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In Vitro Activity of Ceftazidime-avibactam and Comparator Agents against Enterobacterales and *Pseudomonas aeruginosa* Collected from Patients with Bloodstream Infections as Part of the ATLAS Global Surveillance Program, 2017-2020

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Introduction

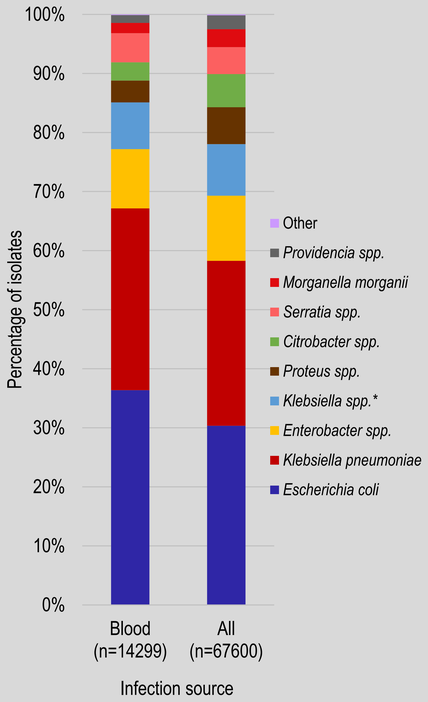
Avibactam (AVI) is a β-lactamase inhibitor with potent inhibitory activity against Class A, Class C, and some Class D serine β-lactamases, but not Class B metallo-β-lactamases (MBLs). The use of ceftazidime-avibactam is approved for several indications. This study evaluates the *in vitro* activity of ceftazidime-avibactam and comparators against Enterobacterales and *Pseudomonas aeruginosa* isolated from the blood of infected patients as part of the ATLAS surveillance program in 2017-2020.

Methods

A total of 67,600 Enterobacterales and 23,128 *P. aeruginosa* non-duplicate, clinically significant isolates, including 14,299 Enterobacterales and 3,021 *P. aeruginosa* isolated from patients with bloodstream infections were collected in 56 countries in Europe, Latin America, Asia/Pacific (excluding mainland China), and the Middle East/Africa. Susceptibility testing was performed by CLSI broth microdilution and analyzed using CLSI 2022 breakpoints (1-2). Meropenem-nonsusceptible Enterobacterales and *P. aeruginosa* isolates were screened for the presence of β-lactamase genes (3). Only 25% of MEM-NS *P. aeruginosa* collected in 2020 were screened for β-lactamase genes.

Results

Figure 1: Distribution of Enterobacterales species among isolates in this study, by infection source



*Species other than *K. pneumoniae*

Figure 2a: Percentage of Enterobacterales isolated from bloodstream infections susceptible to ceftazidime-avibactam and comparator agents

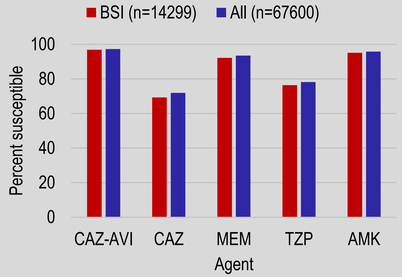
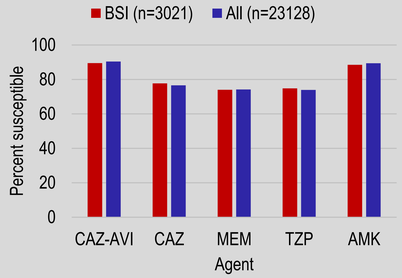


Figure 2b: Percentage of *P. aeruginosa* isolates susceptible to ceftazidime-avibactam and comparator agents, by infection source



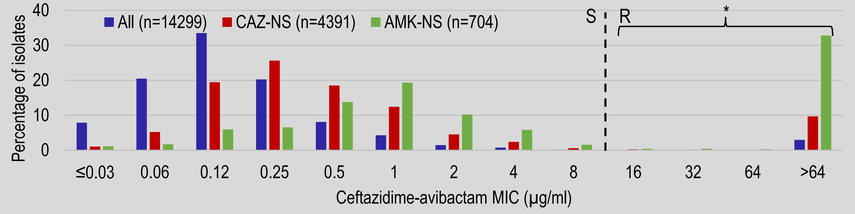
CAZ-AVI, ceftazidime-avibactam; CAZ, ceftazidime; MEM, meropenem; TZP, piperacillin-tazobactam; AMK, amikacin; BSI, bloodstream infection.

Table 1: *In vitro* activity of ceftazidime-avibactam and comparators against isolates by infection source and phenotype and/or genotype

Source	Organism/Phenotype/Genotype (n)	Agent, [MIC_{90} (μg/ml), % Susceptible]									
		CAZ-AVI		CAZ		TZP		MEM		AMK	
		MIC_{90}	%S	MIC_{90}	%S	MIC_{90}	%S	MIC_{90}	%S	MIC_{90}	%S
All	**Enterobacterales (n=67,600)**	0.5	97.3	>64	71.9	>64	78.2	0.12	93.5	8	95.8
Blood	**Enterobacterales (n=14,299)**	0.5	96.9	>64	69.3	>64	76.4	0.25	92.2	8	95.1
	CAZ-NS (n=4,391)	16	89.8	>64	0.0	>64	38.4	>8	75.8	>32	85.6
	MEM-NS (n=1,119)	>64	62.0	>64	5.0	>64	1.0	>8	0.0	>32	55.3
	MEM-NS, MBL-Neg (n=692)	4	97.8	>64	7.7	>64	1.4	>8	0.0	>32	62.4
All	***P. aeruginosa* (n=23,128)**	8	90.4	64	76.6	>64	73.9	>8	74.2	32	89.4
Blood	***P. aeruginosa* (n=3,021)**	16	89.5	64	77.7	>64	74.8	>8	74.0	32	88.5
	CAZ-NS (n=673)	>64	53.0	>64	0.0	>64	7.7	>8	27.2	>32	56.9
	MEM-NS (n=785)	>64	61.3	>64	37.6	>64	30.1	>8	0.0	>32	59.6
	MEM-NS, MBL-Neg (n=437)[a]	32	80.1	>64	47.8	>64	38.0	>8	0.0	>32	72.8

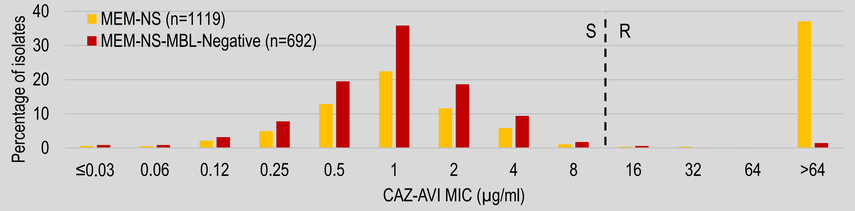
CAZ-AVI, ceftazidime-avibactam; CAZ, ceftazidime; MEM, meropenem; TZP, piperacillin-tazobactam; AMK, amikacin; NS, non-susceptible; MBL, metallo-β-lactamase.
[b] Not all MEM-NS *P. aeruginosa* isolates testing nonsusceptible to meropenem collected in 2020 were screened for MBLs. Only those that were screened are included here.

Figure 3A: ceftazidime-avibactam MIC distribution against Enterobacterales isolated from patients with bloodstream infections, by phenotype



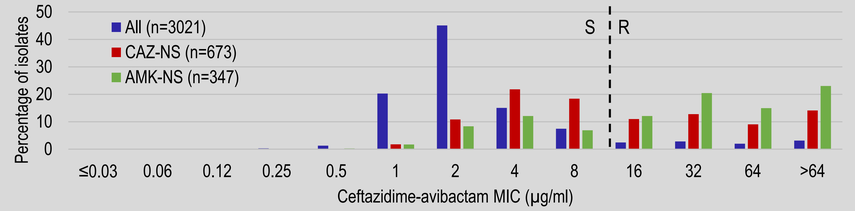
CAZ, ceftazidime; NS, non-susceptible; AMK, amikacin. The dashed line represents the CLSI 2022 breakpoint of ≤8 μg/ml for ceftazidime-avibactam. S, susceptible; R, resistant.
*MBLs were present in isolates testing with MIC values >8 μg/ml for CAZ-AVI: All and CAZ-NS: 408/448 (91.1%); AMK-NS, 230/239 (96.2%).

Figure 3B: ceftazidime-avibactam MIC distribution against meropenem-nonsusceptible Enterobacterales isolated from patients with bloodstream infections, by MBL presence



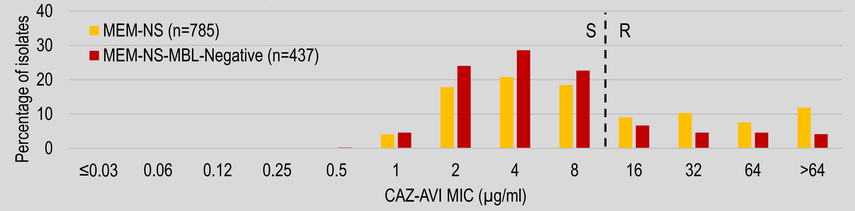
The dashed line represents the CLSI 2022 breakpoint of ≤8 μg/ml for ceftazidime-avibactam. S, susceptible; R, resistant

Figure 4A: ceftazidime-avibactam MIC distribution against *P. aeruginosa* isolated from patients with bloodstream infections, by phenotype



The dashed line represents the CLSI 2022 breakpoint of ≤8 μg/ml for ceftazidime-avibactam. S, susceptible; R, resistant

Figure 4B: ceftazidime-avibactam MIC distribution against meropenem-nonsusceptible *P. aeruginosa* isolated from patients with bloodstream infections, by MBL presence



The dashed line represents the CLSI 2022 breakpoint of ≤8 μg/ml for ceftazidime-avibactam. S, susceptible; R, resistant

Results

- *Escherichia coli* and *Klebsiella pneumoniae* were the most frequently identified species of Enterobacterales among blood isolates collected in this study, accounting for 67.1% of these isolates (Figure 1).
- The percentages of blood isolates susceptible to ceftazidime-avibactam were 96.9% (Enterobacterales) and 89.5% (*P. aeruginosa*), greater than the percent susceptible to the comparators tested (Table 1; Figures 2a-2b).
- Susceptibility of blood isolates was similar to all isolates collected across all comparators, with the greatest difference between blood isolates of Enterobacterales susceptible to ceftazidime (69.3%), which was 2.6 percentage points lower than Enterobacterales isolates collected from all infection sources (Figure 2A, 2B).
- The percentage of Enterobacterales isolates susceptible to ceftazidime-avibactam varied by non-susceptibility to other agents (CAZ-NS, 89.8%; MEM-NS-MBL-negative, 97.8%), with fewer isolates susceptible among populations with a greater proportion of MBL-positive isolates (AMK-NS, 66.1%; MEM-NS, 62.0%) (Figures 3A, 3B; Table 1).
- More isolates within resistant subsets were susceptible to ceftazidime-avibactam than for the comparators tested, except for ceftazidime-nonsusceptible blood isolates of *P. aeruginosa* (53.0% CAZ-AVI-susceptible, 56.9% AMK-susceptible) (Table 1).

Conclusions

- Ceftazidime-avibactam provides a valuable therapeutic option for infections caused by Enterobacterales and *P. aeruginosa*, which can cause life-threatening bloodstream infections.
- The spread of metallo-β-lactamases that compromise the activity of ceftazidime-avibactam and other important agents warrants continued monitoring.

References

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3. Lob SH, Kazmierczak KM, Badal RE, Hackel MA, Bouchillon SK, Biedenbach DJ, Sahm, DF. 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 AstraZeneca (AZ). AZ's rights to ceftazidime-avibactam were acquired by Pfizer in December 2016. ME and DS are employees of IHMA, who received fees from Pfizer for the conduct of the study and were paid consultants to Pfizer in connection with the development of this abstract/poster. GS, an employee of and shareholder in AZ at the time of the study, is currently an employee of Pfizer.

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