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Ceftazidime-Avibactam Antimicrobial Activity and Spectrum when Tested against Gram-Negative Organisms from Pediatric Patients: Results from The INFORM Surveillance Program (USA, 2011-2015)

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Abstract

Background: Avibactam (AVI) is a synthetic non-β-lactam, β-lactamase (BL) inhibitor that inhibits Ambler classes A (e.g., ESBL and KPC), C and some D enzymes. Ceftazidime (CAZ)-AVI was approved by the US-FDA in 2015 for treatment of complicated intra-abdominal and urinary tract infections in adults and is under clinical development for treatment of pneumonia.

Methods: Among 53,381 Gram-negative (GN) organisms (1/patient) collected by the CAZ-AVI INFORM surveillance program in 2011-2015, 8,461 (15.9%) were from pediatric (≤17 years old [yo]) patients. The isolates were collected from 82 USA medical centers and susceptibility (S) tested against CAZ-AVI (AVI at fixed 4 μg/mL) and comparators by reference broth microdilution methods. S results were stratified by patient age as follows: ≤1 yo (3,671 isolates); 2-5 (1,900); 6-12 (1,644) and 13-17 (1,246). 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 8.9 and 8.4% of *E. coli* (EC) and *K. pneumoniae* (KPN), respectively, and rates were highest for the 2-5 yo group (11.9 and 13.1%, respectively). CAZ-AVI inhibited >99.9% of all ENT at the S breakpoint of ≤8 μg/mL, and was highly active against ESBL-phenotype EC and KPN (see Table 1). Overall, 83.6% of ESBL-phenotype KPN were meropenem (MEM)-S. All *E. cloacae* isolates, including CAZ-non-S strains, were CAZ-AVI-S. Only 1 of 4,724 ENT (0.02%) was CAZ-AVI-non-S: an *E. aerogenes* with CAZ-AVI MIC value of 16 μg/mL and negative results for all BL tested. CAZ-AVI was very active against *P. aeruginosa* (PSA; 99.1% S), including isolates non-S to MEM (94.0% S to CAZ-AVI) or piperacillin/tazobactam (PT; 91.7% S) or CAZ (89.6% S). Further, 77.8% of PSA isolates non-S to MEM, PT and CAZ were CAZ-AVI-S. CAZ-AVI activity against PSA did not vary substantially among age groups (98.8-99.3% S) or year of isolation (98.5-100.0% S).

Conclusions: CAZ-AVI demonstrated potent activity against a large collection of GN bacilli isolated from pediatric patients, including PSA and ESBL-phenotype and/or carbapenem-resistant ENT. These results support further evaluation of CAZ-AVI for treatment of pediatric patients.

Introduction

The continued increase of multidrug-resistant (MDR) Gram-negative infections has posed a major clinical problem worldwide. The surge of extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae led to an increase in the clinical use of carbapenems, followed by the emergence and spread of carbapenemase-producing Enterobacteriaceae, mainly KPC-producing organisms. *Pseudomonas aeruginosa* represents another serious therapeutic challenge because it exhibits intrinsically decreased susceptibility to a range of antimicrobials and possesses a great ability to develop resistance to multiple classes of agents. This organism has shown increasing rates of resistance to anti-*Pseudomonas* cephalosporins, penicillins and carbapenems.

Infections caused by MDR Gram-negative organisms result in significant morbidity and mortality in adult and pediatric patients, and requires prompt introduction of effective antimicrobial therapy. Because of the lack of studies addressing treatment options for treatment of MDR Gram-negative pathogens in children, data have to be extrapolated from the adult literature. Thus, pediatric specific studies are needed.

Ceftazidime-avibactam is a combination agent consisting of the β-lactamase inhibitor avibactam and the broad-spectrum cephalosporin, ceftazidime. Avibactam acts as a reversible, covalent inhibitor and is a member of a novel class of non-β-lactam β-lactamase inhibitors, the diazabicyclooctanes. Avibactam is more potent and has a broader spectrum of enzyme inhibition when compared to current clinically available β-lactamase inhibitors.

Ceftazidime-avibactam was approved by the United States Food and Drug Administration (US-FDA) for treatment of complicated intra-abdominal infection (IAI), in combination with metronidazole, as well as complicated urinary tract infections, including pyelonephritis, in patients with limited or no alternative treatment options. Ceftazidime-avibactam is also approved for the treatment of nosocomial pneumonia in Europe and has been studied in pediatric patients (NCT01893346). As part of the International Network for Optimal Resistance Monitoring (INFORM) program, we evaluated the activity of ceftazidime-avibactam against contemporary (2011-2015) isolates causing infection in pediatric patients from US medical centers.

Methods

Bacterial isolates. Among 53,381 Gram-negative organisms (one per infection episode) collected by the INFORM surveillance program in 2011-2015, 8,461 (15.9%) were from pediatric (≤17 years old) patients. The isolates were collected from 82 USA medical centers distributed among 37 states from all nine US Census Bureau regions. Susceptibility results were stratified by patient age as follows: ≤1 yo (3,671 isolates); 2-5 (1,900); 6-12 (1,644) and 13-17 (1,246). 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. CLSI susceptibility breakpoints (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).

Screening for β-lactamases. An ESBL-screen-positive phenotype was defined according to the Clinical and Laboratory Standards Institute (CLSI): i.e., an MIC of ≥2 μg/mL for ceftazidime and/or ceftriaxone and/or aztreonam. 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

- A total of 53,381 Gram-negative organisms were collected by the INFORM surveillance program in 2011-2015, including 8,461 (15.9%) from pediatrics (≤17 years old) and 42,821 from adult patients (the ages for 2,099 were not reported; Figure 1). Among the pediatric isolates, 43.4% were from patients ≤1 years-old (Figure 2).
- Ceftazidime-avibactam ($MIC_{50/90}$, 0.12/0.25 μg/mL) inhibited >99.9% of all Enterobacteriaceae at the susceptible breakpoint of ≤8 μg/mL, and was highly active against ESBL-phenotype *E. coli* ($MIC_{50/90}$, 0.12/0.5 μg/mL; 100.0% susceptible) and *K. pneumoniae* ($MIC_{50/90}$, 0.12/1 μg/mL; 100.0% susceptible; Table 1).
- All *E. cloacae* isolates ($MIC_{50/90}$, 0.12/0.5 μg/mL), including ceftazidime-non-susceptible isolates ($MIC_{50/90}$, 0.5/1 μg/mL), were susceptible to ceftazidime-avibactam (Table 1).
- Only one of 4,724 Enterobacteriaceae isolates from pediatric patients (0.02%) was ceftazidime-avibactam-non-susceptible, an *E. aerogenes* with MIC value of 16 μg/mL and negative results for all β-lactamases tested (Table 1).
- Among Enterobacteriaceae species, susceptibility rates for all comparator agents were very similar across the pediatric age groups, and slightly lower among the isolates from adults compared to those from the pediatric patients (Table 2).
- An ESBL-phenotype was observed among 8.9 and 8.4% of *E. coli* and *K. pneumoniae*, respectively, and ESBL-phenotype rates were highest for the 2-5 years-old group for these two species (11.9 and 13.1%, respectively; Table 3).
- Overall, only 83.6% of ESBL-phenotype *K. pneumoniae* isolates were susceptible to meropenem (data not shown).
- Ceftazidime-avibactam was highly active against *P. aeruginosa* ($MIC_{50/90}$, 1/4 μg/mL; 99.1% susceptible), including isolates non-susceptible to meropenem (94.0% susceptible to ceftazidime-avibactam) or piperacillin-tazobactam (91.7% susceptible) or ceftazidime (89.6% susceptible). Further, 77.8% of *P. aeruginosa* isolates non-susceptible to meropenem, piperacillin-tazobactam and ceftazidime were susceptible to ceftazidime-avibactam (Table 1).
- Ceftazidime-avibactam activity against *P. aeruginosa* did not vary substantially among pediatric age groups (98.8-99.3% susceptibility; Table 2) or year of isolation (98.5-100.0% susceptible; data not shown). Susceptibility rates for the comparator agents were very similar among the pediatric age groups, and generally lower among the isolates from adults compared to those from the pediatric patients (Table 2).

Table 3. ESBL-phenotype rates (positive screening by CLSI criteria) stratified by age group.

ESBL-phenotype rate[a]	Percentage by age groups (years old)					
	≤1	2-5	6-12	13-17	≤17	≥18
E. coli	8.6	11.9	6.8	9.1	8.9	14.3
K. pneumoniae	5.2	13.1	12.3	11.8	8.4	16.9
K. oxytoca	6.3	9.5	12.9	14.3	8.0	12.0
P. mirabilis	2.9	4.4	5.4	1.8	3.5	5.5

a. According to CLSI screening criteria for ESBL-phenotype.

Table 1. Antimicrobial activity of ceftazidime-avibactam tested against the main organisms and organism groups of isolates from pediatric (≤17 years old) patients (USA, 2011-2015).

Organisms / Organism Groups	No. of isolates at MIC (μg/mL; cumulative %)												MIC_{50}	MIC_{90}
	≤0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	>32		
Enterobacteriaceae (4,724)	700 (14.8)	1609 (48.9)	1598 (82.7)	596 (95.3)	174 (99.0)	37 (99.8)	3 (99.9)	6 (>99.9)	0 (>99.9)	1 (100.0)			0.12	0.25
MEM-NS (≥2 μg/mL) (17)	2 (11.8)	1 (17.6)	2 (29.4)	4 (52.9)	1 (58.8)	3 (76.5)	1 (82.4)	3 (100.0)					0.25	4
E. coli (1,788)	370 (20.7)	832 (67.2)	505 (95.5)	64 (99.0)	15 (99.9)	2 (100.0)							0.06	0.12
ESBL-phenotype (160)	9 (5.6)	27 (22.5)	83 (74.4)	24 (89.4)	15 (98.8)	2 (100.0)							0.12	0.5
K. pneumoniae (798)	57 (7.1)	275 (41.6)	352 (85.7)	89 (96.9)	17 (99.0)	4 (99.5)	1 (99.6)	3 (100.0)					0.12	0.25
ESBL-phenotype (67)	5 (7.5)	4 (13.4)	25 (50.7)	20 (80.6)	6 (89.6)	3 (94.0)	1 (95.5)	3 (100.0)					0.12	1
MEM-NS (≥2 μg/mL) (11)	2 (18.2)	0 (18.2)	1 (27.3)	3 (54.5)	0 (54.5)	2 (72.7)	1 (81.8)	2 (100.0)					0.25	4
K. oxytoca (339)	21 (6.2)	165 (54.9)	112 (87.9)	32 (97.3)	6 (99.1)	3 (100.0)							0.06	0.25
P. mirabilis (230)	165 (71.7)	61 (98.3)	4 (100.0)										≤0.03	0.06
E. cloacae (656)	7 (1.1)	59 (10.1)	293 (54.7)	202 (85.5)	73 (96.6)	19 (99.5)	2 (99.8)	1 (100.0)					0.12	0.5
CAZ-NS (≥8 μg/mL) (129)		1 (0.8)	5 (4.7)	49 (42.6)	53 (83.7)	18 (97.7)	2 (99.2)	1 (100.0)					0.5	1
E. aerogenes (138)	4 (2.9)	46 (36.2)	51 (73.2)	29 (94.2)	6 (98.6)	1 (99.3)	0 (99.3)	0 (99.3)	0 (99.3)	1 (100.0)			0.12	0.25
C. freundii (144)	1 (0.7)	33 (23.6)	70 (72.2)	27 (91.0)	13 (100.0)								0.12	0.25
S. marcescens (399)	2 (0.5)	25 (6.8)	177 (51.1)	146 (87.7)	43 (98.5)	6 (100.0)							0.12	0.5
P. aeruginosa (1,163)				17 (1.5)	54 (6.1)	521 (50.9)	431 (88.0)	101 (96.6)	29 (99.1)	4 (99.5)	6 (100.0)		1	4
CAZ-NS (≥16 μg/mL) (96)					2 (2.1)	11 (13.5)	32 (46.9)	26 (74.0)	15 (89.6)	4 (93.8)	6 (100.0)		4	16
MEM-NS (≥4 μg/mL) (100)						15 (15.0)	30 (45.0)	32 (77.0)	17 (94.0)	3 (97.0)	3 (100.0)		4	8
PT-NS (121)					3 (3.5)	16 (15.7)	36 (45.5)	36 (75.2)	20 (91.7)	4 (95.0)	6 (100.0)		4	8
NS to CAZ, MEM and PT (27)						1 (3.7)	6 (25.9)	6 (48.1)	8 (77.8)	3 (88.9)	3 (100.0)		8	32
A. baumannii (111)						4 (3.6)	5 (8.1)	24 (29.7)	27 (54.1)	23 (74.8)	14 (87.4)	14 (100.0)	8	>32
H. influenzae (1,504)	1438 (95.6)	56 (99.3)	9 (99.9)	1 (100.0)									≤0.015	0.03
H. parainfluenzae (105)	97 (92.4)	6 (98.1)	2 (100.0)										≤0.015	0.03
M. catarrhalis (849)	228 (26.9)	449 (79.7)	131 (95.2)	40 (99.9)	1 (100.0)								0.06	0.12

Abbreviations: MEM-NS = meropenem-non-susceptible (MIC, ≥2 μg/mL for Enterobacteriaceae and ≥4 μg/mL for *P. aeruginosa*); ESBL = extended-spectrum β-lactamase phenotype (ESBL-screen-positive phenotype); CAZ-NS = ceftazidime-non-susceptible (MIC, ≥8 μg/mL for Enterobacteriaceae and ≥16 μg/mL for *P. aeruginosa*); PT-NS = piperacillin/tazobactam-non-susceptible (MIC, ≥32 μg/mL for *P. aeruginosa* and Enterobacteriaceae).

Table 2. Activity of ceftazidime-avibactam and comparator antimicrobial agents stratified by age group (USA, 2011-2015).

Organism / Antimicrobial agent	% Susceptible by CLSI criteria[a] (no. tested)						Organism / Antimicrobial agent	% Susceptible by CLSI criteria[a] (no. tested)					
	≤1 year old	2-5 years old	6-12 years old	13-17 years old	All Peds (≤17 years old)	Adult (≥18 years old)		≤1 year old	2-5 years old	6-12 years old	13-17 years old	All Peds (≤17 years old)	Adult (≥18 years old)
Enterobacteriaceae	(2,179)	(884)	(879)	(782)	(4,724)	(31,512)	*P. aeruginosa*	(374)	(251)	(296)	(242)	(1,163)	(6,209)
Ceftazidime-avibactam[b]	100.0	99.9	100.0	100.0	>99.9	99.9	Ceftazidime-avibactam[b]	99.2	99.2	99.3	98.8	99.1	96.5
Ceftazidime	91.5	91.7	92.0	90.5	91.5	88.7	Ceftazidime	93.3	90.0	91.9	90.9	91.7	82.9
Ceftriaxone	88.6	88.2	89.4	87.9	88.6	85.4	Cefepime	95.6	92.9	93.0	92.0	93.6	83.9
Piperacillin-tazobactam	93.6	94.9	94.9	93.3	94.1	92.1	Piperacillin-tazobactam	91.4	89.6	89.9	86.4	89.6	78.7
Meropenem	99.8	99.5	99.5	99.5	99.6	98.2	Meropenem	91.7	92.4	91.5	89.7	91.4	80.2
Levofloxacin	96.0	91.6	91.5	90.3	93.4	80.7	Levofloxacin	95.7	87.6	89.9	85.5	90.4	71.9
Gentamicin	94.7	89.0	90.6	90.8	92.2	90.8	Gentamicin	96.3	88.8	87.2	85.1	90.0	88.3
Colistin[c]	82.2	75.3	82.3	78.6	80.4	77.1	Amikacin	99.2	98.3	95.5	94.1	97.0	97.1
E. coli	(631)	(379)	(439)	(339)	(1,788)	(10,471)	Colistin	100.0	99.2	99.3	99.2	99.5	99.4
Ceftazidime-avibactam[b]	100.0	100.0	100.0	100.0	100.0	>99.9	*A. baumannii*	(46)	(20)	(22)	(23)	(111)	(956)
Ceftazidime	93.5	92.1	95.2	93.8	93.7	89.9	Ceftazidime-avibactam	*d*	*d*	*d*	*d*	*d*	*d*
Ceftriaxone	91.9	88.6	93.6	91.7	91.6	86.7	Ceftazidime	91.3	75.0	86.4	34.8	75.7	41.7
Piperacillin-tazobactam	97.6	96.6	97.9	95.6	97.1	95.3	Cefepime	88.9	65.0	86.4	52.2	76.4	38.7
Meropenem	100.0	100.0	99.8	99.7	99.9	99.8	Piperacillin-tazobactam	76.1	75.0	85.7	43.5	70.9	34.6
Levofloxacin	88.2	84.2	86.6	84.1	86.2	66.9	Ampicillin-sulbactam	95.7	90.0	86.4	60.9	85.6	48.3
Gentamicin	88.6	84.2	90.6	88.8	88.2	87.0	Meropenem	97.8	95.0	100.0	60.9	90.1	43.0
Colistin[c]	100.0	100.0	100.0	99.1	99.8	99.7	Levofloxacin	97.8	85.0	86.4	47.8	82.9	39.0
K. pneumoniae	(442)	(107)	(130)	(119)	(798)	(6,803)	Gentamicin	91.3	85.0	90.9	52.2	82.0	50.0
Ceftazidime-avibactam[b]	100.0	100.0	100.0	100.0	100.0	99.9	Amikacin	97.8	94.7	95.5	65.2	90.0	66.6
Ceftazidime	96.8	86.9	90.0	89.9	93.4	85.2	Colistin	97.8	100.0	100.0	100.0	99.1	94.5
Ceftriaxone	95.2	87.9	90.0	89.1	92.5	84.5	*H. influenzae*	(629)	(434)	(299)	(142)	(1,504)	(2,800)
Piperacillin-tazobactam	97.5	91.5	93.1	93.3	95.3	87.8	Ceftazidime-avibactam	*d*	*d*	*d*	*d*	*d*	*d*
Meropenem	99.5	96.3	97.7	98.3	98.6	93.5	Ceftazidime	100.0	100.0	100.0	100.0	100.0	100.0
Levofloxacin	98.6	95.3	95.3	94.0	97.0	86.6	Ceftriaxone	100.0	100.0	100.0	100.0	100.0	100.0
Gentamicin	95.9	92.5	90.0	90.8	93.7	91.4	Ampicillin[e]	71.2	73.0	69.2	77.5	71.9	75.1
Colistin[c]	98.4	100.0	99.2	99.1	98.9	97.3	Amoxicillin-clavulanate	99.8	100.0	100.0	>99.9	99.9	>99.9
E. cloacae	(393)	(103)	(84)	(76)	(656)	(3,231)	Piperacillin-tazobactam	100.0	100.0	100.0	100.0	100.0	100.0
Ceftazidime-avibactam[b]	100.0	100.0	100.0	100.0	100.0	99.9	Meropenem	100.0	100.0	100.0	100.0	100.0	100.0
Ceftazidime	78.1	84.5	86.9	78.9	80.3	78.7	Azithromycin	99.5	99.5	99.3	97.2	99.3	98.8
Ceftriaxone	74.7	79.2	81.0	73.7	76.1	74.1	Levofloxacin	100.0	100.0	100.0	100.0	100.0	99.8
Piperacillin-tazobactam	82.9	90.1	88.1	86.5	85.1	83.4							
Meropenem	99.5	100.0	100.0	98.7	99.5	98.5							
Levofloxacin	99.7	99.0	98.8	97.4	99.2	93.9							
Gentamicin	98.7	97.1	95.2	96.1	97.7	95.1							
Colistin[c]	79.6	80.2	79.0	78.9	79.5	81.0							

a. Criteria as published by CLSI (2016).
b. Breakpoints from US-FDA Package Insert.
c. Criteria as published by EUCAST (2016).
d. "-" = no breakpoint published by CLSI or US-FDA.
e. Based on β-lactamase production.

Figure 1. Distributions of adult and pediatric isolates by age group.

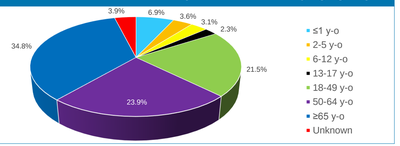
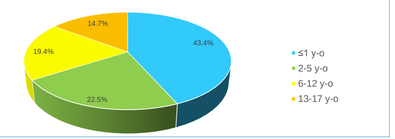


Figure 2. Distributions of pediatric isolates by age group.



Conclusions

- Ceftazidime-avibactam demonstrated potent activity against a large collection of Gram-negative organisms isolated from pediatric patients, including *P. aeruginosa* and ESBL-phenotype and/or carbapenem-resistant Enterobacteriaceae.
- Ceftazidime-avibactam was consistently active against Gram-negative organisms from all age groups.
- These results support further evaluation of ceftazidime-avibactam for the treatment of pediatric patients.

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