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In Vitro Activity of Ceftazidime-Avibactam and Comparator Agents Against Enterobacterales and *Pseudomonas aeruginosa* Collected <48 Hours and ≥48 Hours Post-Admission from Pediatric Patients, ATLAS Surveillance Program 2015-2018

IHMA
2122 Palmer Drive
Schaumburg, IL 60173 USA
www.ihma.com

K. M. Kazmierczak[1], G. G. Stone[2], D. F. Sahm[1] [1]IHMA, Schaumburg IL, USA [2]Pfizer Inc., Groton, CT USA

Introduction

Ceftazidime-avibactam is a β-lactam/non-β-lactam β-lactamase inhibitor combination with *in vitro* activity against Enterobacterales and *Pseudomonas aeruginosa* carrying Class A, C and some Class D β-lactamases. We examined the *in vitro* activity of ceftazidime-avibactam and comparators against isolates from presumed community-acquired infections (cultured <48 h after hospital admission) and presumed hospital-acquired infections (cultured ≥48 h post-admission) collected from pediatric patients as part of the ATLAS surveillance program.

Methods

6025 non-duplicate isolates were collected in 49 countries in Europe (n=3122), Latin America (n=1220), Middle East/Africa (n=1007), and Asia/Pacific (excluding China; n=676) from pediatric patients (newborn to 17 y). Isolates were collected from lower respiratory tract (LRTI; n=1642), urinary tract (UTI; n=1595), skin and soft tissue (SSTI; n=1027), intra-abdominal (IAI; n=949), and bloodstream (BSI; n=812) infections. Susceptibility testing was performed by Clinical and Laboratory Standards Institute (CLSI) broth microdilution and values were interpreted using CLSI 2020 breakpoints for all drugs except tigecycline, for which United States Food and Drug Administration breakpoints were used [1-3]. Ceftazidime-avibactam was tested at a fixed concentration of 4 µg/mL avibactam. Isolates with ceftazidime or aztreonam MICs ≥2 µg/mL (*Escherichia coli*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, *Proteus mirabilis*) or meropenem MICs ≥2 µg/mL (all Enterobacterales species) or ≥4 µg/mL (*P. aeruginosa*) were screened for β-lactamase genes [4,5].

Results

Table 1. *In vitro* activity of ceftazidime-avibactam and comparators against Enterobacterales isolates collected from pediatric patients

Drug	MIC_{90} (µg/ml)/% Susceptible (Infection source/ Length of hospital stay prior to culture)																					
	All infection sources combined						LRTI				UTI				SSTI				IAI				BSI			
	All		<48 h		≥48 h		<48 h		≥48 h		<48 h		≥48 h		<48 h		≥48 h		<48 h		≥48 h		<48 h		≥48 h	
	n=4694 (100%)		n=2156 (45.9%)		n=2538 (54.1%)		n=331 (32.1%)		n=699 (67.9%)		n=838 (59.9%)		n=561 (40.1%)		n=324 (42.0%)		n=447 (58.0%)		n=447 (55.9%)		n=353 (44.1%)		n=216 (31.1%)		n=478 (68.9%)	
	MIC_{90}	%S	MIC_{90}	%S	MIC_{90}	%S	MIC_{90}	%S	MIC_{90}	%S	MIC_{90}	%S	MIC_{90}	%S	MIC_{90}	%S	MIC_{90}	%S	MIC_{90}	%S	MIC_{90}	%S	MIC_{90}	%S	MIC_{90}	%S
CAZ-AVI	0.5	98.5	0.25	98.8	0.5	98.3	0.5	98.2	0.5	99.1	0.25	99.3	0.5	99.3	0.25	98.8	0.5	97.8	0.25	99.3	0.25	98.3	0.5	96.8	0.5	96.4
CAZ	64	75.3	64	80.2	64	71.2	64	76.7	64	72.0	32	79.5	64	71.8	32	84.6	32	77.4	16	87.0	64	77.3	128	67.6	128	59.0
FEP	>16	77.9	>16	82.1	>16	74.4	>16	79.5	>16	76.4	>16	82.5	>16	73.8	16	84.9	>16	80.3	16	87.5	>16	78.8	>16	69.0	>16	63.6
MEM	0.12	97.0	0.12	97.5	0.12	96.7	0.12	96.4	0.12	97.9	0.12	98.2	0.12	97.1	0.12	96.9	0.12	96.2	0.06	98.9	0.12	97.7	0.12	94.4	0.12	93.9
TZP	64	85.2	32	88.4	>64	82.5	64	82.2	>64	82.7	32	87.8	>64	83.4	16	92.0	>64	82.8	8	94.2	64	85.0	>64	82.4	>64	79.3
AMK	8	97.0	8	97.3	8	96.8	8	94.6	8	96.9	8	98.4	8	96.8	4	97.8	4	97.5	4	98.4	8	97.5	8	94.0	8	95.4
LVX	8	78.9	8	81.2	8	76.9	2	82.2	8	80.4	8	81.6	8	75.6	8	80.9	8	76.5	4	83.9	8	80.5	>8	73.1	>8	70.9
TGC	1	97.9	1	98.1	1	97.7	1	98.8	1	98.0	2	97.1	1	96.8	1	96.6	1	96.6	1	99.8	1	98.9	1	99.5	1	98.5

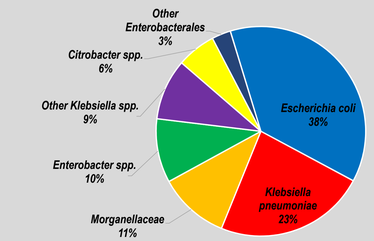
LRTI, lower respiratory tract infection; UTI, urinary tract infection; SSTI, skin and soft tissue infection; IAI, intra-abdominal infection; BSI, bloodstream infection; % S, percent susceptible; CAZ-AVI, ceftazidime-avibactam; CAZ, ceftazidime; FEP, cefepime; MEM, meropenem; TZP, piperacillin-tazobactam; AMK, amikacin; LVX, levofloxacin; TGC, tigecycline. Isolates for which data regarding infection source and length of hospitalization were not available were excluded from analysis

Table 2. *In vitro* activity of ceftazidime-avibactam and comparators against *P. aeruginosa* isolates collected from pediatric patients

Drug	MIC_{90} (µg/ml)/% Susceptible (Infection source/ Length of hospital stay prior to culture)																					
	All infection sources combined						LRTI				UTI				SSTI				IAI				BSI			
	All		<48 h		≥48 h		<48 h		≥48 h		<48 h		≥48 h		<48 h		≥48 h		<48 h		≥48 h		<48 h		≥48 h	
	n=1331 (100%)		n=560 (42.1%)		n=771 (57.9%)		n=230 (37.6%)		n=382 (62.4%)		n=86 (43.9%)		n=110 (56.1%)		n=108 (42.2%)		n=148 (57.8%)		n=95 (63.8%)		n=54 (36.2%)		n=41 (34.7%)		n=77 (65.3%)	
	MIC_{90}	%S	MIC_{90}	%S	MIC_{90}	%S	MIC_{90}	%S	MIC_{90}	%S	MIC_{90}	%S	MIC_{90}	%S	MIC_{90}	%S	MIC_{90}	%S	MIC_{90}	%S	MIC_{90}	%S	MIC_{90}	%S	MIC_{90}	%S
CAZ-AVI	8	93.1	8	94.5	8	92.1	8	94.8	8	91.4	8	93.0	4	92.7	8	95.4	8	95.3	4	94.7	4	92.6	8	92.7	32	88.3
CAZ	32	82.0	32	83.6	32	80.9	32	81.3	64	79.6	16	87.2	32	83.6	32	80.6	32	84.5	16	89.5	32	83.3	32	82.9	128	75.3
FEP	16	85.4	16	86.4	16	84.7	16	82.6	16	84.3	8	90.7	16	87.3	16	88.9	16	86.5	8	90.5	16	87.0	>16	82.9	>16	77.9
MEM	>8	78.1	>8	82.0	>8	75.2	>8	77.8	>8	72.8	2	91.9	>8	79.1	8	79.6	>8	81.1	2	90.5	8	79.6	>8	70.7	16	67.5
TZP	>64	78.3	64	80.5	>64	76.7	>64	78.7	>64	74.9	32	82.6	64	76.4	>64	78.7	64	79.1	32	86.3	64	85.2	>64	78.0	>64	75.3
AMK	8	93.2	8	93.9	16	92.6	16	93.5	16	93.2	8	95.3	8	91.8	8	94.4	8	95.3	8	93.7	8	94.4	8	92.7	>32	84.4
LVX	8	74.9	4	78.2	8	72.5	4	75.2	>8	72.3	8	81.4	8	73.6	4	73.1	4	69.6	4	86.3	4	77.8	2	82.9	>8	74.0

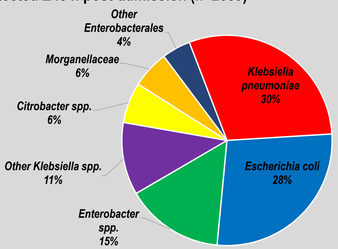
LRTI, lower respiratory tract infection; UTI, urinary tract infection; SSTI, skin and soft tissue infection; IAI, intra-abdominal infection; BSI, bloodstream infection; % S, percent susceptible; CAZ-AVI, ceftazidime-avibactam; CAZ, ceftazidime; FEP, cefepime; MEM, meropenem; TZP, piperacillin-tazobactam; AMK, amikacin; LVX, levofloxacin. Isolates for which data regarding infection source and length of hospitalization were not available were excluded from analysis

Figure 1. Species distribution of Enterobacterales isolates collected <48 h post-admission (n=2157)



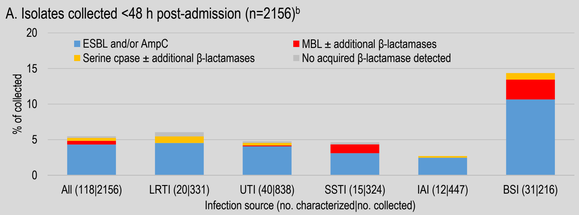
Species (no. of isolates): *E. coli*, n=810; *K. pneumoniae*, n=503; *Morganellaceae* (*P. mirabilis*, n=135; *M. morganii*, n=36; *P. vulgaris*, n=30; *P. stuartii*, n=11; *P. hauseri*, n=10; *P. rettgeri*, n=7; *P. alcalifaciens*, n=4; *P. penneri*, n=1); *Enterobacter* spp. (*E. cloacae*, n=159; *E. asburiae*, n=24; *E. kobei*, n=8; *E. ludwigii*, n=3; *Enterobacter*, species not determined, n=9); Other *Klebsiella* spp. (*K. oxytoca*, n=120; *K. aerogenes*, n=56; *K. varicola*, n=27); *Citrobacter* spp. (*C. freundii*, n=77; *C. koseri*, n=35; *C. braakii*, n=10; *C. farmeri*, n=5; *C. amalonaticus*, n=2; *C. sedlakii*, n=1); Other Enterobacterales (*S. marcescens*, n=57; *R. ornithinolytica*, n=4; *S. rubidaea*, n=1; *Pantoea*, species not determined, n=1).

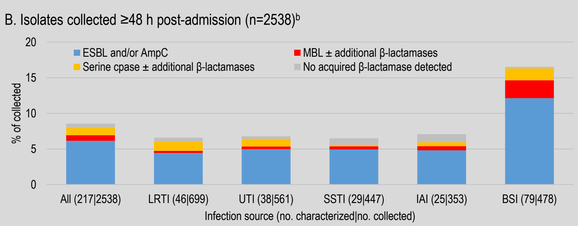
Figure 2. Species distribution of Enterobacterales isolates collected ≥48 h post-admission (n=2539)



Species (no. of isolates): *K. pneumoniae*, n=758; *E. coli*, n=698; *Enterobacter* spp. (*E. cloacae*, n=295; *E. asburiae*, n=38; *E. kobei*, n=16; *E. bugandensis*, n=1; *E. ludwigii*, n=1; *E. xiangfangensis*, n=1; *Enterobacter*, species not determined, n=31); Other *Klebsiella* spp. (*K. oxytoca*, n=187; *K. aerogenes*, n=84; *K. varicola*, n=12); *Citrobacter* spp. (*C. freundii*, n=100; *C. koseri*, n=33; *C. braakii*, n=11; *C. amalonaticus*, n=8; *C. farmeri*, n=4; *C. sedlakii*, n=1; *Citrobacter*, species not determined, n=2); *Morganellaceae* (*P. mirabilis*, n=68; *M. morganii*, n=39; *P. vulgaris*, n=22; *P. rettgeri*, n=8; *P. stuartii*, n=4; *P. hauseri*, n=3; *P. penneri*, n=1); Other Enterobacterales (*S. marcescens*, n=108; *R. ornithinolytica*, n=2; *P. dispersa*, n=1; *S. ureilytica*, n=1).

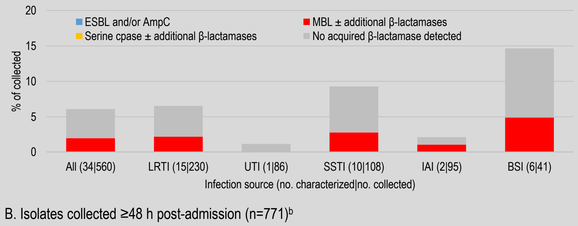
Figure 3. β-lactamase carriage of Enterobacterales from pediatric patients[a]

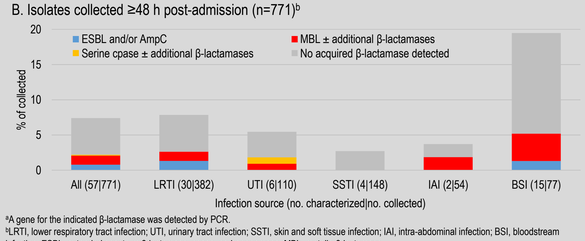




[a]A gene for the indicated β-lactamase was detected by PCR.
[b]LRTI, lower respiratory tract infection; UTI, urinary tract infection; SSTI, skin and soft tissue infection; IAI, intra-abdominal infection; BSI, bloodstream infection; ESBL, extended spectrum β-lactamase; cpase, carbapenemase; MBL, metallo-β-lactamase.

Figure 4. β-lactamase carriage of *P. aeruginosa* from pediatric patients[a]





[a]A gene for the indicated β-lactamase was detected by PCR.
[b]LRTI, lower respiratory tract infection; UTI, urinary tract infection; SSTI, skin and soft tissue infection; IAI, intra-abdominal infection; BSI, bloodstream infection; ESBL, extended spectrum β-lactamase; cpase, carbapenemase; MBL, metallo-β-lactamase.

Results

- The *in vitro* activity of CAZ-AVI exceeded that of meropenem and other tested β-lactams against Enterobacterales (98.5% susceptible) collected globally from pediatric patients (Table 1).
- *E. coli* composed 38% of isolates collected <48 h post hospital admission, while *E. coli* and *K. pneumoniae* were equally common among isolates collected ≥48 h post-admission (28% and 30% of isolates, respectively) (Figure 1, Figure 2).
- Percentages of susceptibility to CAZ-AVI ranged from 96.8-99.3% among Enterobacterales collected <48 h post-admission from different infection types and were reduced 0.4-1.0% among isolates collected ≥48 h post-admission from patients with SSTI, IAI and BSI (Table 1).
- The lowest percentages of susceptibility to the tested β-lactams were observed among isolates from BSI, which included a higher proportion of isolates carrying extended-spectrum β-lactamases and/or carbapenemases (14-16%) than isolates from other infection types (Table 1, Figure 3A, Figure 3B).
- Overall, the percentage of carbapenemase-positive isolates was greater among Enterobacterales from presumed hospital-acquired infections (21% of isolates characterized for β-lactamase genes; 1.8% of collected isolates) than community-acquired infections (17% of characterized isolates; 0.9% of collected) (Figure 3A, Figure 3B).
- Among *P. aeruginosa* isolates collected from pediatric patients, the *in vitro* activity of CAZ-AVI (93.1% susceptible) was comparable to that of amikacin and exceeded that of other tested β-lactams, including meropenem (Table 2).
- Percentages of susceptibility to CAZ-AVI were similar (92.7-95.4% susceptible) among *P. aeruginosa* collected <48 h post-admission from different infection types and was reduced 0.1-4.4% among isolates collected ≥48 h post-admission (Table 2).
- The lowest susceptibility to the tested β-lactams were observed among isolates from BSI, of which 5% were found to carry β-lactamases compared to <3% of isolates from other infection sources (Table 2, Figure 4A, Figure 4B).

Conclusions

CAZ-AVI could provide a valuable therapeutic option for treatment of community-acquired and hospital-acquired infections caused by Enterobacterales and *P. aeruginosa* in pediatric patients.

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Disclosures

This study was sponsored by Pfizer. AZ's rights to ceftazidime-avibactam were acquired by Pfizer in December 2016. IHMA received financial support from Pfizer in connection with the study and the development of this poster. K. Kazmierczak and D. Sahm are employees of IHMA. G. Stone, an employee of and shareholder in AZ at the time of the study, is currently an employee of Pfizer.