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Maximiliano Castro *

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Community-Acquired Klebsiella pneumoniae KPC Invasive Infection: Argentine Case Report

Castro, Maximiliano Gabriel [1,2,*], Rottoli, Erwin Alexander [1], Aguilar, María Tatiana [3], Gambino, Patricia [1,2], Argarañá and María Fernanda [3].

[1] Internal Medicine Department, JB Iturraspe Hospital (Santa Fe, Argentina)
[2] Medical Sciences Faculty, National University of the Littoral (Santa Fe, Argentina)
[3] Microbiology Laboratory, JB Iturraspe Hospital (Santa Fe, Argentina)
* Correspondence: mgabrielcastro@outlook.com

Abstract: The incidence of infections due to carbapenemase-producing Enterobacteriaceae (CPE) is rising worldwide. We present the case of a 48-year-old female patient, diabetic, with previous episodes of urinary tract infections that was admitted due to pyelonephritis, later identified to be caused by KPC and ESBL-producing *Klebsiella pneumoniae*. Both the patient and her family had no strong epidemiological link with the healthcare system, and for this reason, this case stands out in regional literature since similar reports are scarce and therefore constitutes a reason for alert in health institutions. Further studies are needed in order to ascertain the real incidence of these infections in community settings in Latin America and the Caribbean.

Keywords: carbapenem-resistant enterobacteriaceae; drug resistance; microbial; public health

Introduction

Worldwide, there has been an increase in the incidence of infections due to carbapenemase-producing Enterobacteriaceae (CPE), even in countries where shortage of diagnostic resources could be underestimating its true incidence [1].

COVID-19 pandemic accelerated this process, and multiple reports were published worldwide [2,3] and in Latin America in particular [4,5]. This has been linked to excessive antibiotic consumption [6] and high patient-caregiver ratio [7], among other factors.

CPE infectious typically present as healthcare-associated infections and condition higher costs and mortality [8]. Moreover, CPE acquisition usually occurs during hospital stay, specially in patients with invasive devices, Intensive Care unit admission, carbapenem consumption and prolonged hospital stays [9–11].

In our health institution, a tertiary-care level center in the city of Santa Fe (Argentina), we described an increase of 2.5 times in the incidence of infections due to carbapenem-resistant bacteria during the COVID-19 pandemic [12].

We present a case of an invasive infection caused by community-acquired KPC carbapenemase and extended spectrum betalactamase (ESBL)-producing *Klebsiella pneumoniae* during December 2022, that is to our knowledge the **first published case in Latin America and the Caribbean of community-onset CPE infection without a strong epidemiological link to healthcare institutions**. Afterwards, we review the available international literature in Pubmed -including Medline and PMC-, Lilacs, Scielo and Cochrane Library up to January 2023 regarding such infections.

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The patient had **no history of substance abuse** and had a **medical history** of diabetes mellitus type 2, hypertension, hypothyroidism and **repeated urinary tract infections**, with a maximum of two episodes a year, with seldom visits to healthcare centers. She had never been hospitalized.

The last referred episode of pyelonephritis was **8 months prior to admission**, for which she received a 5-day course of ciprofloxacin, subsequently visiting an emergency room -within a

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secondary-level care center- due to the persistence of low back pain. There, she stayed for less than 6 hours in observation and received analgesia.

Now, her chief complaint was an abdominal pain that has lasted more than 2 days and that was focused on the left flank and iliac fossa and radiated to the homolateral lumbar area. She described it as continuous, with an increasing intensity reaching 10/10. She denied digestive symptoms, and referred irritative urinary symptoms.

On **physical examination**, she was hemodynamically stable and presented with fever and abdominal distension, which showed selective tenderness and defense on palpation -but no rebound- in the left hemiabdomen. Positive left lumbar fist percussion.

On admission, blood tests showed leukocytosis (WBC 16910 cells/mm3), neutrophilia (88,4%), increased erythrosedimentation rate (59 mm/h), hyperglycemia (3,79 g/L), acute kidney failure (urea 0,30 mg/dL, creatinine 1,85 mg/dL, urine density 1025) and a negative test for HIV. An urinalysis showed a leukocyte-covered field, negative nitrites.

A **preliminary diagnosis** of pyelonephritis was made. Therefore, we requested a urine sample for culture and prescribed **empiric antibiotic therapy** with ciprofloxacin, since her last use of antibiotics dated back to 6 months previous to consultation and reported no history of infections caused by multidrug-resistant bacteria or use of urinary tract devices.

On kidney ultrasound, she had a mild left pyelic ectasia, without urinary lithiasis. A **CT urography** was performed, which ruled out urinary lithiasis.

48 hours after admission, she developed hemodynamic instability. In the context of **sepsis**, blood culture samples were collected. At the same time, the Microbiology laboratory reported growth in the urine culture of mucous colonies with Blue-carba test positive Gram-negative bacilli. **The empirical antibiotic was switched to** a combined regimen of **amikacin** and **fosfomycin**, based on local epidemiology.

Microbiological Identification: The midstream urine sample sent to the laboratory, presented with abundant leukocytes and red blood cells on microscopic examination. The sample was cultured in CLED agar and incubated at 37°C. A significant growth was obtained at 24 hs, with a count of over 100.000 UFC/mL Gram-negative bacilli with positive Blue-Carba test. Identification and sensitivity tests were carried out with the Vitek 2C system (bioMérieux, Argentina). The result was the isolation of *Klebsiella pneumoniae*, which was sensitive to amikacin (*CIM <2 ug/mL*), tigecycline (*CIM 0.25 ug/mL*) and nitrofurantoin (*CIM <16 ug/mL)*, but showed a **carbapenem-resistance profile** *(imipenem CIM 8 ug/mL and meropenem CIM >16 ug/mL)* and resistance to ciprofloxacin *(CIM >4 ug/mL),* piperacillin-tazobactam (*CIM >128 ug/mL*), gentamicin *(CIM >16 ug/mL)* and trimethoprim-sulfamethoxazole *(>320 ug/mL).* It was also sensitive to colistin (tested by colistin pre-diffusion method with Rosco Neosensitabs; *25 mm)* and to fosfomycin (tested by disk diffusion method, *21mm*)

Carbapenem disks were confronted to phenyl-boronic acid and EDTA and the synergy between aztreonam-boronic acid and EDTA-Ceftazidime Avibactam was assessed, obtaining as a result positive synergies with boronic acid in both plates, **which indicated the presence of KPC carbapenemase**. Moreover, we found a positive synergy test between ceftazidime -as well as cefotaxime- and amoxicillin-clavulanate disks, which phenotypically confirmed the **presence of ESBL** alerted by the VITEK 2C System (bioMérieux, Argentina).

Blood culture samples were incubated in the BactAlert system (bioMérieux, Argentina), which detected significant growth after 15.8 hrs. Gram-negative bacilli were observed, the identification and sensitivity of which matched the findings in the urine sample.

Epidemiological link: The patient lives no further than 3.5 km from our healthcare center, in a house with all basic needs met. There, she lives with her daughter and her male partner. The latter manifested that he had no recent hospitalizations, that he works in a slaughterhouse in the production of charcuterie, and that he has no contact with the poultry industry. Both the patient and her daughter said that their regular line of work consisted of housemaid chores, not related to caring for elders, and that they had no contact with people undergoing illnesses or recently hospitalized. They also mentioned that their employers were a retired physician and a biochemist working in the private sector.

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Evolution: The patient completed a 10-day course of intravenous amikacin (fosfomycin was suspended after the definite antibiogram) and remained in strict contact isolation. She evolved with no fever and the rest of her symptoms improved. After this, she was successfully discharged. During routinary surveillance swabs, we did not identify the spread of this resistant strain within the institution.

Discussion

Antimicrobial resistance is a dynamic and adaptive process of microorganisms.

The main antimicrobials used in ambulatory human and animal health condition the most common resistance mechanisms: at the community level, the higher spectrum resistance is the methicillin-resistance and the production of ESBL [13,14]. Hospitals make up a niche for the development of multidrug-resistant microorganisms.

There are very few reported cases in international literature of infections caused by CPE in the absence of previous contact with the healthcare system [15,16]. These cases pose a threat for hospital outbreaks, since these patients may not present criteria for rectal screening [15].

A revision of 15 markedly heterogeneous studies, which included an Argentinean study (Villar et al., 2013), found a prevalence of 4.9% of CPB intestinal carrying in 164 samples from non-hospitalized patients, but at the expense of non-fermenting Gram-negative bacilli [17].

A surveillance study carried out in 2012-2013 in the county of Michigan (USA) found 102 isolates of CPE, among which 65% met the criteria for community-acquisition. However, most of these patients had been recently hospitalized in acute or long-term acute care settings [18].

In 2016, a study from Taiwan showed that 29,5% of 78 infections due to CPE had their onset in the community setting [19]. Meanwhile, a Spanish study reported that from 780 CPE isolated in clinical samples 20% were community-acquired, but 71,4% of these had been hospitalized in the 90 days prior symptom onset and up to 86,6% the previous year [20]. Afterwards, in 2020 there were 68 reports of infections documented by CPE in 4 years in a hospital in China, 22.1% of those were community-acquired [21]. The same year, the SMART surveillance study in Taiwan presented a report of 1294 Gram-negative bacilli isolations, among which only 20 belonged to CPB. However, 4/20 were community-acquired [22].

The observation of community-acquired cases in these reports by far exceeds the Argentinean experience, where nosocomial acquisition predominates.

In Spain, in 2022, an infection caused by KPC Klebsiella pneumoniae with ceftazidime-avibactam resistance was reported, with community onset and no link to the healthcare system [23].

To our knowledge, a case of an invasive infection caused by a community-acquired **CPE -co-carrying ESBL- with no link to the healthcare system**, has not been published within Latin American or Caribbean literature. Regarding this patient, she presented a community-onset infection and declared no contact with the healthcare system for over 6 months. Even if her **short stay (<6 hs)** in the emergency department of a secondary-care hospital **8 months prior to consultation** was taken into consideration, **colonization with CPE significantly declines after 6 months** [24–26], and the **risk of infection after colonization significantly declines after 1 month** [27]. Risk factors for persistence include prolonged hospital stays, intercurrent admissions and Clostridium difficile infections, **none of which this patient presented** [24–26].

This puts forward questions about the spreading of CPE from hospitals to the environment. Sewage may be one of the main sources of spreading. An Austrian study carried out in 2011 found three CPE isolations in sewage waste through microbiological surveillance [28]. KPC isolations in sewage had been reported four years before in Brazil and concomitantly in rivers in Portugal [29,30]. Later, it was found in river water in Croatia [31]. More recently, a Swiss study found a 10% positivity for CPE in water samples and with a wider diversity of genetic resistance mechanisms [32].

A review showed that even when the isolation of CPE in water samples is a worldwide phenomenon, most of the research comes from Europe and the highest caseload comes from the United States, Brazil and Asia, while there are no Argentinean reports [33].

Recently, in Swiss veterinary clinics, they detected not only invasive infections and rectal colonizations caused by CPE in hospitalized animals, but also the rectal carrying of the same epidemic clones in vets [34].

The high caseload of hospitalized patients during the COVID-19 pandemic together with the rise in CPE infections incidence in hospital settings in Argentina, as well as worldwide, provided an uncontrolled and unassessed source of CPE-colonized patients to the community. Moreover, since these infections are not yet of mandatory reporting, there is no data regarding the approximate caseload in our country or how many of these patients may represent community-acquired or community-onset healthcare-associated infections. No studies have been performed to assess CPE colonization in community settings.

Further studies are needed in order to ascertain the real incidence of these infections in community settings in Latin America and the Caribbean.

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References

1. García-Betancur JC, Appel TM, Esparza G, Gales AC, Levy-Hara G, Cornistein W, et al. Update on the epidemiology of carbapenemases in Latin America and the Caribbean. Expert Rev Anti Infect Ther. 2021 Feb;19(2):197–213.
2. Belvisi V, Borgo CD, Vita S, Redaelli P, Dolce P, Pacella D, et al. Impact of SARS CoV-2 pandemic on carbapenemase-producing Klebsiella pneumoniae prevention and control programme: convergent or divergent action? J Hosp Infect. 2021 Mar;109:29.
3. Gomez-Simmonds A, Annavajhala MK, McConville TH, Dietz DE, Shoucri SM, Laracy JC, et al. Carbapenemase-producing Enterobacterales causing secondary infections during the COVID-19 crisis at a New York City hospital. J Antimicrob Chemother [Internet]. [cited 2021 Aug 26]; Available from: https://www.ncbi.nlm.nih.gov/labs/pmc/articles/PMC7717307/
4. Martinez-Guerra BA, Gonzalez-Lara MF, de-Leon-Cividanes NA, Tamez-Torres KM, Roman-Montes CM, Rajme-Lopez S, et al. Antimicrobial Resistance Patterns and Antibiotic Use during Hospital Conversion in the COVID-19 Pandemic. Antibiotics [Internet]. 2021 Feb [cited 2021 Jul 27];10(2). Available from: https://www.ncbi.nlm.nih.gov/labs/pmc/articles/PMC7917840/
5. Gaspar GG, Ferreira LR, Feliciano CS, Campos Júnior CP, Molina FMR, Vendruscolo ACS, et al. Pre- and post-COVID-19 evaluation of antimicrobial susceptibility for healthcare-associated infections in the intensive care unit of a tertiary hospital. Rev Soc Bras Med Trop. 2021;54:e00902021.
6. Vaughn VM, Gandhi T, Petty LA, Patel PK, Prescott HC, Malani AN, et al. Empiric Antibacterial Therapy and Community-onset Bacterial Co-infection in Patients Hospitalized with COVID-19: A Multi-Hospital Cohort Study. Clin Infect Dis Off Publ Infect Dis Soc Am. 2020 Aug 21;
7. Legeay C, Thépot-Seegers V, Pailhoriès H, Hilliquin D, Zahar JR. Is cohorting the only solution to control carbapenemase-producing Enterobacteriaceae outbreaks? A single-centre experience. J Hosp Infect. 2018 Aug;99(4):390–5.
8. Nelson RE, Hyun D, Jezek A, Samore MH. Mortality, Length of Stay, and Healthcare Costs Associated With Multidrug-Resistant Bacterial Infections Among Elderly Hospitalized Patients in the United States. Clin Infect Dis Off Publ Infect Dis Soc Am. 2021 Oct 7;ciab696.
9. Maseda E, Salgado P, Anillo V, Ruiz-Carrascoso G, Gómez-Gil R, Martín-Funke C, et al. Risk factors for colonization by carbapenemase-producing enterobacteria at admission to a Surgical ICU: A retrospective study. Enferm Infecc Microbiol Clin. 2017;35(6):333–7.
10. Madueño A, González García J, Ramos MJ, Pedroso Y, Díaz Z, Oteo J, et al. Risk factors associated with carbapenemase-producing Klebsiella pneumoniae fecal carriage: A case-control study in a Spanish tertiary care hospital. Am J Infect Control. 2017 Jan 1;45(1):77–9.
11. Torres-Gonzalez P, Cervera-Hernandez ME, Niembro-Ortega MD, Leal-Vega F, Cruz-Hervert LP, García-García L, et al. Factors Associated to Prevalence and Incidence of Carbapenem-Resistant Enterobacteriaceae Fecal Carriage: A Cohort Study in a Mexican Tertiary Care Hospital. PloS One. 2015;10(10):e0139883.
12. Castro MG, Ubiergo L, Vicino M, Cuevas G, Argarañá F. An outbreak inside an outbreak: rising incidence of carbapenem-resistant isolates during the COVID-19 pandemic. Report from a tertiary care center in Argentina [Internet]. medRxiv; 2021 [cited 2022 Jan 30]. p. 2021.11.11.21266237. Available from: https://www.medrxiv.org/content/10.1101/2021.11.11.21266237v1
13. Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. Lancet Lond Engl. 2022 Feb 12;399(10325):629–55.

14. Diekema DJ, Hsueh PR, Mendes RE, Pfaller MA, Rolston KV, Sader HS, et al. The Microbiology of Bloodstream Infection: 20-Year Trends from the SENTRY Antimicrobial Surveillance Program. Antimicrob Agents Chemother. 2019 Jun 24;63(7):e00355-19.
15. Song JE, Jeong H, Lim YS, Ha EJ, Jung IY, Jeong W, et al. An Outbreak of KPC-Producing Klebsiella pneumoniae Linked with an Index Case of Community-Acquired KPC-Producing Isolate: Epidemiological Investigation and Whole Genome Sequencing Analysis. Microb Drug Resist. 2019 Dec;25(10):1475–83.
16. Khatri A, Naeger Murphy N, Wiest P, Osborn M, Garber K, Hecker M, et al. Community-Acquired Pyelonephritis in Pregnancy Caused by KPC-Producing Klebsiella pneumoniae. Antimicrob Agents Chemother. 2015 Aug 1;59(8):4375–8.
17. Kelly AM, Mathema B, Larson EL. Carbapenem-resistant Enterobacteriaceae in the community: a scoping review. Int J Antimicrob Agents. 2017 Aug;50(2):127–34.
18. Brennan BM, Coyle JR, Marchaim D, Pogue JM, Boehme M, Finks J, et al. Statewide surveillance of carbapenem-resistant enterobacteriaceae in Michigan. Infect Control Hosp Epidemiol. 2014 Apr;35(4):342–9.
19. Tang HJ, Hsieh CF, Chang PC, Chen JJ, Lin YH, Lai CC, et al. Clinical Significance of Community- and Healthcare-Acquired Carbapenem-Resistant Enterobacteriaceae Isolates. PloS One. 2016;11(3):e0151897.
20. Paño-Pardo JR, López Quintana B, Lázaro Perona F, Ruiz Carrascoso G, Romero-Gómez MP, Loeches Yagüe B, et al. Community-Onset Bloodstream and Other Infections, Caused by Carbapenemase-Producing *Enterobacteriaceae*: Epidemiological, Microbiological, and Clinical Features. Open Forum Infect Dis. 2016 Sep 1;3(3):ofw136.
21. Hu H, Mao J, Chen Y, Wang J, Zhang P, Jiang Y, et al. Clinical and Microbiological Characteristics of Community-Onset Carbapenem-Resistant Enterobacteriaceae Isolates. Infect Drug Resist. 2020;13:3131–43.
22. Liu PY, Lee YL, Lu MC, Shao PL, Lu PL, Chen YH, et al. National Surveillance of Antimicrobial Susceptibility of Bacteremic Gram-Negative Bacteria with Emphasis on Community-Acquired Resistant Isolates: Report from the 2019 Surveillance of Multicenter Antimicrobial Resistance in Taiwan (SMART). Antimicrob Agents Chemother. 2020 Sep 21;64(10):e01089-20.
23. Machuca I, Guzmán-Puche J, Pérez-Nadales E, Gracia-Ahufinger I, Mendez A, Cano A, et al. Community-acquired bacteraemia by Klebsiella pneumoniae producing KPC-3 and resistant to ceftazidime/avibactam. J Glob Antimicrob Resist. 2022 Sep;30:399–402.
24. Kim YK, Chang IB, Kim HS, Song W, Lee SS. Prolonged Carriage of Carbapenemase-Producing Enterobacteriaceae: Clinical Risk Factors and the Influence of Carbapenemase and Organism Types. J Clin Med [Internet]. 2021 Jan [cited 2021 Aug 29];10(2). Available from: https://www.ncbi.nlm.nih.gov/labs/pmc/articles/PMC7830152/
25. Zimmerman FS, Assous MV, Bdolah-Abram T, Lachish T, Yinnon AM, Wiener-Well Y. Duration of carriage of carbapenem-resistant Enterobacteriaceae following hospital discharge. Am J Infect Control. 2013 Mar;41(3):190–4.
26. Bar-Yoseph H, Hussein K, Braun E, Paul M. Natural history and decolonization strategies for ESBL/carbapenem-resistant Enterobacteriaceae carriage: systematic review and meta-analysis. J Antimicrob Chemother. 2016 Oct;71(10):2729–39.
27. Hoellinger B, Deboscker S, Danion F, Lavigne T, Severac F, Ruch Y, et al. Incidence and Time-to-Onset of Carbapenemase-Producing Enterobacterales (CPE) Infections in CPE Carriers: a Retrospective Cohort Study. Microbiol Spectr. 10(6):e01868-22.
28. Galler H, Feierl G, Petternel C, Reinthaler FF, Haas D, Grisold AJ, et al. KPC-2 and OXA-48 carbapenemase-harbouring Enterobacteriaceae detected in an Austrian wastewater treatment plant. Clin Microbiol Infect Off Publ Eur Soc Clin Microbiol Infect Dis. 2014 Feb;20(2):O132-134.
29. Chagas TPG, Seki LM, da Silva DM, Asensi MD. Occurrence of KPC-2-producing Klebsiella pneumoniae strains in hospital wastewater. J Hosp Infect. 2011 Mar;77(3):281.
30. Poirel L, Barbosa-Vasconcelos A, Simões RR, Da Costa PM, Liu W, Nordmann P. Environmental KPC-Producing Escherichia coli Isolates in Portugal. Antimicrob Agents Chemother. 2012 Mar;56(3):1662–3.
31. Jelić M, Hrenović J, Dekić S, Goić-Barišić I, Tambić Andrašević A. First evidence of KPC-producing ST258 Klebsiella pneumoniae in river water. J Hosp Infect. 2019 Oct 1;103(2):147–50.
32. Bleichenbacher S, Stevens MJA, Zurfluh K, Perreten V, Endimiani A, Stephan R, et al. Environmental dissemination of carbapenemase-producing Enterobacteriaceae in rivers in Switzerland. Environ Pollut. 2020 Oct 1;265:115081.

 doi:10.20944/preprints202407.0750.v1

33. Cherak Z, Loucif L, Moussi A, Rolain JM. Carbapenemase-producing Gram-negative bacteria in aquatic environments: a review. J Glob Antimicrob Resist. 2021 Jun 1;25:287–309.
34. Endimiani A, Brilhante M, Bernasconi OJ, Perreten V, Schmidt JS, Dazio V, et al. Employees of Swiss veterinary clinics colonized with epidemic clones of carbapenemase-producing Escherichia coli. J Antimicrob Chemother. 2020 Mar 1;75(3):766–8.