacae* (26.8% CAZ-non-S), 99.9% of isolates, including 99.6% of CAZ-non-S strains, were CAZ-AVI-S. Only 8 of 6,209 ENT (0.1%) were CAZ-AVI-non-S (3 NDM-1 producing strains with CAZ-AVI MIC values of >32 µg/mL and 5 isolates with CAZ-AVI MIC values of 16 µg/mL and negative results for all BL tested). CAZ-AVI was very active against *P. aeruginosa* (PSA, n=3,402; $MIC_{50/90}$, 2/4 µg/mL; 96.6% S), including isolates non-S to MEM (86.3% S to CAZ-AVI) or piperacillin-tazobactam (PT; 85.6% S) or CAZ (80.6% S). Further, 69.9% of PSA isolates non-S to MEM, PT and CAZ were CAZ-AVI-S. S rates among isolates from VAP were generally similar or slightly higher compared to those from all PHP. No substantial yearly variation of S rates was noted.

Conclusions: CAZ-AVI demonstrated potent activity against a large collection of contemporary (2011-2015) GN bacilli isolated from PHP in USA hospitals, including those from VAP, and provided greater coverage than agents currently available in the USA.

Introduction

Pneumonia represents the second most common infection in hospitalized patients and the initial antimicrobial management of patients with pneumonia is driven mainly by the understanding of causative pathogens. Although *Staphylococcus aureus* is a significant cause of pneumonia in hospitalized patients, the importance of Gram-negative organisms such as *Pseudomonas aeruginosa* and Enterobacteriaceae species, mainly *Klebsiella pneumoniae*, *Enterobacter* spp. and *Escherichia coli*, has increased substantially in recent years.

Avibactam is a member of a novel class of non-β-lactam β-lactamase inhibitors, the diazabicyclooctanes (DBOs). Compared to currently available inhibitors for clinical use, DBOs are more potent, have a broader spectrum and a different mechanism of action. Avibactam effectively inactivates class A (including KPC), class C (AmpC), and some D (OXA) β-lactamases, with low IC_{50} (concentration resulting in 50% inhibition) values and low turnover numbers.

Ceftazidime-avibactam has been approved by the United States (USA) Food and Drug Administration (FDA) for the treatment of complicated intra-abdominal and complicated urinary tract infections, including pyelonephritis, in patients with limited or no alternative treatment options (AVYCAZ®, 2015). Ceftazidime-avibactam is also approved for treatment of nosocomial pneumonia in Europe. In this study, we evaluated the activity of ceftazidime combined with avibactam when tested against a large collection of contemporary clinical isolates recovered from patients hospitalized with pneumonia in USA medical centers in 2011-2015.

Methods

Bacterial isolates: Isolates were collected from 76 medical centers distributed among 37 states from all nine USA Census Regions in 2011-2015 as part of the International Network for Optimal Resistance Monitoring (INFORM) program. Each participant center was requested to collect consecutive bacterial isolates from lower respiratory tract sites determined to be significant by local criteria as the reported probable cause of pneumonia. Only isolates from invasive sampling (transtracheal aspiration, bronchoalveolar lavage, protected brush samples, qualified sputum samples, etc.) were accepted. Although all bacterial species were collected, the INFORM Program only evaluates the antimicrobial susceptibility of Enterobacteriaceae, *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. Therefore, the frequency of occurrence of organisms causing PHP described in the results section was based on all organisms collected from PHP in the same participant medical centers in 2015 (n=5,417, including 543 from VAP). Species identification was confirmed by standard biochemical tests and using the MALDI Biotyper (Bruker Daltonics, Billerica, Massachusetts, USA) according to the manufacturer instructions, where necessary.

Susceptibility testing: Broth microdilution test methods conducted according to the Clinical and Laboratory Standards Institute (CLSI) were performed to determine the antimicrobial susceptibility of ceftazidime-avibactam (inhibitor at fixed concentration of 4 µg/mL) and comparator agents. Concurrent quality control (QC) testing was performed to assure proper test conditions and procedures. QC strains included: *Escherichia coli* ATCC 25922 and 35218 and *Pseudomonas aeruginosa* ATCC 27853. All QC results were within published ranges. CLSI susceptibility interpretive criteria (M100-S26) were used to determine susceptibility/resistance rates for comparator agents, and US-FDA breakpoint criteria were applied for ceftazidime-avibactam when testing Enterobacteriaceae and *P. aeruginosa*, i.e. susceptible at ≤8 µg/mL and resistant at ≥16 µg/mL.

Resistant subsets: An ESBL-screen-positive phenotype was defined according to the CLSI, i.e. a MIC of ≥2 µg/mL for ceftazidime and/or ceftriaxone and/or aztreonam. Carbapenem-resistant Enterobacteriaceae (CRE) was defined as resistant (MIC, ≥4 µg/mL [CLSI]) to imipenem (excluding *Proteus mirabilis* and indole-positive Proteeae), meropenem or doripenem. Further, isolates were categorized as multidrug-resistant (MDR), extensively drug-resistant (XDR) or pan drug-resistant (PDR) according to criteria published by Magiorakos *et al.* (2012).

Screening for β-lactamases. All *E. coli* and *Klebsiella* spp. isolates displaying the CLSI ESBL phenotypic criteria as described above were tested for β-lactamase-encoding genes using the microarray based assay Check-MDR CT101 kit (Check-points, Wageningen, Netherlands). The assay was performed according to the manufacturer's instructions. This kit has the capabilities to detect CTX-M Groups 1, 2, 8+25 and 9, TEM wild-type (WT) and ESBL, SHV WT and ESBL, ACC, ACT/MIR, CMYII, DHA, FOX, KPC and NDM-1.

Results

- The frequency of occurrence of organisms isolated from patients hospitalized with pneumonia (PHP) and those with VAP are shown in Figure 1. The five most common organisms in both groups were (% of total, PHP/VAP): *S. aureus* (29.8/27.1%), *P. aeruginosa* (20.9/22.7%), *Klebsiella* spp. (9.9/11.8%), *E. coli* (6.6/9.0%) and *Enterobacter* spp. (6.4/6.8%). Overall, Gram-negative organisms were isolated from 66.0% of patients, including 70.5% of those with VAP.
- Ceftazidime-avibactam was very active against *P. aeruginosa* (n=3,402; $MIC_{50/90}$, 2/4 µg/mL; 96.6% susceptible), including isolates non-susceptible to meropenem (86.3% susceptible to ceftazidime-avibactam) or piperacillin-tazobactam (85.6% susceptible) or ceftazidime (80.6% susceptible; Tables 1 and 2).
- Furthermore, ceftazidime-avibactam retained potent *in vitro* activity against *P. aeruginosa* isolates with MDR ($MIC_{50/90}$, 4/16 µg/mL; 82.7% susceptible) and XDR phenotypes ($MIC_{50/90}$, 8/32 µg/mL; 76.2% susceptible), as well as isolates non-susceptible to meropenem, piperacillin-tazobactam and ceftazidime ($MIC_{50/90}$, 8/32 µg/mL; 69.9% susceptible; Table 1 and Figure 2).
- Ceftazidime-avibactam inhibited 99.9% of all Enterobacteriaceae at the susceptible breakpoint of ≤8 µg/mL (Table 2), and was highly active against CRE, n=189; $MIC_{50/90}$, 0.5/2 µg/mL; 97.9% susceptible), MDR (n=674; $MIC_{50/90}$, 0.25/1 µg/mL; 98.8% susceptible) and XDR isolates (n=156; $MIC_{50/90}$, 0.5/2 µg/mL; 98.1% susceptible; Table 1 and Figure 3).
- An ESBL-phenotype was observed among 19.2, 19.2 and 12.2% of *E. coli*, *Klebsiella* spp. and *P. mirabilis*, respectively; and ceftazidime-avibactam retained potent *in vitro* activity against these organisms (Table 1).
- Ceftazidime-avibactam inhibited 99.5% of ESBL-phenotype *K. pneumoniae* (n=371; $MIC_{50/90}$, 0.25/1 µg/mL) isolates; whereas only 59.8% of these organisms were susceptible to meropenem ($MIC_{50/90}$, ≤0.06/>8 µg/mL). In addition, 98.7% of meropenem-non-susceptible *K. pneumoniae* (n=150; $MIC_{50/90}$, 0.5/2 µg/mL) isolates were susceptible to ceftazidime-avibactam (Table 1 and Figure 4).
- Among *E. cloacae* (26.8% ceftazidime-non-susceptible), 99.9% of isolates, including 99.6% of ceftazidime-non-susceptible strains, were ceftazidime-avibactam-susceptible (data not shown).
- Only 8 of 6,209 Enterobacteriaceae (0.1%) were ceftazidime-avibactam-non-susceptible (3 NDM-1 producing strains with ceftazidime-avibactam MIC values of >32 µg/mL and 5 isolates with ceftazidime-avibactam MIC values of 16 µg/mL and negative results for all β-lactamases tested (data not shown).
- Susceptibility rates among isolates from VAP were generally similar or slightly higher compared to those from all PHP (Table 2), and no substantial yearly variation of susceptibility rates was noted (data not shown).

Figure 1. Frequency of occurrence of organisms isolated from patients hospitalized with pneumonia.

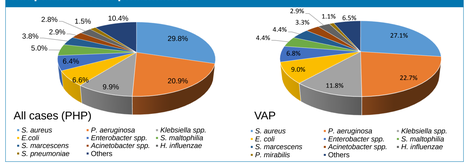


Table 1. Summary of ceftazidime-avibactam activity (MIC distributions) when tested against the main Gram-negative organisms isolated from patients hospitalized with pneumonia in United States medical centers (2011-2015).

Organism/subset (no. of isolates)	No. of isolates (cumulative %) inhibited at ceftazidime-avibactam MIC (µg/mL) of:											MIC (µg/mL)	
	≤0.06	0.12	0.25	0.5	1	2	4	8	16	32	>32	50%	90%
P. aeruginosa (3,402)			96 (2.8)	221 (9.3)	1,152 (43.2)	1,108 (75.7)	503 (90.5)	206 (96.6)[a]	68 (98.6)	19 (99.1)	29 (100.0)	2	4
MEM-NS (710)			2 (0.3)	7 (1.3)	69 (11.0)	177 (35.9)	221 (67.0)	137 (86.3)	53 (93.8)	17 (96.2)	27 (100.0)	4	16
P/T-NS (743)			2 (0.3)	12 (1.9)	63 (10.4)	176 (34.1)	229 (64.9)	154 (85.6)	61 (93.8)	18 (96.2)	28 (100.0)	4	16
CAZ-NS (599)			2 (0.3)	7 (1.5)	52 (10.2)	146 (34.6)	170 (62.9)	106 (80.6)	98 (92.0)	19 (95.2)	29 (100.0)	4	16
MDR (613)			4 (0.7)	6 (1.6)	46 (9.1)	140 (32.0)	173 (60.2)	138 (82.7)	60 (92.5)	18 (95.4)	28 (100.0)	4	16
XDR (365)			1 (0.3)	3 (1.1)	18 (6.0)	61 (22.7)	97 (49.3)	98 (76.2)	44 (88.2)	16 (92.6)	27 (100.0)	8	32
Enterobacteriaceae (6,209)	2,264 (36.5)	2,218 (72.2)	1,091 (89.8)	428 (96.7)	144 (99.0)	40 (99.6)	12 (99.8)	4 (99.9)	5 (>99.9)	0 (>99.9)	3 (100.0)	0.12	0.5
CRE (189)	11 (5.8)	13 (12.7)	25 (25.9)	55 (55.0)	58 (85.7)	19 (95.8)	3 (97.4)	1 (97.9)	1 (98.4)	0 (98.4)	3 (100.0)	0.5	2
MDR (674)	126 (18.7)	115 (35.8)	125 (54.3)	156 (77.4)	103 (92.7)	30 (97.2)	7 (98.2)	4 (98.8)	5 (99.6)	0 (99.6)	3 (100.0)	0.25	1
XDR (156)	10 (6.4)	9 (12.3)	18 (23.7)	48 (54.5)	48 (85.3)	12 (96.2)	2 (96.2)	3 (98.1)	1 (98.7)	0 (98.1)	2 (100.0)	0.5	2
Klebsiella spp. (2,260)	916 (40.5)	818 (76.7)	292 (89.6)	146 (96.1)	61 (98.8)	21 (99.7)	3 (99.9)	1 (99.9)	0 (99.9)	0 (99.9)	2 (100.0)	0.12	0.5
ESBL (433)	53 (12.2)	98 (34.9)	96 (57.0)	99 (79.9)	60 (93.8)	21 (98.6)	3 (99.3)	1 (99.5)	0 (99.5)	0 (99.5)	2 (100.0)	0.25	1
MEM-NS KPN (150)	10 (6.7)	11 (14.0)	19 (26.7)	44 (56.0)	45 (86.0)	17 (97.3)	2 (98.7)	0 (98.7)	0 (98.7)	0 (98.7)	2 (100.0)	0.5	2
Enterobacter spp. (1,304)	211 (16.2)	551 (58.4)	341 (84.6)	132 (94.7)	54 (98.8)	7 (99.4)	6 (99.8)	0 (99.8)	2 (100.0)	--	--	0.12	0.5
CAZ-NS (324)	12 (4.6)	40 (17.0)	100 (47.8)	105 (80.2)	49 (95.4)	7 (97.5)	6 (99.4)	0 (99.4)	2 (100.0)	--	--	0.25	1
E. coli (1,222)	621 (50.8)	423 (85.4)	139 (96.8)	27 (99.0)	9 (99.8)	2 (99.9)	0 (99.9)	0 (99.9)	0 (99.9)	0 (99.9)	1 (100.0)	0.12	0.25

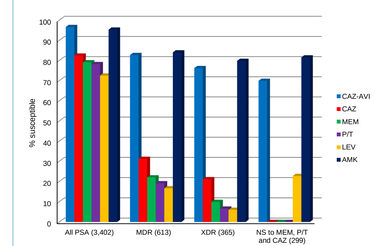
a. Value in bold indicates susceptibility rate.
Abbreviations: MEM-NS = meropenem-non-susceptible (MIC, ≥4 µg/mL for *P. aeruginosa* and ≤2 µg/mL for Enterobacteriaceae; P/T-NS = piperacillin-tazobactam-non-susceptible (MIC, ≥16 µg/mL for *P. aeruginosa* and Enterobacteriaceae; CAZ-NS = ceftazidime-non-susceptible (MIC, ≥16 µg/mL for *P. aeruginosa* and ≥8 µg/mL for Enterobacteriaceae; CRE = carbapenems-resistant Enterobacteriaceae; MDR = multidrug-resistant; XDR = extensive-drug resistant; ESBL = extended-spectrum β-lactamase phenotype (ESBL-screen-positive phenotype).

Table 2. Activity of ceftazidime-avibactam and comparator antimicrobial agents when tested against Gram-negative organisms isolated from patients hospitalized with pneumonia (USA, 2011-2015).

Antimicrobial Agent	MIC_{50}	MIC_{90}	CLSI[a] %S	CLSI[a] %I	CLSI[a] %R
P. aeruginosa (all cases; 3,402)					
Ceftazidime-avibactam[b]	2	4	96.6	-	3.4[b]
Ceftazidime	2	32	82.4	4.6	13.0
Cefepime	4	16	83.4	10.0	6.6
Piperacillin-tazobactam	4	>64	78.2	10.6	11.3
Meropenem	0.5	8	79.1	7.0	13.9
Imipenem	1	8	71.9	9.4	18.8
Levofloxacin	0.5	>4	72.5	8.0	19.5
Gentamicin	2	>8	84.8	4.8	10.4
Amikacin	4	16	95.3	1.8	2.8
Colistin	1	2	99.6	0.3	0.1
P. aeruginosa (VAP; 415)					
Ceftazidime-avibactam[b]	2	4	97.8	-	2.2[b]
Ceftazidime	2	16	85.8	5.1	9.2
Cefepime	2	16	88.5	7.3	4.2
Piperacillin-tazobactam	8	64	79.5	11.3	9.2
Meropenem	0.5	8	78.8	5.8	15.4
Imipenem	1	--	80.0	20.0	0.0
Levofloxacin	0.5	>4	78.3	5.8	15.9
Gentamicin	≤1	4	90.1	2.7	7.2
Amikacin	2	8	98.0	1.0	1.0
Colistin	1	2	99.8	0.2	0.0
Enterobacteriaceae (all cases, 6,209)					
Ceftazidime-avibactam[b]	0.12	0.5	99.9	-	0.1[b]
Ceftazidime	0.25	32	85.0	1.5	13.5
Ceftriaxone	0.12	>8	80.7	1.3	18.0
Cefepime	0.06	8	88.0	3.2	8.8[c]
Piperacillin-tazobactam	2	64	87.6	4.8	7.6
Meropenem	≤0.06	≤0.06	96.8	0.5	2.8
Imipenem	≤0.12	1	94.3	2.4	3.3
Aztreonam	≤0.12	>16	84.5	1.4	14.1
Levofloxacin	≤0.12	>4	83.4	1.7	14.9
Gentamicin	≤1	4	91.1	1.6	7.2
Tigecycline	0.25	1	98.5	1.5	<0.1[c]
Colistin[c]	≤0.5	>8	77.8	--	22.2
Enterobacteriaceae (VAP, 604)					
Ceftazidime-avibactam[b]	0.12	0.5	99.7	-	0.3[b]
Ceftazidime	0.25	32	86.6	1.3	12.1
Ceftriaxone	0.12	>8	83.4	1.5	15.1
Cefepime	0.06	4	88.9	2.6	8.5[c]
Piperacillin-tazobactam	2	64	88.6	4.8	6.6
Meropenem	≤0.06	≤0.06	97.7	0.3	2.0
Imipenem	0.25	1	95.5	2.5	2.0
Aztreonam	≤0.12	>16	86.4	1.5	12.1
Levofloxacin	≤0.12	>4	87.1	1.5	11.4
Gentamicin	≤1	2	94.0	1.3	4.7
Tigecycline	0.25	1	98.3	1.5	0.2[c]
Colistin[c]	≤0.5	>8	79.4	--	20.6

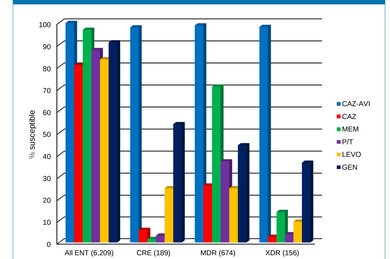
a. Criteria as published by CLSI [2016].
b. Breakpoints from FDA Package Insert.
c. Criteria as published by EUCAST [2016].
Abbreviation: VAP = ventilator-associated pneumonia.

Figure 2. Antimicrobial susceptibility of *P. aeruginosa*.



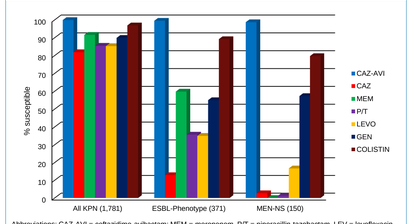
Abbreviations: CAZ-AVI = ceftazidime-avibactam; MEM = meropenem, P/T = piperacillin-tazobactam, LEV = levofloxacin and AMK = amikacin.

Figure 3. Antimicrobial susceptibility of Enterobacteriaceae.



Abbreviations: CAZ-AVI = ceftazidime-avibactam; MEM = meropenem, P/T = piperacillin-tazobactam, LEV = levofloxacin and GEN = gentamicin.

Figure 4. Antimicrobial susceptibility of *K. pneumoniae*.



Abbreviations: CAZ-AVI = ceftazidime-avibactam; MEM = meropenem, P/T = piperacillin-tazobactam, LEV = levofloxacin, GEN = gentamicin, KPN = *K. pneumoniae*, ESBL-phenotype = positive screening for extended-spectrum β-lactamase according to CLSI criteria, and NS = non-susceptible.

Conclusions

- Ceftazidime-avibactam demonstrated potent activity against a large collection of contemporary (2011-2015) Gram-negative bacilli isolated from PHP in USA hospitals, including those from VAP, and provided greater coverage than agents currently available in the USA
- Notably, ceftazidime-avibactam remained highly active against CRE as well as Enterobacteriaceae and *P. aeruginosa* isolates with MDR and XDR phenotypes.
- These *in vitro* results support further development of ceftazidime-avibactam for the treatment of nosocomial pneumonia in the USA.

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