

CEFTAZIDIME-AVIBACTAM SUSCEPTIBILITY AMONG KPC-PRODUCING ENTEROBACTEREALES IN SOUTHERN BRAZIL

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ABSTRACT

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Carbapenem-resistant *Enterobacterales* (CRE) are a subject of global concern as limited therapeutic options are available. New combinations of β -lactams and β -lactamase inhibitors, such as ceftazidime-avibactam (CAZ-AVI), have recently been approved in Brazil for the treatment of CRE infections. Cases of resistance during treatment or even without previous CAZ-AVI use have been published and it is worrisome in scenarios where KPC-producing Gram-negative bacilli are endemic, as in Brazil. We aimed to assess CAZ-AVI susceptibility among a CRE population recovered from hospitalized patients in Southern Brazil from 2015 to 2021. CAZ-AVI minimal inhibitory concentration (MIC) was determined by antibiotic gradient strips. All the 238 evaluated KPC-producing *Enterobacterales* were susceptible to CAZ-AVI (MIC = 0.25 to 8 μ g/mL), with seven isolates presenting borderline MICs (8 μ g/mL). Considering the clinical importance of this new antibiotic in Brazil, we emphasize the importance of surveillance studies to eventually detect resistance phenotypes or even increasing CAZ-AVI MICs.

Keywords: Ceftazidime-avibactam; *Enterobacterales*; Carbapenemase; Resistance

INTRODUCTION

Carbapenem-resistant *Enterobacterales* (CRE) are considered especially worrisome by the Centers for Disease Control and Prevention (CDC) and World Health Organization (WHO) due to its increased transmissibility and limited treatment options, leading to high mortality rates¹⁻⁵. Production of class A carbapenemase, specially *Klebsiella pneumoniae* Carbapenemase (KPC), is the most important mechanism of carbapenem resistance in many regions of the world, including Brazil⁶⁻¹⁰.

CRE are usually resistant to various classes of antimicrobials. Some “last-line” drugs, such as polymyxins, may remain active against these group of bacteria. However, these antibiotics present important disadvantages, including suboptimal pharmacokinetic characteristics and nephrotoxicity¹¹. On the other hand, β -lactams are one of the safest antibiotics and new combinations of β -lactams and β -lactamase inhibitors such as ceftazidime-avibactam (CAZ-AVI) have become available. Results clearly demonstrate they are more effective in treating infections caused by CRE compared to other antibiotics, particularly polymyxin regimens^{3,12}.

CAZ-AVI was approved by FDA in 2015¹³ and by ANVISA in 2018¹⁴. It is indicated for the treatment of complicated urinary tract infections, mechanical ventilation-associated bacterial pneumonia and complicated intra-abdominal infections^{13,14}. Avibactam is a synthetic non- β -lactam inhibitor that inactivates some β -lactamases, including class A β -lactamases (extended-spectrum β -lactamases and carbapenemases), C (AmpC) and some Ambler’s class D (especially OXA-48), but are not able to inhibit metallo- β -lactamases (MBL – class B)^{12,14-17}.

The introduction of this new combination in clinical practice has increased the ability to treat infections caused by multidrug-resistant *Enterobacterales*. However, reports of resistance to CAZ-AVI are a subject of concern¹⁸⁻²⁷. Cases of resistance to CAZ-AVI have been reported with¹⁸⁻²⁰ or without prior treatment with the drug^{18,21,22}.

As KPC is endemic in Brazil, the country presents an appropriate environment for CAZ-AVI usage. That is the reason why we intended to determine the susceptibility to CAZ-AVI against CRE recovered from inpatients in Southern Brazil in order to monitor its activity.

METHODS

We evaluated 238 CRE recovered from August 2015 to July 2021 in two hospitals in Porto Alegre city, Southern Brazil. Isolates were identified and carbapenem resistance was determined phenotypically, following the routines of microbiology laboratories of each hospital. Susceptibility to meropenem (Sigma-Aldrich) was confirmed by broth microdilution (concentration range: 0.5 to 256 µg/mL), according to ISO 20776-1²⁸ and interpreted according to European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints²⁹. The presence of *bla*_{KPC} and absence of a MBL gene were also confirmed by multiplex high resolution melting real-time PCR (qPCR-HRM)³⁰.

Susceptibility to polymyxin B (Sigma-Aldrich) was determined by broth microdilution, according to ISO 20776-1²⁸ and results were interpreted according to EUCAST and Clinical and Laboratory Standards Institute (CLSI)³¹.

The minimal inhibitory concentration (MIC) of CAZ-AVI was determined using antibiotic gradient strips (0.016/4 – 256/4 µg/mL) following

manufacturer's recommendation and interpreted according to EUCAST breakpoints²⁹. Isolates that presented borderline MICs (8 µg/mL) were confirmed by broth microdilution, according to ISO 20776-1²⁸ and interpreted based on EUCAST²⁹. The tested range of ceftazidime (Sigma-Aldrich) concentration was 0.5 to 256 µg/mL, with a fixed concentration of avibactam (ChemScene) of 4 µg/mL.

RESULTS

Enterobacterales included in the study were recovered from clinical specimens (n = 209; 87.8%) and from surveillance cultures (rectal swabs, n = 29; 12.2%). Clinical specimens were mainly blood (n = 86; 41.1%), urine (n = 68; 32.5%) and tracheal aspirate (n = 29; 13.9%). Isolates were identified as *K. pneumoniae* (n = 217; 91.2%), *Serratia marcescens* (n = 13; 5.5%), *Enterobacter* spp. (n = 5; 2.1%), *Escherichia coli* (n = 1; 0.4%) and *Klebsiella oxytoca* (n = 2; 0.8%). All isolates were resistant to meropenem and presented positive results for *bla*_{KPC}. None isolates presented MBL genes. All these results were detailed in supplementary table 1.

CAZ-AVI MICs ranged from 0.25 to 8 µg/mL. MIC50 and MIC90 were 1 and 2 µg/mL, respectively. We did not observe resistance to this compound (Table 1). However, seven isolates presented borderline MICs of 8 µg/mL, which was confirmed by broth microdilution.

Table 1: Susceptibility profile of KPC-producing *Enterobacterales* to polymyxin b and ceftazidime-avibactam.

Hospital	ID	Material	MIC polymyxin B (µg/mL)	MIC CAZ-AVI (µg/mL)	n
A	<i>Enterobacter cloacae</i>	Blood culture	0.5	1	1
A	<i>Enterobacter cloacae</i>	Abdominal fluid	0.5	0.5	1
A	<i>Enterobacter cloacae</i>	Tracheal aspirate	2	4	1
A	<i>Klebsiella oxytoca</i>	Rectal swab	1	1	1
A	<i>Klebsiella pneumoniae</i>	Tracheal aspirate	0.25	1	2
A	<i>Klebsiella pneumoniae</i>	Tracheal aspirate	0.25	2	1
A	<i>Klebsiella pneumoniae</i>	Sputum	0.25	1	1
A	<i>Klebsiella pneumoniae</i>	Blood culture	0.25	1	2
A	<i>Klebsiella pneumoniae</i>	Blood culture	0.25	4	1
A	<i>Klebsiella pneumoniae</i>	Peripancreatic secretion	0.25	1	1
A	<i>Klebsiella pneumoniae</i>	Rectal swab	0.25	1	1
A	<i>Klebsiella pneumoniae</i>	Rectal swab	0.25	2	1
A	<i>Klebsiella pneumoniae</i>	Urine	0.25	0.5	2
A	<i>Klebsiella pneumoniae</i>	Urine	0.25	1	3
A	<i>Klebsiella pneumoniae</i>	Urine	0.25	2	2
A	<i>Klebsiella pneumoniae</i>	Tracheal aspirate	0.5	2	3
A	<i>Klebsiella pneumoniae</i>	Tracheal aspirate	0.5	1	1

Continue...

Table 1: Continuation

Hospital	ID	Material	MIC polymyxin B (µg/mL)	MIC CAZ-AVI (µg/mL)	n
A	<i>Klebsiella pneumoniae</i>	Sputum	0.5	1	1
A	<i>Klebsiella pneumoniae</i>	Sputum	0.5	4	1
A	<i>Klebsiella pneumoniae</i>	Blood culture	0.5	0.5	1
A	<i>Klebsiella pneumoniae</i>	Blood culture	0.5	0.5	1
A	<i>Klebsiella pneumoniae</i>	Blood culture	0.5	2	6
A	<i>Klebsiella pneumoniae</i>	Blood culture	0.5	4	3
A	<i>Klebsiella pneumoniae</i>	Abdominal fluid	0.5	2	1
A	<i>Klebsiella pneumoniae</i>	Rectal swab	0.5	1	2
A	<i>Klebsiella pneumoniae</i>	Urine	0.5	1	3
A	<i>Klebsiella pneumoniae</i>	Tracheal aspirate	1	4	1
A	<i>Klebsiella pneumoniae</i>	Sputum	1	2	1
A	<i>Klebsiella pneumoniae</i>	Blood culture	1	4	2
A	<i>Klebsiella pneumoniae</i>	Urine	1	0.5	1
A	<i>Klebsiella pneumoniae</i>	Tracheal aspirate	2	0.5	1
A	<i>Klebsiella pneumoniae</i>	Tracheal aspirate	2	2	1
A	<i>Klebsiella pneumoniae</i>	Sputum	2	1	1
A	<i>Klebsiella pneumoniae</i>	Blood culture	2	2	1
A	<i>Klebsiella pneumoniae</i>	Tracheal aspirate	4	1	1
A	<i>Klebsiella pneumoniae</i>	Sputum	4	2	1
A	<i>Klebsiella pneumoniae</i>	Blood culture	4	1	1
A	<i>Klebsiella pneumoniae</i>	Blood culture	4	4	2
A	<i>Klebsiella pneumoniae</i>	Urine	4	2	3
A	<i>Klebsiella pneumoniae</i>	Tracheal aspirate	8	1	1
A	<i>Klebsiella pneumoniae</i>	Tracheal aspirate	8	2	1
A	<i>Klebsiella pneumoniae</i>	Blood culture	8	1	2
A	<i>Klebsiella pneumoniae</i>	Blood culture	8	2	1
A	<i>Klebsiella pneumoniae</i>	Rectal swab	8	1	1
A	<i>Klebsiella pneumoniae</i>	Urine	8	1	4
A	<i>Klebsiella pneumoniae</i>	Urine	8	2	2
A	<i>Klebsiella pneumoniae</i>	Tracheal aspirate	16	4	3
A	<i>Klebsiella pneumoniae</i>	Sputum	16	2	3
A	<i>Klebsiella pneumoniae</i>	Sputum	16	4	2
A	<i>Klebsiella pneumoniae</i>	Blood culture	16	2	2
A	<i>Klebsiella pneumoniae</i>	Blood culture	16	0.5	1
A	<i>Klebsiella pneumoniae</i>	Blood culture	16	8	1
A	<i>Klebsiella pneumoniae</i>	Bronchoalveolar lavage	16	0.5	1
A	<i>Klebsiella pneumoniae</i>	Rectal swab	16	0.5	1
A	<i>Klebsiella pneumoniae</i>	Rectal swab	16	2	1
A	<i>Klebsiella pneumoniae</i>	Urine	16	0.25	1
A	<i>Klebsiella pneumoniae</i>	Urine	16	2	1
A	<i>Klebsiella pneumoniae</i>	Urine	16	4	3

Continue...

Table 1: Continuation

Hospital	ID	Material	MIC polymyxin B (µg/mL)	MIC CAZ-AVI (µg/mL)	n
A	<i>Klebsiella pneumoniae</i>	Tracheal aspirate	32	2	3
A	<i>Klebsiella pneumoniae</i>	Tracheal aspirate	32	4	4
A	<i>Klebsiella pneumoniae</i>	Blood culture	32	2	3
A	<i>Klebsiella pneumoniae</i>	Blood culture	32	1	1
A	<i>Klebsiella pneumoniae</i>	Blood culture	32	8	2
A	<i>Klebsiella pneumoniae</i>	Blood culture	32	4	5
A	<i>Klebsiella pneumoniae</i>	Rectal swab	32	4	1
A	<i>Klebsiella pneumoniae</i>	Urine	32	0.25	1
A	<i>Klebsiella pneumoniae</i>	Urine	32	1	3
A	<i>Klebsiella pneumoniae</i>	Urine	32	2	7
A	<i>Klebsiella pneumoniae</i>	Urine	32	4	1
A	<i>Klebsiella pneumoniae</i>	Urine	32	8	1
A	<i>Klebsiella pneumoniae</i>	Tracheal aspirate	64	2	1
A	<i>Klebsiella pneumoniae</i>	Tracheal aspirate	64	4	2
A	<i>Klebsiella pneumoniae</i>	Blood culture	64	4	5
A	<i>Klebsiella pneumoniae</i>	Blood culture	64	8	1
A	<i>Klebsiella pneumoniae</i>	Blood culture	64	2	1
A	<i>Klebsiella pneumoniae</i>	Urine	64	1	1
A	<i>Klebsiella pneumoniae</i>	Urine	64	2	1
A	<i>Klebsiella pneumoniae</i>	Urine	64	4	2
A	<i>Klebsiella pneumoniae</i>	Tracheal aspirate	> 64	2	1
A	<i>Klebsiella pneumoniae</i>	Tracheal aspirate	> 64	4	1
A	<i>Klebsiella pneumoniae</i>	Fascia	> 64	1	1
A	<i>Klebsiella pneumoniae</i>	Blood culture	> 64	1	1
A	<i>Klebsiella pneumoniae</i>	Blood culture	> 64	8	1
A	<i>Klebsiella pneumoniae</i>	Blood culture	> 64	4	2
A	<i>Klebsiella pneumoniae</i>	Urine	> 64	0.25	1
A	<i>Klebsiella pneumoniae</i>	Urine	> 64	0.5	1
A	<i>Klebsiella pneumoniae</i>	Urine	> 64	1	6
A	<i>Klebsiella pneumoniae</i>	Urine	> 64	2	2
A	<i>Klebsiella pneumoniae</i>	Urine	> 64	4	1
A	<i>Serratia marcescens</i>	Blood culture	> 64	2	4
A	<i>Serratia marcescens</i>	Blood culture	> 64	4	1
A	<i>Serratia marcescens</i>	Rectal swab	> 64	4	1
B	<i>Enterobacter hormaechei</i>	Blood culture	0.25	1	1
B	<i>Enterobacter</i> sp.	Blood culture	> 64	2	1
B	<i>Escherichia coli</i>	Blood culture	> 64	2	1
B	<i>Klebsiella oxytoca</i>	Blood culture	1	0.25	1
B	<i>Klebsiella pneumoniae</i>	Blood culture	0.25	1	1
B	<i>Klebsiella pneumoniae</i>	Blood culture	0.25	2	1

Continue...

Table 1: Continuation

Hospital	ID	Material	MIC polymyxin B (µg/mL)	MIC CAZ-AVI (µg/mL)	n
B	<i>Klebsiella pneumoniae</i>	Blood culture	0.25	1	1
B	<i>Klebsiella pneumoniae</i>	Urine	0.25	0	2
B	<i>Klebsiella pneumoniae</i>	Urine	0.25	1	3
B	<i>Klebsiella pneumoniae</i>	Urine	0.25	2	1
B	<i>Klebsiella pneumoniae</i>	Blood culture	0.5	1	3
B	<i>Klebsiella pneumoniae</i>	Blood culture	0.5	2	3
B	<i>Klebsiella pneumoniae</i>	Rectal swab	0.5	1	1
B	<i>Klebsiella pneumoniae</i>	Rectal swab	0.5	2	4
B	<i>Klebsiella pneumoniae</i>	Urine	0.5	4	1
B	<i>Klebsiella pneumoniae</i>	Urine	0.5	1	1
B	<i>Klebsiella pneumoniae</i>	Urine	0.5	0	1
B	<i>Klebsiella pneumoniae</i>	Spine	1	1	1
B	<i>Klebsiella pneumoniae</i>	Blood culture	1	2	1
B	<i>Klebsiella pneumoniae</i>	Urine	1	2	1
B	<i>Klebsiella pneumoniae</i>	Blood culture	2	2	2
B	<i>Klebsiella pneumoniae</i>	Blood culture	2	4	2
B	<i>Klebsiella pneumoniae</i>	Skin	2	1	1
B	<i>Klebsiella pneumoniae</i>	Rectal swab	2	1	1
B	<i>Klebsiella pneumoniae</i>	Rectal swab	2	2	2
B	<i>Klebsiella pneumoniae</i>	Urine	2	1	1
B	<i>Klebsiella pneumoniae</i>	Skin	2	4	1
B	<i>Klebsiella pneumoniae</i>	Urine	4	8	1
B	<i>Klebsiella pneumoniae</i>	Rectal swab	8	2	1
B	<i>Klebsiella pneumoniae</i>	Blood culture	16	1	1
B	<i>Klebsiella pneumoniae</i>	Blood culture	16	2	1
B	<i>Klebsiella pneumoniae</i>	Rectal swab	16	1	1
B	<i>Klebsiella pneumoniae</i>	Sputum	32	1	1
B	<i>Klebsiella pneumoniae</i>	Blood culture	32	1	1
B	<i>Klebsiella pneumoniae</i>	Blood culture	32	4	1
B	<i>Klebsiella pneumoniae</i>	Rectal swab	32	2	1
B	<i>Klebsiella pneumoniae</i>	Rectal swab	32	1	2
B	<i>Klebsiella pneumoniae</i>	Urine	64	2	1
B	<i>Klebsiella pneumoniae</i>	Bronchoalveolar lavage	> 64	1	1
B	<i>Klebsiella pneumoniae</i>	Rectal swab	> 64	1	1
B	<i>Klebsiella pneumoniae</i>	Rectal swab	> 64	1	1
B	<i>Klebsiella pneumoniae</i>	Urine	> 64	2	1
B	<i>Klebsiella pneumoniae</i>	Sputum	≤ 0.125	1	1
B	<i>Klebsiella pneumoniae</i>	Sputum	≤ 0.125	2	1
B	<i>Klebsiella pneumoniae</i>	Blood culture	≤ 0.125	2	2
B	<i>Klebsiella pneumoniae</i>	Blood culture	≤ 0.125	1	1
B	<i>Klebsiella pneumoniae</i>	Abdominal fluid	≤ 0.125	2	1

Continue...

Table 1: Continuation

Hospital	ID	Material	MIC polymyxin B (µg/mL)	MIC CAZ-AVI (µg/mL)	n
B	<i>Klebsiella pneumoniae</i>	Abdominal fluid	≤ 0.125	1	1
B	<i>Klebsiella pneumoniae</i>	Rectal swab	≤ 0.125	1	4
B	<i>Klebsiella pneumoniae</i>	Urine	≤ 0.125	2	1
B	<i>Serratia marcescens</i>	Blood culture	> 64	1	5
B	<i>Serratia marcescens</i>	Sputum	> 64	1	1
B	<i>Serratia marcescens</i>	Blood culture	> 64	2	1

Polymyxin B MICs ranged from ≤ 0.125 to > 64 µg/mL (Table 1). MIC50 and MIC90 were 4 and 8 µg/mL, respectively. Polymyxin B resistant bacteria did not present higher CAZ-AVI MICs in general. Mean CAZ-AVI MIC for polymyxin B in susceptible isolates was 2 µg/mL, as well as for resistant isolates. However, isolates that presented borderline CAZ-AVI MICs (8 µg/mL) had polymyxin MICs ranging from 4 to > 64 µg/mL.

DISCUSSION

We evaluated susceptibility of 238 CRE to CAZ-AVI in order to monitor the activity of this combination of antibiotics. *K. pneumoniae* was the predominant specie in this study. None of the KPC-producers that we evaluated were resistant to CAZ-AVI, similarly to what was found by other authors worldwide and in Brazil³²⁻³⁴.

A study performed in Poland evaluated *bla*_{KPC}-positive isolates recovered from various clinical specimens between 2012-2016 and found 100% susceptibility for CAZ-AVI³⁴. Results of the China Antimicrobial Surveillance Network (CHINET) in 2017 demonstrated 94.6% of CAZ-AVI susceptibility among all *Enterobacterales* tested, with MICs ranging from ≤ 0.125 to > 32 µg/mL³⁵. Zou et al. found 70.68% of isolates susceptible to CAZ-AVI in CRE recovered from patients with bacteremia between 2016 and 2018, and resistant isolates had MICs ranging from 8 up to 64 µg/mL³⁶.

A study performed in Brazil with several species of *Enterobacterales* showed almost 100% susceptibility to CAZ-AVI among 387 isolates with unknown carbapenemase and 30 selected *bla*_{KPC}-positive. *Citrobacter freundii*, *Citrobacter koseri*, *Enterobacter aerogenes*, *Enterobacter cloacae*, *E. coli*, *K. oxytoca*, *K. pneumoniae*, *Morganella morganii*, *Proteus mirabilis* and *Proteus vulgaris* were evaluated and were fully susceptible to CAZ-AVI. However, *K. pneumoniae* harboring *bla*_{KPC}, *Providencia stuartii*, *S. marcescens*

and *Pseudomonas aeruginosa* were highly susceptible to CAZ-AVI, although with a variable percentage of susceptibility to this drug: 96.7%, 95.5%, 96.2% and 84%, respectively³³.

The International Network for Optimal Resistance Monitoring (INFORM) surveillance program published a study demonstrating that meropenem-non-susceptible *Enterobacterales* (n = 1460) from around the world, collected between 2015 and 2017, identified as carbapenemase-positive (MBL genes or serino-β-lactamases), were highly susceptible to CAZ-AVI (99.8%)³⁵.

Studies with isolates producing β-lactamases other than KPC have shown similar results. Viala et al., from France, found 97% (60/62) of susceptibility to CAZ-AVI among *Enterobacterales*. Two resistant *K. pneumoniae* isolates produced NDM-carbapenemase and extended-spectrum β-lactamase (ESBL). Furthermore, 96% (26/27) of OXA-48-producing isolates were susceptible to CAZ-AVI³⁷. Viaggi et al. observed 100% of susceptibility to CAZ-AVI in ESBL producers from Italy³⁸ and in the US, Castanheira et al. had similar results³⁹.

In some studies, KPC mutations causing CAZ-AVI resistance decreased meropenem MICs and some strains became even susceptible to meropenem. Raisanen et al.²¹ and Hemarajata and Humphries²² demonstrated this meropenem MICs reduction in *K. pneumoniae* carrying KPC gene, while Castanheira et al.¹⁹ presented same findings with *C. freundii* harboring *bla*_{KPC}. We did not observe reduced meropenem MICs when comparing the CAZ-AVI borderline MICs isolates with other isolates.

As ceftazidime-avibactam was recently approved in Brazil for clinical usage, surveillance studies such ours are vital to, eventually, detect resistance phenotypes or even trends of increasing MICs, which may precede occurrence of full resistance. Because KPC is endemic in Brazil, it is expected that CAZ-AVI usage will be widespread in many health institutions, reinforcing the need for this kind of surveillance studies.

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