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In vitro Activities of Ceftazidime-Avibactam and Comparator Agents against Enterobacterales and *Pseudomonas aeruginosa* Collected <48 Hours and ≥48 Hours Post-Admission from Hospitalized Pediatric Patients, ATLAS Global Surveillance Program 2017-2020

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Introduction

Ceftazidime-avibactam (CAZ-AVI) is a 3rd generation cephalosporin combined with a diazabicyclooctane-β-lactamase inhibitor for treatment of infections caused by Gram-negative pathogens. CAZ-AVI is active against Enterobacterales and *Pseudomonas aeruginosa* isolates that produce Class A, C and some Class D β-lactamases. This study examined the *in vitro* activity of CAZ-AVI and comparators against Enterobacterales and *P. aeruginosa* from presumed community-acquired (CA; cultured <48 hrs after hospital admission) and presumed hospital-acquired (HA; cultured ≥48 hrs post-admission) infections collected from pediatric patients as part of the ATLAS surveillance program, 2017-2020.

Methods

- 5,765 non-duplicate Enterobacterales and 1,987 *P. aeruginosa* isolates from pediatric patients (age ≤17 y.o.) were collected from 241 sites in 54 countries as part of ATLAS 2017-2020 (excluding North America) for which the length of hospitalization stay was specified.
- Antimicrobial susceptibility testing was by broth microdilution according to CLSI guidelines and analyzed using CLSI 2022 breakpoints [1,2].
- All Enterobacterales isolates testing with meropenem MICs >1 µg/mL and *Escherichia coli, Klebsiella pneumoniae, K. oxytoca, K. variicola*, and *Proteus mirabilis* testing with ceftazidime and/or aztreonam MICs >1 µg/mL were genetically screened for β-lactamases by PCR and sequencing [3]. For *P. aeruginsoa*, meropenem MIC >2 µg/mL triggered β-lactamase screening. In 2020, approximately 25% of the meropenem non-susceptible isolates were screened.

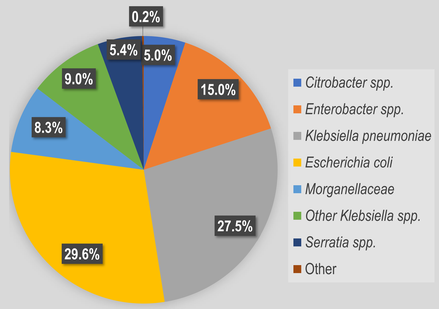
Results

Table 1. *In vitro* activity of CAZ-AVI and comparators against Enterobacterales and *P. aeruginosa* collected from pediatric patients <48 hrs or ≥48 hrs post-admission

Organism group/patient length of stay/ (n)	Drug[a]															
	CAZ-AVI		CAZ		AMK		ATM		FEP		LVX		MEM		TZP	
	% S	MIC_{90} (mg/L)	% S	MIC_{90} (mg/L)	% S	MIC_{90} (mg/L)	% S	MIC_{90} (mg/L)	% S	MIC_{90} (mg/L)	% S	MIC_{90} (mg/L)	% S	MIC_{90} (mg/L)	% S	MIC_{90} (mg/L)
Enterobacterales <48 hrs (n=2,576)	97.5	0.5	76.1	64	96.5	8	76.0	64	78.0	32	79.3	8	96.2	0.06	83.5	32
Enterobacterales, MBL-neg <48 hrs (n=2,513)	99.9	0.25	78.0	32	97.9	4	77.6	64	79.9	>16	80.6	8	98.5	0.06	85.6	32
Enterobacterales ≥48 hrs (n=3,189)	96.1	0.5	62.2	>64	93.6	8	62.0	>64	65.3	>32	71.1	>8	92.7	0.25	72.7	>64
Enterobacterales, MBL-neg ≥48 hrs (n=3,078)	99.4	0.5	64.4	64	95.1	8	63.8	>64	67.7	>32	72.3	>8	95.9	0.12	75.3	>64
P. aeruginosa, <48 hrs (n=852)	93.3	8	85.0	32	91.2	16	76.3	32	86.6	16	75.8	8	81.2	>8	83.5	64
P. aeruginosa, MBL-neg <48 hrs (n=829)	95.8	8	87.3	16	93.4	8	78.0	32	89.0	16	77.8	8	83.5	8	85.6	64
P. aeruginosa ≥48 hrs (n=1,135)	89.8	16	77.8	64	89.1	32	70.2	32	80.4	32	72.0	>8	73.8	16	75.5	>64
P. aeruginosa, MBL-neg ≥48 hrs (n=1,089)	93.5	8	81.0	64	91.4	16	72.3	32	83.7	16	74.6	8	77.0	16	78.4	>64

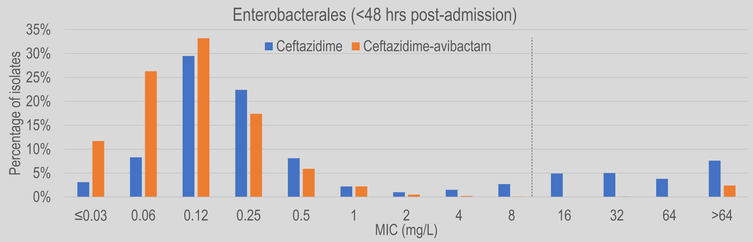
[a]CAZ-AVI, ceftazidime-avibactam; CAZ, ceftazidime; AMK, amikacin; ATM, aztreonam; FEP, cefepime; LVX, levofloxacin; MEM, meropenem; TZP, piperacillin-tazobactam; S = susceptible; MBL, metallo-β-lactamase.

Figure 1. Taxonomical distribution of Enterobacterales (n=5765) in this study



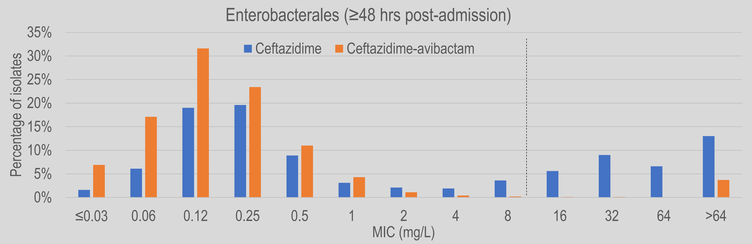
Other: *Pantoea agglomerans* (n=1), *P. dispersa* (n=1), *Pantoea* sp. (n=1), *Raoultella ornithinolytica* (n=7), *R. planticola* (n=1) and *Salmonella* sp. (n=1)

Figure 2. CAZ-AVI and CAZ MIC distributions against presumed community-acquired Enterobacterales



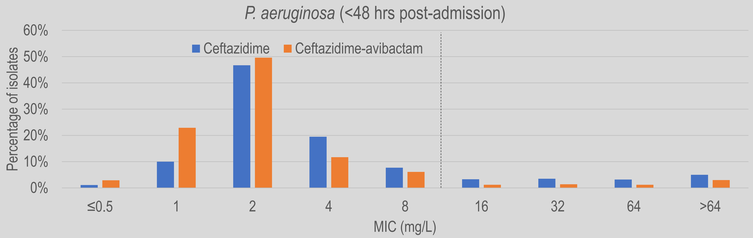
Dashed line represents the ceftazidime-avibactam MIC susceptible breakpoint of ≤8 mg/L

Figure 3. CAZ-AVI and CAZ MIC distributions against presumed hospital-acquired Enterobacterales



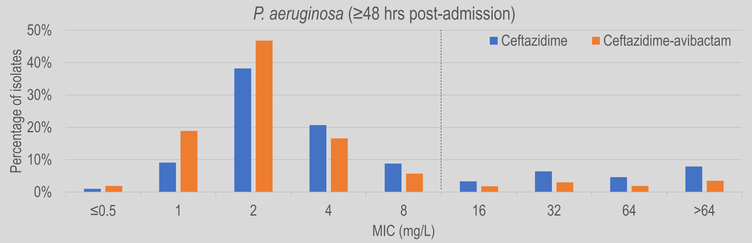
Dashed line represents the ceftazidime-avibactam MIC susceptible breakpoint of ≤8 mg/L

Figure 4. CAZ-AVI and CAZ MIC distributions against presumed community-acquired *P. aeruginosa*



Dashed line represents the ceftazidime-avibactam MIC susceptible breakpoint of ≤8 mg/L

Figure 5. CAZ-AVI and CAZ MIC distributions against presumed hospital-acquired *P. aeruginosa*



Dashed line represents the ceftazidime-avibactam MIC susceptible breakpoint of ≤8 mg/L

Results

Enterobacterales

- Against Enterobacterales, the *in vitro* activity of CAZ-AVI exceeded that of meropenem and other tested agents for both the presumed CA- and HA-infection sets (Table 1).
- The addition of AVI to CAZ increased the % susceptible from 76.1% to 97.5% for the CA-infection population, and from 62.2% to 96.1% for the HA-infection population (Table 1, Fig. 2 and Fig. 3).
- Excluding MBL-positive isolates from the CA-infection and HA-infection sets increased the percentage susceptible to CAZ-AVI to 99.9% and 99.4%, respectively.

P. aeruginosa

- For *P. aeruginosa*, there was a larger difference between the % susceptible to CAZ-AVI of the CA-infection set (93.3% S) versus the HA-infection set (89.8% S), as compared to the difference observed for Enterobacterales.
- The addition of AVI to CAZ increased the % susceptible from 85.0% to 93.3% for the CA-infection population, and from 77.8% to 89.8% for the HA-infection population (Table 1, Fig. 4 and Fig.5).
- For both *P. aeruginosa* populations, CAZ-AVI was the most active drug among the comparator agents.
- As expected, CAZ-AVI activity was higher against isolates that did not carry MBLs (Table 1).

Conclusions

CAZ-AVI demonstrated potent *in vitro* activity against Enterobacterales and *P. aeruginosa* isolates collected globally from pediatric patients in 2017-2020, regardless of whether is infection was community-or hospital-acquired. CAZ-AVI remains a valuable therapeutic option for treating non-MBL producing isolates resistant to other commonly used agents.

References

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3. Lob SH, Kazmierczak KM, Badal RE, et al. 2015. *Trends in susceptibility of Escherichia coli from intra-abdominal infections to ertapenem and comparators in the United States according to data from the SMART program, 2009 to 2013*. Antimicrob Agents Chemother 59:3606-3610.

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. MW and DS are employees of IHMA. GS, an employee of and shareholder in AZ at the time of the study, is currently an employee of Pfizer.