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.

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Keywords:
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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. For this reason, the combination of new molecules has been studied, such as ceftazidime/avibactam (CAZ/AVI).
Studies have shown that CAZ/AVI had excellent in vitro activity against carbapenem-resistant Enterobacteriales (CRE), 2 Enterobacteriales producing KPC-type carbapenemases and carbapenem-resistant Pseudomonas aeruginosa. 3 Additionally, different publications have reported that CAZ/AVI showed high activity against ceftazidime-resistant Enterobacteriales, 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 Enterobacteriales, 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 1) 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 Enterobacteriales and Pseudomonas aeruginosa obtained from patients with cUTI and cIAI in four hospitals in Colombia from 2014 to 2018. 9 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 Enterobacteriales and 95 Pseudomonas aeruginosa were collected from patients with cUTI, and 345 Enterobacteriales and 65 P. aeruginosa from patients with cIAI were isolated (Tables 1 and 2). More than 25% of Enterobacteriales 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 Enterobacteriales from cIAI patients (Table 1). In vitro activity showed susceptibility to CAZ/AVI greater than 99% for Enterobacteriales (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). This in vitro activity was

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

| Antimicrobial  | Enterobacteriales n = 565  | CRE n = 31  | MBL negative n = 31 | Enterobacteriales n = 345  | CRE n = 35  | MBL negative n = 25 |
|---------------|--------------------------|-------------|---------------------|--------------------------|-------------|---------------------|
|               | cUTI                     |             |                     | cIAI                     |             |                     |
| Amikacin      | 96.46                    | 3.54        | 67.74               | 32.26                    | 67.74       | 32.26               |
| Aztreonam     | 66.74                    | 33.26       | 0                   | 100                      | 0           | 100                 |
| Cefepime      | 70.97                    | 29.03       | 6.45                | 93.55                    | 6.45        | 93.55               |
| CZA           | 99.58                    | 0.42        | 96.15               | 3.85                     | 96.15       | 3.85                |
| Colistin      | NA                       | 100         | NA                  | 100                      | NA          | 100                 |
| Levofloxacin  | 63.54                    | 36.46       | 25.81               | 74.19                    | 25.81       | 74.19               |
| Meropenem     | 93.81                    | 6.19        | 0                   | 100                      | 0           | 100                 |
| Pip/taz       | 82.83                    | 17.17       | 0                   | 100                      | 0           | 100                 |
| Pip/taz       | 100                      | 0           | 72.5                | 27.5                     | 91.24       | 8.76                |
| Cefazidime    | 61.39                    | 38.1        | 25                  | 75                       | 16.57       | 73.71               |
| CZA           | 33.33                    | 66.67       | 22.5                | 77.5                     | 26.29       |                    |
| Cefepime      | 100                      | 0           | 98.9                | 1.1                      |             |                     |
| Colistin      | 61.39                    | 38.1        | 27.5                | 72.5                     | 30.93       | 69.07               |
| Levofloxacin  | 100                      | 0           | 22.5                | 77.5                     | 82.47       | 17.53               |
| Meropenem     | 38.1                     | 61.9        | 5                   | 95                       | 62.37       | 37.63               |
| Tigecycline   | 85.71                    | 14.29       | 97.5                | 2.5                      |             |                     |
| Pip/taz       | 100                      | 0           | 81.25               | 18.75                    | 91.59       | 8.41                |
| CZA           | 52.63                    | 47.37       | 18.75               | 81.25                    | 36.45       | 63.55               |
| Cefepime      | 36.84                    | 63.16       | 15.63               | 84.37                    |             |                     |
| Colistin      | 100                      | 0           | 96.67               | 3.33                     | 98.84       | 1.16                |
| Levofloxacin  | 73.68                    | 26.32       | 21.88               | 78.12                    | 40.19       | 59.81               |
| Meropenem     | 94.74                    | 5.26        | 9.38                | 90.62                    | 63.55       | 36.45               |
| Pip/taz       | 47.37                    | 52.63       | 0                   | 100                      | 29.91       | 70.09               |
| Tigecycline   | 89.47                    | 10.53       | 100                 | 0                        |             |                     |

Pip/taz, Piperacillin-tazobactam; CZA, Cefazidime-Avibactam; 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 against Enterobacterales, showing carbapenem-resistant *P. aeruginosa* strains, which decreases CAZ/AVI activity, as reported in other studies. 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. 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.

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 Enterobacteriales. 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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