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Brief Communication

In vitro activity of ceftazidime-avibactam against Gram-negative strains in patients with complicated urinary tract infection and complicated intra-abdominal infection in Colombia 2014-2018

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ABSTRACT

Ceftazidime/avibactam (CAZ/AVI) has excellent *in vitro* activity against enterobacterales and *Pseudomonas aeruginosa*. The study aimed to analyze the *in vitro* antimicrobial activity of CAZ/AVI and other antibiotics against isolates of enterobacterales and *P. aeruginosa* from patients with complicated urinary tract infection (cUTI) and complicated intra-abdominal infection (cIAI) in Colombian hospitals between 2014 and 2018, using the Antimicrobial Testing Leadership and Surveillance (ATLAS) database. Enterobacterales and *P. aeruginosa* samples were obtained from patients with cUTI and cIAI. Susceptibility was determined using The Clinical and Laboratory Standards Institute (CLSI) breakpoints. Meropenem-non-susceptible isolates were screened for extended-spectrum β-lactamase (ESBL) production. Isolates that were positive for ESBL activity were examined by Multiplex Polymerase Chain Reaction (Multiplex PCR) to detect genotypic resistance. A total of 565 Enterobacterales and 95 *P. aeruginosa* from patients with cUTI and 345 Enterobacterales and 65 *P. aeruginosa* from patients with cIAI were isolated. *In vitro* activity showed susceptibility to CAZ/AVI greater than 99% for Enterobacterales and in lower percentages for *P. aeruginosa* in cUTI (78.46%) and cIAI (83.33%). CAZ/AVI showed good *in vitro* activity against multidrug-resistant (MDR) Enterobacterales and *P. aeruginosa* in patients with cUTI and cIAI.

Complicated Urinary tract infection (cUTI) and intra-abdominal infection (cIAI) are mainly caused by multidrug-resistant (MDR) Gram-negative bacteria. The treatment of cUTI and cIAI caused by MDR Gram-negative bacteria is a problem in medical practice because of the unavailability of molecules with activity against these microorganisms, or the serious adverse effects of current therapy.[1] For this reason, the combination of new molecules has been studied, such as ceftazidime/avibactam (CAZ/AVI).

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Table 1 – Antimicrobial activity among isolates of Enterobacterales, Carbapenem Resistant Enterobacterales, metallo β-lactamase negative producing, extended-spectrum β-lactamase, *Klebsiella pneumoniae* carbapenemase (KPC)-producing and multidrug-resistant enterobacterales in patients with cIAI or cUTI collected in Colombia between 2014 – 2018.

	cUTI						cIAI					
	Enterobacterales n = 565		CRE n = 31		MBL negative n = 31		Enterobacterales n = 345		CRE n = 35		MBL negative n = 25	
ntimicrobial	S	NS	S	NS	S	NS	S	NS	S	NS	S	NS
Amikacin	96.46	3.54	67.74	32.26	67.74	32.26	97.1	2.9	80	20	76	24
Aztreonam	66.74	33.26	0	100	0	100	70.83	29.17	0	100	0	100
Cefepime	70.97	29.03	6.45	93.55	6.45	93.55	77.39	22.61	2.86	97.14	4	96
CZA	99.58	0.42	96.15	3.85	96.15	3.85	99.58	0.42	95.65	4.35	95.65	4.35
Colistin	NA	100	NA	100	NA	100	NA	100	NA	100	NA	100
Levofloxacin	63.54	36.46	25.81	74.19	25.81	74.19	71.59	28.41	20	80	24	76
Meropenem	93.81	6.19	0	100	0	100	88.41	11.59	0	100	0	100
Pip/taz	82.83	17.17	0	100	0	100	76.23	23.77	0	100	0	100
	cUTI						cIAI					
	ESBL n = 21		KPC n = 40		MDR n = 194		ESBL n = 19		KPC n = 32		MDRn = 107	
Antimicrobial	S	NS	S	NS	S	NS	S	NS	S	NS	S	NS
Amikacin	100	0	72.5	27.5	91.24	8.76	100	0	81.25	18.75	91.59	8.41
Cefepime	61.9	38.1	25	75	16.57	73.71	52.63	47.37	18.75	81.25	36.45	63.55
Ceftazidime	33.33	66.67	22.5	77.5	26.29		36.84	63.16	15.63	84.37		
CZA	100	0	100	0	98.9	1.1	100	0	96.67	3.33	98.84	1.16
Colistin	NA	100	NA	100	NA	100	NA	100	NA	100	NA	100
Levofloxacin	61.9	38.1	27.5	72.5	30.93	69.07	73.68	26.32	21.88	78.12	40.19	59.81
Meropenem	100	0	22.5	77.5	82.47	17.53	94.74	5.26	9.38	90.62	63.55	36.45
Pip/taz	38.1	61.9	5	95	62.37	37.63	47.37	52.63	0	100	29.91	70.09
Tigecycline	85.71	14.29	97.5	2.5			89.47	10.53	100	0		

Pip/taz, Piperacillin-tazobactam; CZA, Ceftazidime-Avibactam; cIAI, complicated intra-abdominal infection; cUTI, complicated Urinary Tract Infection; S, Susceptible; NS, Not susceptible; NA, No breakpoint available.

Studies have shown that CAZ/AVI had excellent *in vitro activity* against carbapenem-resistant Enterobacterales (CRE),[2] Enterobacterales producing KPC-type carbapenemases and carbapenem-resistant *Pseudomonas aeruginosa*.[3] Additionally, different publications have reported that CAZ/AVI showed high activity against ceftazidime-resistant Enterobacterales,[4] and ESBL-producing *E. coli* and *K. pneumoniae* in patients with cUTI and cIAI.[5] CAZ/AVI has also been found to have a good *in vitro* response against carbapenemase-producing Enterobacterales, specifically KPC (100% susceptibility) and OXA-48 (100% susceptibility); the *in vitro* activity is maintained even in those strains resistant to ceftazidime and meropenem.[6]

In Colombia, ceftazidime/avibactam(Zavicefta®) has had a registration certificate since 2019, and it is indicated for the treatment of cIAI, in combination with metronidazole, cUTI (including pyelonephritis), and hospital-acquired pneumonia (including ventilator-associated pneumonia) in adults, infants from 3 months onwards, children and adolescents.[7] For this reason, it is important to conduct studies that evaluate *in vitro* activity of this molecule against Gram-negative strains in patients with cUTI and cIAI.

The study aimed to evaluate the *in vitro* antimicrobial activity of CAZ/AVI and other antibiotics against isolates of Gram-negative microorganisms found in patients with cUTI and cIAI in Colombian hospitals between 2014 and 2018, using the Antimicrobial Testing Leadership and Surveillance (ATLAS) database.[8]

We evaluated Enterobacterales and *Pseudomonas aeruginosa* obtained from patients with cUTI and cIAI in four hospitals in Colombia from 2014 to 2018.[8] Each hospital selected different bacterial species regardless of their antimicrobial susceptibility. Abdominal fluid and urine samples were collected from adult, pediatric, and neonatal patients.[9] Details for the identification, testing, detection of ESBL production, and identification of the genes have been previously described.[10]

During the period of 2014 and 2018, 565 Enterobacterales and 95 *Pseudomonas aeruginosa* were collected from patients with cUTI, and 345 Enterobacterales and 65 *P. aeruginosa* from patients with cIAI were isolated (Tables 1 and 2). More than 25% of Enterobacterales from cUTI patients were not susceptible to aztreonam (33.26%), cefepime (29.03%), and levofloxacin (36.46%), while non susceptibility to aztreonam (29.17%) and levofloxacin (28.41%) was observed in Enterobacterales from cIAI patients (Table 1). *In vitro* activity showed susceptibility to CAZ/AVI greater than 99% for Enterobacterales (Table 1) and in lower percentages for *P. aeruginosa* from cUTI patients (78.46%) and cIAI patients (83.33%) (Table 2). The proportion of CRE was 6.19% for isolates from cUTI patients and 11.59% for isolates from cIAI patients (Table 1).

CRE isolates from both cUTI and cIAI patients showed reduced susceptibility to most antibiotics. The antibiotic with best susceptibility profile for CRE was CAZ/AVI, with 96.15% of CRE isolates from cITU patients and 95.65% of CRE isolates from cIAI patients (Table 1). This *in vitro* activity was

Table 2 – Antimicrobial activity among isolates of *P. aeruginosa*, carbapenem resistant, *Klebsiella pneumoniae* carbapenemase (KPC)-producing and multidrug-resistant *Pseudomonas aeruginosa* in patients with cIAI or cUTI collected in Colombia between 2014 – 2018.

	cUTI				cIAI			
	P. aeruginosa n = 95		Carbapenem R n = 37		*P. aeruginosa* n = 65		Carbapenem R n = 20	
Antimicrobial	**S**	**NS**	**S**	**NS**	**S**	**NS**	**S**	**NS**
Amikacin	76.84	23.16	40.54	59.46	78.46	21.54	35	65
Aztreonam	56.06	43.94	9.52	90.48	66.67	33.33	8.33	91.67
Cefepime	57.89	42.11	10.81	89.19	75.38	24.62	25	75
CZA	78.46	21.54	38.1	61.9	83.33	16.67	41.67	58.33
Colistin	NA	100	NA	100	NA	100	NA	100
Levofloxacin			16.22	83.78	63.08	36.92	5	95
Meropenem			0	100	58.46	41.54	0	100
Pip/taz	53.68	46.32	18.92	81.08	64.62	35.38	15	85
	cUTI				cIAI			
	KPC n = 8		MDR n = 35		KPC n = 3		MDR n = 18	
Antimicrobial	**S**	**NS**	**S**	**NS**	**S**	**NS**	**S**	**NS**
Amikacin	37.5	62.5	40	60	0	100	22.22	77.78
Aztreonam	0	100	4.35	95.65	0	100	9.09	90.91
Cefepime	0	100	0	100	0	100	11.11	88.89
CZA	50	50	43.48	56.52	33.33	66.67	27.27	72.73
Colistin	NA	100	NA	100	NA	100	NA	100
Levofloxacin	12.5	87.5	17.14	82.86	0	100	5.56	94.44
Meropenem	0	100	14.29	85.71	0	100	0	100
Pip/taz	0	100	5.71	94.29	0	100	11.11	88.89

Pip/taz, Piperacillin-tazobactam; CZA, Ceftazidime-Avibactam; Carbapenem R, Carbapenem resistant; MDR, Multidrug-resistant; cIAI, complicated intra-abdominal infection; cUTI, complicated Urinary Tract Infection; S, Susceptible; NS, Not susceptible; NA, No breakpoint available.

maintained in non-MBL-producing Enterobacterales, which showed susceptibility to CAZ/AVI of 96.15% for cUTI and 95.65% for cIAI (Table 1). The CAZ/AVI was the antibiotic with the best *in vitro* activity against ESBL-producing, KPC-producing, and MDR Enterobacterales in both types of infection (Table 1).

Regarding *P. aeruginosa*, CAZ/AVI was also the antibiotic with the best susceptibility profile, especially for isolates from cUTI patients (Table 2). For isolates from cIAI patients, *P. aeruginosa* with the highest susceptibility to CAZ/AVI was meropenem-resistant *P. aeruginosa* (41.67%), followed by KPC-producing *P. aeruginosa* (33.33%) (Table 2).

This study aimed to describe the *in vitro* susceptibility of Enterobacterales and *P. aeruginosa* to CAZ/AVI in patients with cUTI or cIAI. This antibiotic was found to present excellent *in vitro* activity, especially against Enterobacterales. In the case of *P. aeruginosa*, CAZ/AVI was the antibiotic that showed the best *in vitro* activity with susceptibility to it of less than 50%.

In several clinical trials, CAZ/AVI has shown noninferior efficacy for the treatment of cUTI and cIAI caused by MDR Gram-negative bacteria compared to the standard therapy.[11] Similar safety and risk of adverse events[12,13] have also been observed in the use of CAZ/AVI. Even CAZ/AVI is cost-effective for the treatment of cUTI[14] and management of carbapenem-resistant *K. pneumoniae*, having an impact on the number of deaths and patients' quality of life.[15] For this reason, CAZ/AVI has been approved in the United States of America, China, the European Union, and Colombia for the treatment of cUTI, cIAI, hospital-acquired pneumonia (including ventilator-associated pneumonia), and secondary bacteremia due to cUTI and cIAI.[16]

The CAZ/AVI showed excellent *in vitro* activity against CRE, MDR Enterobacterales, ESBL-producing, and KPC-producing Enterobacterales from patients with cUTI and cIAI, similar to other results reported in the scientific literature.[4,5] The *in vitro* activity of CAZ/AVI against *P. aeruginosa* was lower than the *in vitro* activity against Enterobacterales, showing carbapenem-resistant, KPC-producing, and MDR *Pseudomonas*. This result could be due to the presence of class B or D enzymes in some *P. aeruginosa* strains, which decreases CAZ/AVI activity, as reported in other studies.[5] This result could also be due to the increase of *P. aeruginosa* that carry bla_{KPC-2}, bla_{KPC-3}, and bla_{VIM} genes identified in Colombian hospitals.[17] In this study, Enterobacterales were not susceptible to colistin because the CLSI in 2020 did not establish breakpoints for this category due to the limited clinical effectiveness of colistin when intermediate antimicrobial resistance is obtained.[18]

Some limitations of this study are related to the limited number of medical centers surveyed, the number of organisms tested, and the possible methodological variability, such as the participation of different hospitals, the years of the study, and the ways samples were collected and analyzed. There are clinical variables, such as the type of infection, antibiotic use, patients' comorbidities, and the use of medical devices, that can modify the effectiveness of the antibiotic in clinical practice.

Conclusion

The CAZ/AVI is a therapeutic option to manage cUTI and cIAI caused by Enterobacterales. For *P. aeruginosa*, CAZ/AVI was the antibiotic that rated the best susceptibility, especially for cUTI.

Authors' contributions

JAR analyzed the data, interpreted the findings and wrote the manuscript. EVL, SRR and PC interpreted the findings and wrote the manuscript. All authors critically reviewed this report and approved the final version.

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Conflicts of interest

EVL, SR, PC. Work in Medical Affairs Pfizer S.A.S Colombia.

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