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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 Adult Patients, ATLAS Global Surveillance Program 2017-2020

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Introduction

Effective treatments for Gram-negative infections have dwindled with the emergence and dissemination of multi-drug resistant Enterobacterales and *Pseudomonas aeruginosa*. Fortunately, ceftazidime-avibactam (CAZ-AVI) has activity against 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 adult patients as part of the ATLAS surveillance program, 2017-2020.

Methods

- 59,918 non-duplicate Entero-bacterales and 20,511 *P. aeruginosa* isolates from adult patients (age ≥18 y.o.) were collected from 271 sites in 57 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 mg/L 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.

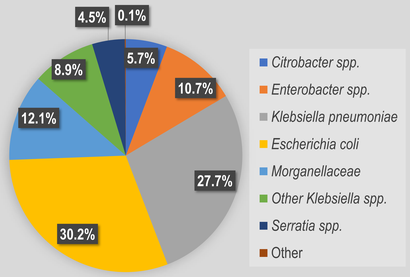
Results

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

Organism /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=25,118)	97.8	0.5	76.9	64	96.8	8	76.5	64	78.1	32	69.4	>8	95.2	0.12	83.2	64
Enterobacterales, MBL-neg <48 hrs (n=24,606)	99.8	0.5	78.5	32	97.8	4	77.7	64	79.7	>16	70.6	>8	97.1	0.12	84.9	32
Enterobacterales ≥48 hrs (n=34,800)	96.8	1	68.0	>64	94.5	8	67.7	>64	74.2	>64	63.8	>8	91.5	0.5	74.2	>64
Enterobacterales, MBL-neg ≥48 hrs (n=33,784)	99.6	0.5	70.0	>64	96.0	8	69.2	>64	72.6	>32	65.4	>8	94.1	0.12	76.4	>64
P. aeruginosa, <48 hrs (n=7,277)	92.4	8	81.0	64	90.8	16	71.2	32	82.5	>16	68.8	>8	79.6	>8	78.2	>64
P. aeruginosa, MBL-neg <48 hrs (n=7,073)	94.9	8	83.2	32	92.9	16	72.4	32	84.7	16	70.7	>8	81.9	8	80.4	>64
P. aeruginosa ≥48 hrs (n=13,234)	89.2	16	73.0	64	89.2	32	63.4	64	75.0	32	63.8	>8	69.9	16	69.1	>64
P. aeruginosa, MBL-neg ≥48 hrs (n=12,667)	93.0	8	76.2	64	92.4	16	65.0	64	78.2	32	66.5	>8	73.1	16	72.0	>64

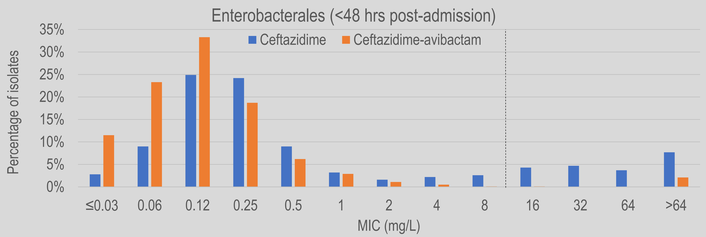
[a]CAZ-AVI, ceftazidime-avibactam; CAZ, ceftazidime; AMK, amikacin; ATM, aztreonam; FEP, cefepime; LVX, levofloxacin; MEM, meropenem; TZP, piperacillin-tazobactam; S = susceptible; MBL, metallo-β-lactamase..

Figure 1. Taxonomic distribution of Enterobacterales (n=59,918) in this study



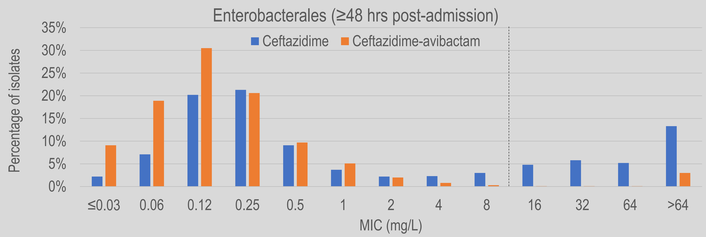
Other: *Cronobacter sakazakii* (n=1), *Cronobacter* sp. (n=1), *Escherichia* sp. (n=1), *Escherichia vulneris* (n=1), *Hafnia alvei* (n=1), *Lelliottia amnigena* (n=2), *Pantoea agglomerans* (n=3), *Pantoea dispersa* (n=1), *Pantoea septica* (n=1), *Pluralibacter gergoviae* (n=9), *Raoultella ornithinolytica* (n=51), *Raoultella planticola* (n=8), *Raoultella* sp. (n=1), *Raoultella terrigena* (n=1), *Salmonella* sp. (n=5), *Escherichia* sp. (n=1), *Escherichia vulneris* (n=1).

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



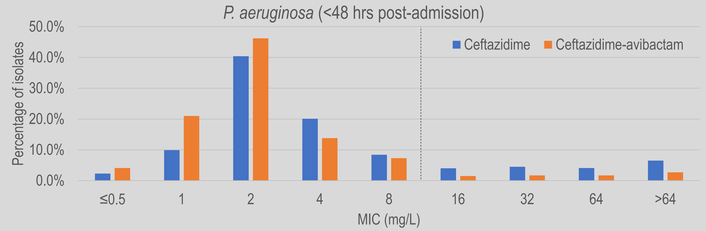
Dashed line represents the ceftazidime-avibactam MIC susceptible breakpoint of ≤8 mg/L

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



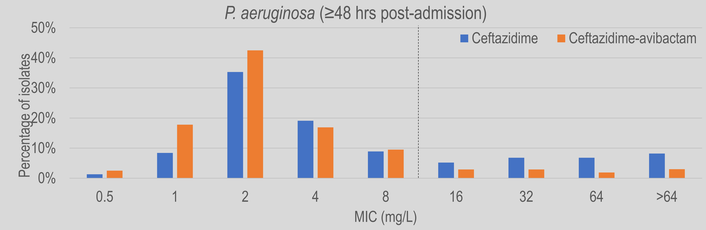
Dashed line represents the ceftazidime-avibactam MIC susceptible breakpoint of ≤8 mg/L

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

- CAZ-AVI was the most active agent examined against both the presumed CA- and HA-infection population of isolates (Table 1).
- The percentage of Enterobacterales isolates susceptible to CAZ-AVI was 2.6% and 5.3% higher than percentages susceptible to meropenem for the CA- and HA-infection sets, respectively.
- The addition of AVI to CAZ increased the % susceptible from 76.9% to 97.8% for the CA-infection population, and from 68.0% to 96.8% for the HA-infection population (Table 1, Fig. 2 and Fig. 3).
- Excluding MBL-positive isolates from the CA-infection set increased the percentage susceptible to CAZ-AVI to 99.8%. Against the MBL-negative HA-infection set, the percentage susceptible to CAZ-AVI was 99.6% (Table 1).

P. aeruginosa

- Considering both the presumed CA- and HA- infection *P. aeruginosa* isolates, CAZ-AVI was the most active agent among comparators, showing percentage susceptible rates 12.8% and 19.3% higher than meropenem, respectively (Table 1).
- The addition of AVI to CAZ increased the % susceptible from 81.0% to 92.4% for the CA-infection population, and from 73.0% to 89.2% for the HA-infection population (Table 1, Fig. 4 and Fig.5).
- Excluding isolates carrying MBLs from the CA-set increased the percentage susceptible to CAZ-AVI from 92.4% to 94.9%. Excluding MBL positive isolates from the HA-set increased the percentage susceptible to CAZ-AVI from 89.2% to 93.0% (Table 1).

Conclusions

Against Enterobacterales and *P. aeruginosa* from adult patients, CAZ-AVI exhibited excellent *in vitro* activity regardless of whether the pathogen was isolated <48 hrs. or ≥48 hrs. post hospital admission. The slightly decreased susceptibility to CAZ-AVI for the HA *P. aeruginosa* isolates as compared to the CA isolates, as well as the relatively low susceptibility percentage rates for comparators, reinforces the difficult-to-treat nature of nosocomial infections.

References

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2. Clinical and Laboratory Standards Institute. *Performance Standards for Antimicrobial Susceptibility Testing – 32nd ed*. CLSI Supplement M100. 2022. CLSI, Wayne, PA.
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.