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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, 2015-2018

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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. The combination of ceftazidime (CAZ) with AVI has been approved in Europe and in the United States for several indications. This study evaluated the *in vitro* activity of CAZ-AVI and comparators against Enterobacterales and *Pseudomonas aeruginosa* isolates collected from patients with bloodstream infections as part of the ATLAS surveillance program in 2015-2018.

Methods

- A total of 57048 Enterobacterales and 15813 *P. aeruginosa* non-duplicate clinically significant isolates, including 7720 Enterobacterales and 1286 *P. aeruginosa* isolated from bloodstream infections, were collected in 52 countries in Europe, Latin America, Asia/Pacific (excluding mainland China), and the Middle East/Africa region in 2015-2018.
- Susceptibility testing was performed by CLSI broth microdilution and interpreted according to CLSI 2020 breakpoints [1, 2]. MICs of tigecycline were interpreted using US FDA breakpoints [3].
- CAZ-AVI was tested at a fixed concentration of 4 μg/ml AVI.
- Meropenem-nonsusceptible (MEM-NS) Enterobacterales and *P. aeruginosa* isolates were screened for the presence of β-lactamase genes by PCR and sequencing [4, 5].

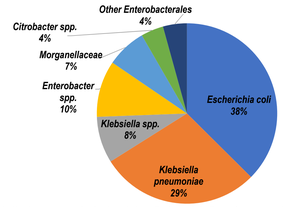
Results

Table 1: *In vitro* activity of ceftazidime-avibactam and comparators against Enterobacterales and *P. aeruginosa* collected from patients with bloodstream infections[a]

Source/Organism/Phenotype (no. of isolates)		Drug (MIC_{90} [μg/ml]/% Susceptible)															
		CAZ-AVI		CAZ		FEP		MEM		TZP		AMK		LVX		TGC	
		MIC_{90}	%S	MIC_{90}	%S	MIC_{90}	%S	MIC_{90}	%S	MIC_{90}	%S	MIC_{90}	%S	MIC_{90}	%S	MIC_{90}	%S
All	Enterobacterales, All (57048)	0.5	98.6	64	74.5	>16	77.0	0.12	95.6	>64	84.0	8	97.0	>8	68.2	1	96.7
Blood	All (7720)	0.5	98.1	64	71.6	>16	73.3	0.12	94.2	>64	83.7	8	96.6	>8	66.7	1	97.3
	CAZ-NS (2192)	2	93.4	>128	0.0	>16	16.2	>8	81.0	>64	52.8	32	89.7	>8	28.2	2	96.4
	MEM-NS (445)	>128	69.4	>128	6.5	>16	3.4	>8	0.0	>64	1.1	>32	62.9	>8	11.2	2	91.2
	MEM-NS, MBL-negative (312)	4	99.0	>128	9.3	>16	4.5	>8	0.0	>64	1.0	>32	69.6	>8	10.6	2	93.6
	TZP-NS (1255)	128	89.1	>128	17.6	>16	26.8	>8	64.9	>64	0.0	>32	83.7	>8	29.3	2	94.8
	AMK-NS (263)	>128	71.1	>128	14.1	>16	8.0	>8	37.3	>64	22.1	>32	0.0	>8	11.4	2	90.1
	LVX-NS (2568)	2	95.3	>128	38.8	>16	37.1	>8	84.6	>64	65.5	16	90.9	>8	0.0	2	95.2
	TGC-NS (210)	8	90.0	>128	61.9	>16	57.1	>8	81.4	>64	69.1	32	87.6	>8	41.4	8	0.0
All	*P. aeruginosa*, All (15813)	8	90.9	64	76.5	>16	78.4	>8	73.2	>64	72.2	32	89.9	>8	63.4	>8	NA
Blood	All (1286)	16	89.4	64	76.9	>16	78.3	>8	71.6	>64	73.9	>32	87.0	>8	66.7	>8	NA
	CAZ-NS (297)	128	54.2	>128	0.0	>16	14.1	>8	23.6	>64	7.7	>32	53.5	>8	29.3	>8	NA
	MEM-NS (365)	128	63.8	>128	37.8	>16	39.5	>8	0.0	>64	31.5	>32	58.1	>8	25.5	>8	NA
	MEM-NS, MBL-negative (288)	32	80.2	>128	47.2	>16	48.6	>8	0.0	>64	38.2	>32	69.8	>8	31.3	>8	NA
	TZP-NS (336)	128	60.7	>128	18.5	>16	20.5	>8	25.6	>64	0.0	>32	57.1	>8	27.7	>8	NA
	AMK-NS (167)	>128	34.1	>128	17.4	>16	17.4	>8	8.4	>64	13.8	>32	0.0	>8	5.4	>8	NA
	LVX-NS (428)	64	69.9	>128	50.9	>16	50.2	>8	36.5	>64	43.2	>32	63.1	>8	0.0	>8	NA

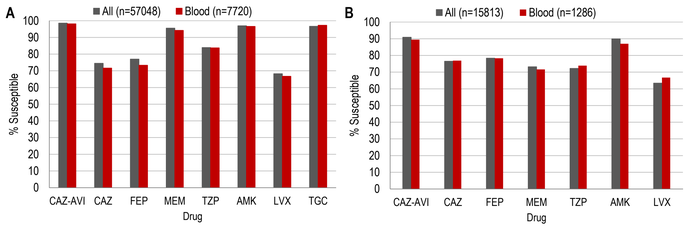
[a]CAZ-AVI, ceftazidime-avibactam; CAZ, ceftazidime; FEP, cefepime; MEM, meropenem; TZP, piperacillin-tazobactam; AMK, amikacin; LVX, levofloxacin; TGC, tigecycline; NS, non-susceptible; MBL-negative, no gene encoding a metallo-β-lactamase (MBL) was detected by PCR; NA, no breakpoint assigned. % susceptible was determined using CLSI 2020 breakpoints, except for tigecycline (US FDA).

Figure 1. Species distribution of Enterobacterales isolated from bloodstream infections (n=7220)



Klebsiella spp. included *K. oxytoca* (n=319), *K. aerogenes* (n=244) and *K. variicola* (n=81). *Enterobacter* spp. included *E. cloacae* (n=625), *E. asburiae* (n=76), *E. kobei* (n=22), *E. ludwigii* (n=5), *E. xianfangensis* (n=3), *E. hormaechei* (n=2), *E. bugandensis* (n=1), and *Enterobacter*, species not determined (n=46). *Morganellaceae* included *Proteus mirabilis* (n=263), *Morganella morganii* (n=123), *Providencia stuartii* (n=65), *Proteus vulgaris* (n=50), *Providencia rettgeri* (n=34), *Proteus hauseri* (n=14), *Proteus penneri* (n=1), and *Providencia alcalifaciens* (n=1). *Citrobacter* spp. included *C. freundii* (n=173), *C. koseri* (n=99), *C. braakii* (n=19), *C. amalonaticus* (n=8), *C. sedlakii* (n=7), *C. farmeri* (n=2), *C. gillenii* (n=1), *C. youngae* (n=1), and *Citrobacter*, species not determined (n=2). Other Enterobacterales included *Serratia marcescens* (n=312), *Raoultella ornithinolytica* (n=7), *Raoultella planticola* (n=2), *Pantoea septica* (n=3), *Pantoea agglomerans* (n=1), *Pantoea dispersa* (n=1), *Pantoea*, species not determined (n=1), *E. vulneris* (n=1), *Pluralibacter gergoviae* (n=1), *Salmonella*, species not determined (n=1), *Serratia liquefaciens* (n=1), and *Serratia ureilytica* (n=1).

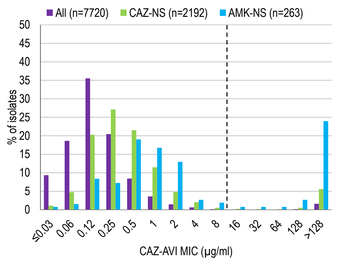
Figure 2A and 2B. Percentages of susceptibility to ceftazidime-avibactam and comparators among (A) Enterobacterales and (B) *P. aeruginosa*[a]



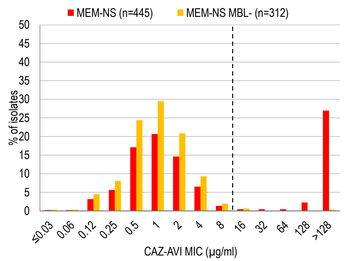
[a]CAZ-AVI, ceftazidime-avibactam; CAZ, ceftazidime; FEP, cefepime; MEM, meropenem; TZP, piperacillin-tazobactam; AMK, amikacin; LVX, levofloxacin; TGC, tigecycline.

Figure 3A and 3B. Ceftazidime-avibactam MIC distributions against Enterobacterales from bloodstream infections

A. MIC distributions against all, ceftazidime-non-susceptible (CAZ-NS), and amikacin-non-susceptible (AMK-NS) isolates [a,b]



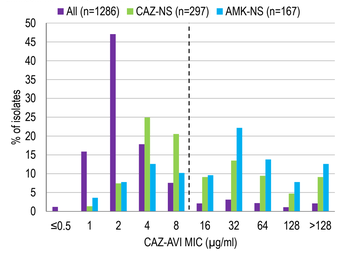
B. MIC distributions against meropenem-non-susceptible (MEM-NS) and meropenem-non-susceptible, MBL-negative (MEM-NS, MBL-) isolates [a,b]



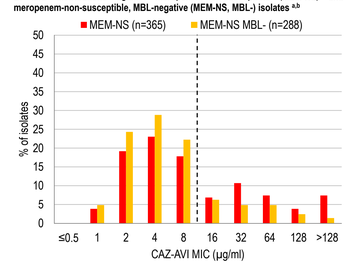
[a]CAZ-NS (MIC >4 μg/ml), AMK-NS (MIC >16 μg/ml), MEM-NS (MIC >1 μg/ml). Dashed line represents the CLSI susceptibility breakpoint of 8 μg/ml for CAZ-AVI. [b]93.8% (135 of 144) CAZ-AVI-R (MIC >8 μg/ml) Enterobacterales carried MBLs. Among isolates with drug resistant phenotypes, 93.8% (135/144) of CAZ-NS, CAZ-AVI-R isolates, 93.4% of AMK-NS, CAZ-AVI-R isolates (71/76), and 97.8% of MEM-NS, CAZ-AVI-R isolates (133/136) carried MBLs.

Figure 4A and 4B. Ceftazidime-avibactam MIC distributions against *P. aeruginosa* from bloodstream infections

A. MIC distributions against all, ceftazidime-non-susceptible (CAZ-NS), and amikacin-non-susceptible (AMK-NS) isolates [a,b]



B. MIC distributions against meropenem-non-susceptible (MEM-NS) and meropenem-non-susceptible, MBL-negative (MEM-NS, MBL-) isolates [a,b]



[a]CAZ-NS (MIC >8 μg/ml), AMK-NS (MIC >16 μg/ml), MEM-NS (MIC >2 μg/ml). Dashed line represents the CLSI susceptibility breakpoint of 8 μg/ml for CAZ-AVI. [b]55.1% (75 of 136) CAZ-AVI-R (MIC >8 μg/ml) *P. aeruginosa* carried MBLs. Among isolates with drug resistant phenotypes, 55.1% (75/136) of CAZ-NS, CAZ-AVI-R isolates, 59.1% of AMK-NS, CAZ-AVI-R isolates (65/110), and 56.8% (75/132) of MEM-NS, CAZ-AVI-R isolates carried MBLs.

Results

Enterobacterales

- Ceftazidime-avibactam (CAZ-AVI) was active *in vitro* (MIC ≤8 μg/ml) against 98.1% of all Enterobacterales collected from bloodstream infections (MIC_{90}, 0.5 μg/ml) (Table 1, Figure 1). Percentages of susceptibility (% S) to the tested agents were 0.3-3.7% lower among blood isolates compared to isolates from combined sources in most cases (Figure 2A).
- CAZ-AVI showed good *in vitro* activity, which exceeded that of all tested comparators except tigecycline, against isolates with drug-resistant phenotypes, including ceftazidime (CAZ)-non-susceptible (NS), levofloxacin (LVX)-NS and tigecycline (TGC)-NS isolates (MIC_{90}, 2-8 μg/ml, 90.0-95.3% S) (Table 1, Figure 3A, Figure 3B).
- Reduced activity against meropenem (MEM)-NS, piperacillin-tazobactam (TZP)-NS and amikacin (AMK)-NS isolates was attributable to carriage of class B metallo-β-lactamases (MBLs). 99% of MEM-NS MBL-negative isolates (MIC_{90}, 4 μg/ml) were susceptible to CAZ-AVI (Table 1, Figure 3A, Figure 3B).

P. aeruginosa

- CAZ-AVI also demonstrated good *in vitro* activity against *P. aeruginosa* bloodstream isolates (MIC_{90}, 16 μg/ml, 89.4% S) (Table 1). Susceptibilities to CAZ-AVI, AMK and MEM were 1.5-2.9% lower among bloodstream isolates compared to isolates from combined sources (Figure 2B).
- CAZ-AVI activity was reduced against subsets of drug-resistant *P. aeruginosa* (34.1-69.9% S), which included isolates carrying MBLs, but exceeded the activity of all other tested comparators including AMK by 1-70% (Table 1, Figure 4A, Figure 4B).
- As expected, activity was improved against isolates that did not harbor MBLs, with 80.2% of MEM-NS MBL-negative isolates susceptible to CAZ-AVI (Table 1).

Conclusions

- Regardless of the resistant phenotype analyzed, CAZ-AVI was the most active or second most active agent after TGC against Enterobacterales isolated from bloodstream infections, and the most active against *P. aeruginosa* isolates.
- CAZ-AVI provides a valuable therapeutic option for treating bloodstream infections caused by MBL-negative Enterobacterales and *P. aeruginosa* with intermediate or resistant MICs to commonly-used antimicrobials, including the last-line agents AMK and TGC.

References

1. Clinical and Laboratory Standards Institute. 2018. M07-A11. *Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; Approved standards – Eleventh Edition*. Clinical and Laboratory Standards Institute, Wayne, PA.
2. Clinical and Laboratory Standards Institute. 2020. M100-S30. *Performance standards for antimicrobial susceptibility testing, thirtieth informational supplement*. Clinical and Laboratory Standards Institute, Wayne, PA.
3. Pfizer, Inc. 2016. Tygacil (tigecycline) prescribing information. Pfizer, Inc., Collegeville, PA.
4. 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.
5. Nichols WW, de Jonge BL, Kazmierczak KM, *et al*. *In vitro susceptibility of global surveillance isolates of Pseudomonas aeruginosa to ceftazidime-avibactam (INFORM 2012 to 2014)*. 2016. Antimicrob Agents Chemother 60:4743-4749.

Disclosures

This study was sponsored by AstraZeneca (AZ). AZ's rights to ceftazidime-avibactam were acquired by Pfizer in December 2016. KK, SL 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 development of the abstract. GS was an employee of and shareholder in AZ at the time of the study and is currently an employee of Pfizer. This study was funded in part by BARDA under OT number HHSO100201500029C.