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Change in *Klebsiella pneumoniae* susceptibility profile after the arrival of ceftazidime-avibactam in an Argentinean intensive care unit: a new ecological landscape

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ABSTRACT

Introduction. Ceftazidime-avibactam (CZA) is a good option for Gram-negative bacilli infections that produce carbapenemase Classes A (especially *blaKPC*) and D (*blaOXA*). However, it is unknown whether it would have an impact on metallo-β-lactamases (*blaMBL*) selection. The aim of the study was to compare carbapenem and CZA *Klebsiella pneumoniae* (KPN) susceptibility profiles for a period of two years following the introduction of CZA.

Material and methods. The study was conducted in a 36-bed adult ICU of a tertiary hospital in Buenos Aires, Argentina. Antimicrobial consumption was expressed as days of treatment per 100 patients-day (DOT).

Results. A total of 123 KPN strains in the first year and 172 in the second year were analyzed. An alarming decrease in carbapenem susceptibility was detected in the second year (OR 0.5 [0.3-0.8] p<.001). In parallel, there was a decrease in CZA susceptibility (OR 0.5 [0.3-0.9] p<.05). These findings were linked to a rise in *blaMBL*-KPN (32.1% vs. 45.1%, OR 1.7 [1.1-2.9], p <.04) during the second year. This new KPN susceptibility profile promoted an increment in CZA (1.0 DOT vs. 6.6 DOT, OR 6.6 [4.9-9.1] p<.001) and aztreonam (0.3 DOT vs. 4.1 DOT, OR 16.3 [9.1-29.3] p<.001) consumption. Thus, there was a decrease in carbapenem prescription (17.8 DOT vs. 15.4 DOT, OR 0.8 [0.8-0.9] p<.001).

Conclusions. There was an escalation of *blaMBL*-KPN rate two years after CZA introduction, leading to a decrease in CZA and carbapenem susceptibility and an increase in CZA and aztreonam prescriptions.

Keywords: *Klebsiella pneumoniae*, ceftazidime-avibactam, antimicrobial resistance.

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Cambio en el perfil de susceptibilidad de *Klebsiella pneumoniae* después de la llegada de ceftazidima-avibactam en una unidad de cuidados intensivos argentina: un nuevo panorama ecológico

RESUMEN

Introducción. Ceftazidima-avibactam (CZA) es una buena opción para las infecciones por bacilos gramnegativos que producen carbapenemasas de clases A (especialmente *blaKPC*) y D (*blaOXA*). Se desconoce su impacto en la selección de metalo-β-lactamasas (*blaMBL*). El objetivo del estudio fue comparar los perfiles de sensibilidad de *Klebsiella pneumoniae* (KPN) a carbapenémicos y CZA dos años después de la introducción de CZA.

Material y métodos. Estudio realizado en una UCI de adultos de 36 camas de un hospital terciario de Buenos Aires, Argentina. El consumo de antimicrobianos se expresó como días de tratamiento por 100 días-paciente (DDT).

Resultados. un total de 123 cepas de KPN el primer año y 172 el segundo año fueron analizadas. Se detectó una disminución en la sensibilidad a carbapenémicos en el segundo año (OR 0,5 [0,3-0,8] p<0,001). Paralelamente, la sensibilidad a CZA disminuyó (OR 0,5 [0,3-0,9] p<0,05). Estos hallazgos estuvieron relacionados con un aumento de *blaMBL*-KPN (32,1% vs. 45,1%, OR 1,7 [1,1-2,9], p <0,04). Esto promovió un incremento en el consumo de CZA (1,0 DDT vs. 6,6 DDT, OR 6,6 [4,9-9,1] p<0,001) y aztreonam (0,3 DDT vs. 4,1 DDT, OR 16,3 [9,1-29,3] p<0,001). Por lo tanto, se produjo una disminución en la prescripción de carbapenémicos (17,8 DDT vs. 15,4 DDT, OR 0,8 [0,8-0,9] p<0,001).

Conclusiones. La tasa de *blaMBL*-KPN aumentó dos años después de la introducción de CZA, lo que llevó a una disminución en la sensibilidad a CZA y carbapenémicos, y un aumento en las prescripciones de CZA y aztreonam.

Palabras clave: *Klebsiella pneumoniae*, ceftazidima-avibactam, resistencia antimicrobiana.

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INTRODUCTION

Starting from 2009, there has been a gradual increase in Argentina in the prevalence of Gram-negative bacteria that produce carbapenemases, specifically *Klebsiella pneumoniae* (CP-KPN) [1]. These microorganisms have not only established as colonizers but also emerged as significant contributors to diverse infections, including bacteremia, healthcare-associated pneumonia, surgical site infections, urinary tract infections, etc [2]. Among CP-KPN isolates, those carrying Ambler Class A enzymes like *blaKPC* have effectively disseminated throughout many Latin American nations, resulting in elevated levels of endemicity [3].

It is important to highlight that infections caused by CP-KPN are associated with significant morbidity and mortality [4,5]. This is primarily attributed to the limited range of treatment options available, which historically included combinations of drugs like aminoglycosides, colistin, tigecycline, fosfomycin, and extended infusion of high doses of carbapenems [6]. However, with the introduction of new compounds capable of inhibiting the activity of these enzymes, such as CZA (available in Argentina since 2018), meropenem-vaborbactam, and imipenem-cilastatin-relebactam, more effective therapeutic approaches have emerged, leading to improved clinical outcomes compared to the aforementioned treatments [7,8].

Nevertheless, it is crucial to acknowledge that these novel agents are not immune to the selection of antimicrobial resistance mechanisms that previously had a low prevalence in our environment, such as metallo-β-lactamases (*blaMBL*), which remain unaffected by these antibiotics [9,10]. Consequently, the introduction of these new therapies has the potential to significantly alter the composition of the hospital microbiota [11,12].

The aim of this study was to compare the prevalence of different carbapenemase Classes and CZA susceptibility profiles of KPN from an ecological point of view in intensive care units (ICU) clinical samples during the first and second year after CZA introduction in our hospital. The secondary objectives were to compare the CZA, aztreonam and carbapenems prescriptions trends during both periods; and to compare the antimicrobial consumption rate in accordance with WHO´s AWaRe classification.

MATERIAL AND METHODS

Study design and setting. A comparative analysis was conducted to evaluate data from January to December 2020 (P1: first year after the introduction of CZA at our center) and January to December 2021 (P2: second year after the introduction of CZA). The study took place in a 36-bed adult ICU located in a tertiary hospital in the City of Buenos Aires, Argentina. Data on KPN, the most prevalent microorganism in cultures from ICU patients at our hospital, was collected from non-contaminated positive clinical cultures. To avoid the analysis of microorganisms with identical antibiogram from different samples of the same individual, only the first isolate from each patient was taken into account. During the same period, the antimicrobial consumption in those areas was also monitored.

Bacterial identification, antimicrobial susceptibility, and microbiological data processing. For the purpose of conducting microbiological analysis, all KPN isolates obtained from clinical samples were considered, including significant blood cultures, urine cultures, respiratory samples, among others. Isolates categorized as contaminants or colonizers were excluded from the analysis. When microorganisms with identical antibiotic susceptibility profiles derived from different samples of the same individual, only the initial isolate from each patient was analyzed.

The bacterial identification was accomplished by mass spectrometry (MALDI BiotyperTM, Bruker Daltonics Inc.TM, United States). Sensitivity testing was performed using nephelometric methods with specialized panels specifically designed for this purpose, (NMIC-406TM-PhoenixTM panels, Becton DickinsonTM, United States). The interpretation of antibiogram results for the mentioned isolates followed the recommendations outlined by the Clinical and Laboratory Standards Institute (CLSI 31st edition 2021). CLSI. 2021. Performance standards for antimicrobial susceptibility testing [13].

Ceftazidime-avibactam, susceptibility was assessed by disk-diffusion using Mueller Hinton agar (BritaniaTM, Argentina) with ceftazidime-avibactam 10/4 µg disks (BritaniaTM, Argentina). Susceptibility to colistin was confirmed by dropcol test over Mueller Hinton agar (BritaniaTM, Argentina), according to previous report [14]. In this sense, both the interpretation of the antibiogram concerning CZA and colistin were performed according to the standards established by the *European Committee on Antimicrobial Susceptibility Testing* clinical breakpoints [15]. Finally, interpretation of fosfomycin and tigecycline susceptibilities were determined following the adaptation breakpoints proposed by Pasterán *et al.* [16].

Resistance mechanisms were detected using an *in-house* blue-carba test as a screening tool for the presence of carbapenemases production [17]. Subsequently, synergy studies were conducted on Mueller Hinton agar plates using meropenem 10µg (Britania™, Argentina), boronic acid 300µg (Britania™, Argentina), ethylenediaminetetraacetic acid/ sodium mercaptoacetate 372/900µg (EDTA, Britania™, Argentina), amoxicillin/ clavulanic acid 20/10µg (Britania™, Argentina) and aztreonam 30 µg (Britania™, Argentina) disks [18]. When available, the production of carbapenemases was confirmed by commercially immunochromatography kits designed to detect specific types of carbapenemases (including *blaKPC*, *blaNDM*, *blaVIM*, *blaIMP*, *blaOXA48-like*, and *blaOXA163*; NG-test CARBA5, NG BioNTechTM, Germany) in accordance with the national current guidelines [19].

The microbiological cumulative susceptibility data was expressed by following the latest CLSI guidelines [20] using the Whonet software 5.6.

Antimicrobial consumption data. The monitoring of antimicrobial consumption was performed as part of the local antimicrobial stewardship program, utilizing a daily manual check of prescription appropriateness with feedback provided to the prescribing staff at the patient's bedside. Days of treatment per 100 patients-day (DOT) was used as the comparator for each agent. Consumption of the following antimicrobials was assessed: penicillin, aminopenicillins (includes amoxicillin and ampicillin), ampicillin-sulbactam, piperacillin-tazobactam, injectable first-generation cephalosporins (1GC), injectable third-generation cephalosporins (3GC; includes ceftriaxone and ceftazidime), cefepime, ceftazidime-avibactam, ceftolozane-tazobactam, carbapenems (includes ertapenem, imipenem and meropenem), aztreonam, clindamycin, fluoroquinolones (includes ciprofloxacin and levofloxacin), tigecycline, fosfomycin, colistin, macrolides (includes azithromycin and clarithromycin), aminoglycosides (includes gentamicin and amikacin), vancomycin, linezolid, daptomycin and trimethoprim-sulfamethoxazole.

Furthermore, these antimicrobials were categorized according to the WHO's AWaRe groups as 'access' (penicillin, amoxicillin, ampicillin, ampicillin-sulbactam, 1GC, aminoglycosides, clindamycin and trimethoprim-sulfamethoxazole); 'watch' (piperacillin-tazobactam, 3GC, cefepime, carbapenems, fluoroquinolones, macrolides and vancomycin); or 'reserve' (CZA, aztreonam, tigecycline, fosfomycin, colistin, linezolid and daptomycin) categories for the purpose of consumption analysis [21].

Statistical analysis. Categorical variables are reported with the number (n) and percentage (%). *Chi*-square test or *Fisher*'s exact test, as appropriate, was used for proportion comparisons. Additionally, non-adjusted odds ratio (*non-adjusted* OR) was calculated. A 95% confidence interval (CI95%) was considered for all determinations, and a significance level of 5% ($p<0.05$) was established for all comparisons. Statistical analysis was performed using R-Statistics 4.0.3TM.

Ethical clearance. After analyzing the presented results, the members of the ethics and research committee of the healthcare system of the Malvinas Argentinas County (Buenos Aires, Argentina) considered that said study did not require the approval of an ethics committee, as it was an intervention within the framework of an epidemiological surveillance program with necessary action to ensure the health of the participating subjects. Resolution 1480/2011 'Guidelines for Research with Human Subjects' of the Argentine Ministry of Health, stipulates in section A2.b that this type of interventions is exempt from the approval of an ethics research committee, as long as the personal data of the participating individuals are not involved.

RESULTS

***Klebsiella pneumoniae* antimicrobial susceptibility profile.** A comprehensive analysis was conducted on a total of 123 KPN strains in P1 and 172 strains in P2, derived from clin-

Table 1 ***Klebsiella pneumoniae* (KPN) antimicrobial susceptibility profile.**

	KPN susceptibility n (%)				
	P1	P2	non-adjusted OR	CI95%	p value
Ceftazidime-avibactam	106 (67.9)	144 (53.5)	0.5	0.3-0.9	<.05
Ceftolozane-tazobactam	57 (61.4)	104 (29.8)	0.3	0.1-0.5	<.001
Ampicillin-sulbactam	121 (12.4)	170 (12.4)	0.9	0.5-2	0.1
Piperacillin-tazobactam	122 (29.5)	170 (17.6)	0.5	0.3-0.9	<.02
Third generation cephalosporins and cefepime	123 (13.8)	170 (15,3)	1.1	0.6-2.2	.7
Ertapenem*	123 (40.7)	170 (24.1)	0.5	0.3-0.8	<.001
Imipenem	122 (44.3)	170 (27.6)	0.5	0.3-0.8	<.001
Meropenem	122 (44.3)	170 (25.9)	0.4	0.3-0.7	<.001
Amikacin	122 (50.8)	171 (33.3)	0.5	0.3-0.8	<.001
Gentamycin	122 (44.3)	170 (27.1)	0.5	0.3-0.8	<.001
Ciprofloxacin	122 (18.9)	169 (15.4)	0.8	0.4-1.5	.4
Trimethoprim-sulfamethoxazole	122 (23.8)	169 (19.5)	0.8	0.4-1.4	.4
Fosfomycin	123 (80.5)	170 (68.2)	0.5	0.3-0.9	<.05
Colistin	122 (44.4)	169 (62.1)	2.1	1.3-3.3	<.001
Tigecycline	123 (69.1)	170 (71.8)	0.7	0.4-1.1	.1

***Note: carbapenem susceptibility was reported with the surrogate being the susceptibility rate of KPN to ertapenem.**

Table 2 ***Klebsiella pneumoniae*** **carbapenems and ceftazidime-avibactam resistance rate by mechanism.**

	KPN strains n (%)				
	P1	P2	non-adjusted OR	CI95%	p value
Carbapenem-resistant KPN	73 (59.3)	131 (76)	2.2	1.3-3.6	<.001
Ceftazidime-avibactam-resistant KPN	34 (32)	67 (46.5)	1.8	1.1-3.1	<.02
bla_{MBL} (total)*	34 (32.1)	65 (45.1)	1.7	1.1-2.9	<.04
bla_{MBL} and bla_{ESBL}	31 (29.2)	53 (36.8)	1.4	0.8-2.4	.2
bla_{MBL} and bla_{KPC}	3 (2.8)	12 (8.3)	3.1	0.8-11.3	<.07
bla_{KPC}	34 (27.6)	57 (33.1)	1.3	0.8-2.2	.3
$bla_{OXA-163}$	3 (1.7)	3 (2.4)	0.7	0.1-3.6	.7
bla_{ESBL} and impermeability	2 (2.1)	4 (2.3)	1.4	0.3-7.9	.7

*It includes KPN strains that harbor at least bla_{MBL}, although this is not the only mechanism of resistance against β-lactams.

ical samples collected in the ICU. Notably, in P2, there was a decline in the carbapenems susceptibility of these strains, with rates dropping significantly from 40.7% to 24.1% (*non-adjusted* OR 0.5 [0.3-0.8], p<.001). Similarly, there was a significant decrease in CZA susceptibility, from 67.9% to 53.5% (*non-adjusted* OR 0.5 [0.3-0.9], p<.05) during the second year following its introduction.

These changes have prompted modifications in the resistance profile of KPN in ICU by affecting other antimicrobial agents such as 3GC, piperacillin-tazobactam and ceftolozane-tazobactam, which experienced significant declines in their susceptibility rates (Table 1). Moreover, alternative therapeutic options for CP-KPN, including aminoglycosides and fosfomycin, also exhibited reduced rates of susceptibility in P2. Within this context, it is worth mentioning that no significant alterations were observed in the resistance profile of the isolates to tigecycline, as it maintained modest susceptibility rates just about 70% (Table 1).

The KPN resistance to carbapenem and CZA was primarily attributed to the increased prevalence of strains carrying the *blaMBL* enzymes (*non-adjusted* OR 2.2 [1.3-3.6], p <.001). However, when analyzing each resistance profile separately for *blaNDM*-KPN strains, including those co-harboring *blaMBL-blaESBL*, and *blaMBL-blaKPC*, no significant trend was observed (Table 2).

Furthermore, a significant increase in the rate of CZA-resistant CP-KPN isolates was observed during P2 (*non-adjusted* OR 1.8 [1.1-3.1], p <.02). However, there were no notable changes in the rate of isolates producing *blaKPC* and *blaOXA-163*, and no strains carrying *blaOXA-48* were detected. Besides, we identified during P2, a CZA-resistant isolate that produced a novel variant of *blaESBL*, which corresponded to *blaPER*, which had not been previously identified in our ICU (Table 2).

Ceftazidime-avibactam, aztreonam, and carbapenems prescriptions trends. The prescription rates of CZA in the ICU increased from 1.1 DOT to 6.6 DOT (*non-adjusted* OR 6.6 [4.9-9.1], p<.001). Aztreonam prescription was similarly affected, with a shift from 0.3 DOT to 4.1 DOT (*non-adjusted* OR 16.3 [9.1-29.3], p<.001) as CZA / aztreonam combination was predominantly prescribed as initial empirical treatment in patients colonized by Gram-negative bacilli carrying *blaMBL* (as it was frequently found together with *blaESBL*) in patients who displayed clinical signs of infection and in patients with documented infections caused by these microorganisms.

Conversely, as a consequence of the marked increase in carbapenem resistance in P2 (Table 3), the consumption of these agents decreased from 17.8 DOT to 15.4 DOT (*non-adjusted* OR 0.8 [0.8-0.9], p<.001). These findings shows a significant increase in the utilization of 'reserve' agents (36.4 DOT vs. 46.4 DOT; *non-adjusted* OR 1.5 [1.4-1.7], p<.001) with a reduced consumption of antimicrobials from the 'watch' group (45.7 DOT vs. 38.5 DOT; *non-adjusted* OR 0.7 [0.7-0.8], p<.001), and agents from the 'access' group, in P2 (17.9 DOT vs. 15.1 DOT; *non-adjusted* OR 0.8 [0.7-0.9], p<.001).

DISCUSSION

In the present study, after the introduction of CZA in the ICU, an increase in resistance to both, CZA and carbapenems was observed due to an increase in the prevalence of *blaMBL* producing isolates. It is worth noting that this phenomenon, in the case of our country, coincided with the arrival of the SARS-CoV2 pandemic [22], which may blur the role that the ecological pressure generated by CZA could have had on our CP-KPN strains [23]. However, this observation contrasts with the fact that several regions worldwide, such as Greece and Italy, which had licensed this antimicrobial combination prior to the pandemic, experienced an increase in rates of *blaMBL*-producing *Enterobacteriaceae* with a similar trend to what we

Table 3 **Antimicrobial prescriptions trends.**

	Days of treatment per 100 patients-day				
	P1	P2	non-adjusted OR	CI95%	p value
Penicillin	0.4	0.1	0.3	[0.1-0.8]	<.001
Aminopenicillins	0.6	2.3	3.8	[2.5-5.7]	<.001
Ampicillin-sulbactam	8.2	4.0	0.5	[0.4-0.6]	<.001
Piperacillin-tazobactam	6.7	6.8	1.0	[0.8-1.2]	0.9
Injectable first generation cephalosporins	0.7	2.4	3.3	[2.2-4.8]	<.001
Third generation cephalosporins	0.9	0.6	0.7	[0.4-1.2]	.2
Cefepime	1.1	1.7	1.6	[1.1-2.2]	<.02
Carbapenems	17.8	15.4	0.8	[0.8-0.9]	<.001
Aztreonam	0.3	4.1	16.3	[9.1-29.3]	<.001
Ceftazidime-avibactam	1.0	6.6	6.6	[4.9-9.1]	<.001
Clindamycin	0.2	0.1	0.4	[0.1-1.4]	.2
Ciprofloxacin	1.9	0.5	0.3	[0.2-0.4]	<.001
Tigecycline	1.7	1.0	0.6	[0.4-0.8]	<.001
Fosfomycin	10.1	11.1	1.2	[1.0-1.3]	<.03
Colistin	21.3	20.3	1.0	[0.9-1.1]	.5
Macrolides	5.9	1.3	0.2	[0.2-0.3]	<.001
Aminoglycosides	5.9	2.5	0.4	[0.3-0.5]	<.001
Vancomycin	9.6	11.6	1.2	[1.1-1.4]	<.001
Linezolid	1.9	1.9	1.0	[0.7-1.3]	.9
Daptomycin	0.3	0.6	2.0	[1.0-3.7]	<.03
Trimethoprim-sulfamethoxazole	2.0	3.7	1.9	[1.4-2.4]	<.001
'Access' group	17.9	15.1	0.8	[0.7-0.9]	<.001
'Watch' group	45.7	38.5	0.7	[0.7-0.8]	<.001
'Reserve' group	36.4	46.4	1.5	[1.4-1.7]	<.001

observed in our center [24]. This was not an isolated event at our hospital, as since 2020, infections caused by *blaMBL*-producing Gram-negative bacilli have increased throughout the country [25,26]. Furthermore, as has been observed in other reports, this scenario suggests an ecological phenomenon promoted by the exposure of hospital flora to this novel antibiotic combination designed ideally for the treatment of infections caused by Classes A and D carbapenemase-producing microorganisms [9]. The possibility that this new resistance scenario is a clonal event could be ruled out by the fact that the enzyme profiles that accompanied our CP-KPN strains were diverse, i.e., *blaMBL* plus *blaKPC*, or the new appearance of *blaPER* [27]. As a counterpoint to this hypothesis, the most up-to-date information we have, indicates the presence of a dominant KPN clone in multiple jurisdictions as responsible for an interhospital and interregional CP-KPN clonal outbreak [28].

This abrupt change in the ecological niche that dominated our country from 2009 to 2019, where the leading carbapenemase was undoubtedly *blaKPC*, seems to have emerged based on certain predisposing circumstantial factors, such as: 1) incorporation of CZA into the therapeutic arsenal in our setting; 2) non-existence, during the study, of other combinations of new β-lactamase inhibitors such as meropenem-vaborbactam or imipenem-relebactam that could justify this new scenario; 3) throughout the analyzed period, drugs for treating ventilator-associated pneumonia in COVID patients, which possess carbapenem-sparing properties (thus avoiding the described ecological condition), such as ceftolozane-tazobactam, were unavailable at our hospital; 4) SARS-CoV2 pandemic, which overwhelmed the healthcare system and compromised the quality of intra-hospital infection control, favoring the rapid dissemination of different types of carbapenemase-producing bacteria; 5) preexistence, albeit low prevalence, of hospital epidemiological foci of *blaMBL*-producing *Enterobacteriaceae* (even in our own center) in which *blaNDM* served as a substrate (non-published data); and, 6) the possible introduction or *de novo* selection of a hyperepidemic clone. Regarding this

last mention, it is important to note that in countries similarly affected by COVID-19 but where class B carbapenemases were not consistently found in *Enterobacteriaceae* isolates, such as Spain, the introduction of CZA did not have a similar impact as it had in Argentina, Italy, and Greece among others [11,26]. This highlights the fact that the linearity between the introduction of a resistance-selecting agent and the emergence of resistance mechanisms is without doubt a multifactorial conjunction of events.

From an antimicrobial stewardship perspective, the introduction of CZA as an advanced strategy for the treatment of *blaKPC-Enterobacteriaceae* infections resulted in a 'brick removal effect', where the rapidly changing use of numerous antimicrobials, especially within the β-lactam family, was not unexpected. Understanding institutional changes in antimicrobial use that occurs during the introduction of new drugs is crucial for developing policies and protocols that optimize antibiotic use and minimize impacts on healthcare-associated infections. In this regard, it is important to highlight that this analysis is the first in the region to focus on changes in antimicrobial prescribing patterns promoted by the inclusion of CZA in a hospital *vademecum*. Thus, during P2, not only did the consumption of CZA increase significantly but also that of aztreonam, which together became the best available strategy (considering that cefiderocol was not available in Argentina) to treat *blaMBL* and *blaESBL* or *blaKPC*-KPN infections [7,8]. This new antimicrobial consumption pattern led to an increase in the use of drugs from the 'reserve' group. On the contrary, agents with a lower ecological impact as a whole (from the 'access' and 'watch' groups) were substantially less prescribed. In this scenario, where CP-KPN strains of different classes have taken over the ecological landscape of our ICU, the consumption of antimicrobial agents was substantially altered. Therefore, drugs considered to have a 'narrow-spectrum', such as penicillin and older-generation aminopenicillins with β-lactamase inhibitors (such as ampicillin-sulbactam), had an important prescription decline. These findings result in a pernicious cycle in which the introduction of CZA entails selective pressure on *blaMBL*-producing strains, along with other mechanisms, promoting even greater CZA and aztreonam consumption, ultimately leading to an increase in CZA-resistant strain infections. In this ominous reality, infection control and antimicrobial stewardship programs are invaluable for identifying and mitigating changes related to the new consumption pattern in order to optimize care for infected patients, complete treatments with optimal timing, restrict the use of high-ecological impact drugs as much as possible, adjust drug doses, and monitor the emergence of epidemiological epiphenomena such as *Clostridioides difficile* infections associated with the use of these agents [29]. As a further issue, it is necessary to have other pan-carbapenemase therapeutic options in our country that allow for an ecological 'recovery' from CZA, such as cefiderocol7,8, in order to achieve a renewal of the bacterial flora of the hospital environment as one of the infection control strategies.

The present study had several limitations: 1) interrupted time series analysis was not employed due to the comparison of only two distinct time periods and the scarce number of isolates collected in each period (monthly); 2) as an ecological observation, clinical origin assessment of isolates was not conducted as it was not within the scope of this analysis; 3) data regarding the carriage status of multidrug-resistant *Enterobacteriaceae* was not evaluated due to the suspension of our epidemiological surveillance program during 2020, in context of the first COVID-19 pandemic year; as well as predisposing factors to its acquisition such as previous use of antimicrobials, hemodialysis, cancer, etc.; 4) inter-hospital patient movement was not considered; and lastly, 5) this was a single-center study, hence its findings should not be extrapolated to other settings.

CONCLUSIONS

We observed a worrisome decrease of carbapenem and CZA susceptibilities in KPN from clinical ICU patients' samples, due to the escalation in the rate of *blaMBL*-KPN, two years after the introduction of CZA. This increase in the prevalence of *blaMBL*-KPN is not only seen as a separate mechanism of resistance but also as a combined one, often in conjunction with *blaESBL*. Additionally, this framework suggests that the simultaneous rise of double-producing *blaKPC* and *blaMBL* strains is driving to an overlapping problem that is gaining significance.

In this context, 'reserve' antimicrobial prescriptions rate, primarily driven by the increased use of CZA and ATM, becomes uncontrollable. Finally, as a consequence of the aforementioned factors, both the new KPN susceptibility profile and the rise in consumption of the 'reserve' agents led to a compensatory decrease in the prescription of 'access' and 'watch' agents like carbapenems.

FUNDING

None to declare

CONFLICTS OF INTEREST

The authors declare no conflicts of interest

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