Epidemiological Alert

Emergence and increase of new combinations of carbapenemases in Enterobacterales in Latin America and the Caribbean

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Given the change in the geographic distribution of carbapenemases and the emergence and dissemination of bacteria that produce more than one of these enzymes, the Pan American Health Organization / World Health Organization (PAHO / WHO) emphasizes the importance of appropriate microbiological diagnosis and the effective and articulated implementation of infection prevention and control programs, as well as regulations for the optimal use of antimicrobials.

Background

During the COVID-19 pandemic, the emergence of extensively antimicrobial-resistant microorganisms and an increase in the incidence of resistance to carbapenems,[1] possibly related to the increased use of broad-spectrum antibiotics in patients with COVID-19, has been documented.[2-7] At the same time, an increase in the rate of device-associated healthcare-associated infections has been observed in intensive care units (ICUs), mainly due to central vascular catheter and mechanical ventilation.[8]

What are Enterobacterales?

Enterobacterales constitute an order of gram-negative bacteria comprised of seven families, of which the most relevant from a clinical perspective are *Enterobacteriaceae* (which includes the bacterial genera such as *Salmonella*, *Shigella*, *Escherichia*, *Klebsiella*, *Enterobacter*, and *Citrobacter*, amongst others), *Yersiniaceae* (e.g., *Yersinia* and *Serratia*), and *Morganellaceae* (e.g., *Morganella*, *Proteus*, and *Providencia*).

While Enterobacterales are commonly associated with human disease, many are also part of the normal intestinal flora.

Even prior to the COVID-19 pandemic, the emergence of gram-negative pathogens resistant to carbapenem antibiotics due to the presence of carbapenemases was recognized as a public health problem.[9] Currently, enzymes of the *Klebsiella pneumoniae* carbapenemase (KPC), Oxacillinase (OXA), New Delhi Metallo-beta-lactamase (NDM), Verona Integron-Encoded Metallo-beta-lactamase (VIM), and Imipenemase (IMP) families are the most frequently detected worldwide. Some of these carbapenemases emerged in bacterial species that facilitated their rapid dissemination, increased incidence,[10] or caused large hospital outbreaks.[11]

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However, the geographical distribution is heterogeneous, and certain countries and regions have been more affected by some types while other types have not been detected.[12] Isolates of Enterobacterales that co-produce two or more types of carbapenemases have also been described sporadically.[13,14] An additional consideration is the increased interaction between humans and companion animals, given the occurrence of documented cases of carbapenemase-producing pathogens among these animals and the potential animal-human transmission.[15]

Summary of the situation in Latin America and the Caribbean

The Latin American Antimicrobial Resistance Surveillance Network (ReLAVRA as per its acronym in Spanish) has been monitoring resistance to carbapenems in gram-negative bacilli for more than 15 years. Between 2006 and 2010, resistance to carbapenems in *K. pneumoniae* was detected sporadically in some countries. Between 2010 and 2019, the countries within this network reported a slow but sustained increase in resistance, with a wide heterogeneity in magnitude and reaching a prevalence greater than 60% in some countries. This high prevalence must be interpreted with caution, as there could be some bias in the selection of strains for surveillance.

In literature reviews of the epidemiology of these enzymes in Latin America and the Caribbean published in 2017 and 2021, the wide dissemination of Enterobacterales throughout the Region was described, notably KPC-type carbapenemases, which have become endemic in some countries. The presence of other carbapenemases such as NDM, and to a lesser extent IMP and VIM, was also described.[16,17]

Since the beginning of the pandemic, the national authorities of several countries in the Region, based on the results of the national reference laboratories that are members of ReLAVRA, have issued alerts on the emergence of **carbapenemase-producing Enterobacterales (CPE)** not previously described, or an increasing number of isolates that co-express two or more of these enzymes. A selection of these is listed below:

- **Argentina** describes in its alert that during the period May to November 2020, the co-production of KPC and NDM was identified as the most prevalent combination of carbapenemases (16%) among the carbapenem-resistant *Enterobacteriaceae* (CRE) received in the national reference laboratory. This combination had not been previously documented in the country.[18]

- In **Uruguay**, an increase in isolates producing KPC and NDM was observed, from 1% during 2017-2019 to 3.3% between January 2020 and May 2021.[19]

- In **Ecuador**, alerts were issued regarding the first co-producing isolates of KPC and NDM (*K. pneumoniae*) and of KPC and OXA-48 (*Escherichia coli*) in early 2021.[20]

- In **Guatemala**, an alert was issued regarding the detection of the first isolates belonging to the *Enterobacter cloacae* complex producing KPC and NDM in July 2021.[21]

- In **Paraguay**, in July 2021, the first isolates co-producing the carbapenemases KPC and NDM were reported in two isolates of *K. pneumoniae*.[22]

Additionally, the emergence of carbapenemases that had not previously been detected at the national level was reported: the first isolates of NDM-producing Enterobacterales were identified in **Belize**,[23] and the first isolates of the OXA-48 carbapenemase were identified in **Chile** and in **Guatemala**. [24,25]

Due to the plasmid nature of the genes encoding these enzymes and the multi-resistant phenotype of these clinical enterobacteria, the probability of dissemination of these resistance mechanisms is very high. Their emergence, resulting in a significant increase in resistance to carbapenems in Enterobacterales, along with the co-existence of resistance mechanisms to polymyxins, limits the antimicrobial treatment for these pathogens. The spread of double carbapenemases is also being observed regionally in non-fermenting bacteria such as *Pseudomonas* spp. and *Acinetobacter* spp.

Recommendations

Given these findings, PAHO / WHO recommends that Member States implement and strengthen epidemiological surveillance and investigation to detect and characterize resistance mechanisms to carbapenems in order to take timely measures to prevent transmission in health facilities, as well as to effectively implement programs to optimize the use of antimicrobials.[26,27]

It is recommended that all sectors involved at the human-animal-environment interface work in a coordinated and effective manner in order to mitigate the current situation.

Surveillance and epidemiological investigation

The finding of isolates producing carbapenemases not previously described, or double / multiple carbapenemases, should be considered a high epidemiological risk due to their ability to generate outbreaks, and must be detected and contained in a timely manner. For this purpose, the following actions are suggested:

- Increase the participation of clinical laboratories in surveillance systems for the timely detection of bacteria that produce (double / multiple) carbapenemases in order to guide timely control measures.

- At the level of national reference laboratories, apply a regional protocol for the detection of carbapenemases.[18]

- Immediately notify the detection of microorganisms with these types of resistance mechanisms to the infection control committees in health establishments, as well as to the competent public health authorities at the national level, and if applicable, at the international level through the International Health Regulations (IHR) National Focal Points (NFPs).

- Disseminate the information obtained and make recommendations to alert health workers and decision-makers at all levels.

Laboratory detection

In order to strengthen the capacity in microbiology laboratories, it is recommended to:

1) Detect microorganisms producing two or more carbapenemases. Conventional phenotypic tests may not detect the presence of two or more carbapenemases, which would underestimate the presence of one or both.

    - Therefore, clinical microbiology laboratories must have the necessary tools for the phenotypic detection of isolates producing two or more carbapenemases, using the algorithms designed by the regional reference laboratory adapted to the national resources and epidemiology, or flow charts that include more than one detection strategy, combining different methodologies to be applied for those isolates suspected of producing this type of enzymes.

2) Characterize the types of carbapenemases.

    - Immunochromatography or molecular methods such as polymerase chain reaction (PCR) can be used, either by means of commercial systems or techniques developed in-house.

    - The clinical microbiology laboratory should have the capacity to identify the type of carbapenemase using defined work protocols in addition to having the capacity to identify alternative antibiotic treatments.

If unusual carbapenemases or more than one enzyme are suspected, it is recommended to send the strain to the national or regional reference laboratory for confirmation and molecular typing.

Infection prevention and control

The emergence of bacteria harboring these genes demonstrates the ability of these microorganisms to evolve rapidly, acquire plasmids carrying multiple resistance genes, persist in the hospital environment, and spread successfully. Therefore, strict administrative measures and techniques for the prevention and control of infections in the hospital environment are indicated for patients colonized or infected by carbapenemase-producing pathogens.

As stated in the 2019 WHO manual to prevent and control the spread of organisms resistant to carbapenems, [28,29] it is essential to establish multimodal strategies that include, at least:

- hand hygiene;
- surveillance of infections and colonizations (particularly CPE);
- contact precautions;
- isolation of patients (in individual rooms or cohort); and
- environmental cleaning.

• Conducting screening (cultures of samples taken by rectal or perianal swabs) to detect CPE colonization must be guided by local epidemiology and risk assessment. Populations that should be considered for such surveillance of colonized patients include:

- patients with previous colonization / infection by CPE;
- contacts of patients colonized or infected by CPE;
- patients with a history of recent hospitalization in CPE-endemic institutions.

• The purpose of these surveillance cultures is to inform the measures to prevent the spread / dissemination of CPE; therefore, it is necessary to implement contact precautionary measures until the results of the cultures are obtained.

Antimicrobial treatment

Due to the complexity of the treatment, there is no international consensus on the optimal combination or dosage for the treatment of microorganisms that produce two or more carbapenemases to date. Therefore, infectious disease specialists should prescribe antimicrobial treatment based on the local context. Therefore, it is essential to understand the local resistance patterns so that the measures are targeted and appropriate, thus guiding and optimizing the antibiotic treatment for patients.

It is recommended to reinforce the proper use of antimicrobials through the implementation of optimization programs for their use (PROAs) to preserve their activity.

References

1. Farfour E, Lecuru M, Dortet L, Le Guen M, Cerf C, Karnycheff F, Bonnin RA, Vasse M, Lesprit P, SARS-CoV-2 Hospital Foch study group. 2020. Carbapenemase-producing Enterobacterales outbreak: Another dark side of COVID-19. Am J Infect Control. 48(12):1533-36.
2. Rawson TM, Moore LSP, Zhu N, Ranganathan N, Skolimowska K, Gilchrist M, Satta G, Cooke G, Holmes A. 2020. Bacterial and fungal coinfection in individuals with coronavirus: a rapid review to support COVID-19 antimicrobial prescribing. Clin Infect Dis. 71(9):2459–68.
3. Founou RC, Blocker AJ, Noubom M, Tsayem C, Choukem SP, Dongen MV, Founou LL. 2021. The COVID-19 pandemic: a threat to antimicrobial resistance containment. Future Sci OA. 7(8):FSO736.
4. Ghosh S, Bornman C, Zafer mm. 2021. Antimicrobial resistance threats in the emerging COVID-19 pandemic: where do we stand? J Infect Public Health. 14(5):555-60.
5. Knight GM, Glover RE, McQuaid CF, Olaru ID, Gallandat K, Leclerc QJ, Fuller M, Willcocks SJ, Hasan R, van Kleef E, Chandler CI. 2021. Antimicrobial resistance and COVID-19: Intersections and implications. Elife. 10:e64139.
6. US Centers for Disease Control and Prevention. COVID-19 and antibiotic resistance.

Available at: https://www.cdc.gov/drugresistance/covid19.html

7. Lucien MAB, Canarie MF, Kilgore PE, Jean-Denis G, Fénélon N, Pierre M, Cerpa M, Joseph GA, Maki G, Zervos MJ, Dely P, Boncy J, Sati H, Del Rio A, Ramon-Pardo P. 2021. Antibiotics and antimicrobial resistance in the COVID-19 era: Perspective from resource-limited settings. Int J Infect Dis. 104:250-4.
8. Weiner-Lastinger LM, Pattabiraman V, Konnor RY, Patel PR, Wong E, Xu SY, Smith B, Edwards JR, Dudeck MA. 2021. The impact of coronavirus disease 2019 (COVID-19) on healthcare-associated infections in 2020: A summary of data reported to the National Healthcare Safety Network. Infect Control Hosp Epidemiol. 3:1-14.
9. Lynch JP 3rd, Clark NM, Zhanel GG. 2021. Escalating antimicrobial resistance among *Enterobacteriaceae*: focus on carbapenemases. Expert Opin Pharmacother. 22(11):1455-73.
10. Logan LK, Weinstein RA. 2017. The epidemiology of carbapenem-resistant *Enterobacteriaceae*: the impact and evolution of a global menace. J Infect Dis. 215(suppl_1):S28-S36.
11. French CE, Coope C, Conway L, Higgins JP, McCulloch J, Okoli G, Patel BC, Oliver I. 2017. Control of carbapenemase-producing *Enterobacteriaceae* outbreaks in acute settings: an evidence review. J Hosp Infect. 95(1):3-45.
12. Bonomo RA, Burd EM, Conly J, Limbago BM, Poirel L, Segre JA, Westblade LF. 2018. Carbapenemase-producing organisms: a global scourge. Clin Infect Dis. 66(8):1290-7.
13. Lalaoui R, Djukovic A, Bakour S, Hadjadj L, Sanz J, Salavert M, López-Hontangas JL, Sanz MA, Ubeda C, Rolain J-M. 2019. Genomic characterization of *Citrobacter freundii* strains coproducing OXA-48 and VIM-1 carbapenemase enzymes isolated in leukemic patient in Spain. Antimicrob Resist Infect Control. 8:167.
14. Tang Y, Zhou Y, Meng C, Huang Y, Jiang X. 2020. Co-occurrence of a novel VIM-1 and FosA3-encoding multidrug-resistant plasmid and a KPC-2-encoding pKP048-like plasmid in a clinical isolate of *Klebsiella pneumoniae* sequence type 11. Infect Genet Evol. 85:104479.
15. Sellera FP, Da Silva LCBA, Lincopan N. 2021. Rapid spread of critical priority carbapenemase-producing pathogens in companion animals: a One Health challenge for a post-pandemic world. J Antimicrob Chemother. 76(9):2225-9.
16. Escandón-Vargas K, Reyes S, Gutiérrez S, Villegas MV. 2017. The epidemiology of carbapenemases in Latin America and the Caribbean. Expert Rev Anti Infect Ther. 15(3):277-97.
17. García-Betancur JC, Appel TM, Esparza G, Gales AC, Levy-Hara G, Cornistein W, Vega S, Nuñez D, Cuellar L, Bavestrello L, Castañeda-Méndez PF, Villalobos-Vindas JM, Villegas MV. 2021. Update on the epidemiology of carbapenemases in Latin America and the Caribbean. Expert Rev Anti Infect Ther. 19(2):197-213.
18. Antimicrobial Agents Service. National Institute of Infectious Diseases Dr. Carlos G. Malbrán. Epidemiological Alert. Emergence of double carbapenemase-producing Enterobacterales. Newsletter No. 4. April 2021. Available at: http://antimicrobianos.com.ar/2021/04/alerta-epidemiologica-enterobacterales-doble-productores-de-carbapenemasas/
19. Statement: Double carbapenem-producing *Enterobacteriaceae* in Uruguay. Bacteriology Unit of the Department of Public Health Laboratories (DLSP, per its acronym in Spanish),

August 2021.

20. Co-production of carbapenemases in Enterobacterales isolates in 2 hospitals in Ecuador, 2021. National Reference Center for Antimicrobial Resistance. National Institute for Public Health Research (INSPI, per its acronym in Spanish) - Dr. Leopoldo Izquieta Pérez. Approved for dissemination, March 11, 2021.
21. Ministry of Public Health and Social Assistance of Guatemala. Department of Epidemiology. Alert Update due to the appearance of OXA-48-like carbapenemase-producing isolates. July 1, 2021. Available at: http://portal.lns.gob.gt/media/attachments/2021/09/14/circular-no.-27-alerta-cabapenemasa-oxa-1.pdf
22. Ministry of Public Health and Social Welfare of Paraguay. Antimicrobial resistance alert to all laboratories in the country. July 12, 2021. Available at: https://www.mspbs.gov.py/portal/23539/alerta-por-resistencia-antimicrobiana-a-todos-los-laboratorios-del-pais.html
23. Belize. Alert Information received via personal communication. Central Medical Laboratory (CML).
24. Chile. Alert Information received via personal communication. Institute of Public Health (ISP, per its acronym in Spanish).
25. Ministry of Public Health and Social Assistance of Guatemala. Department of Epidemiology. Epidemiological Alert for the first finding of OXA-48 type carbapenemases in Guatemala. December 8, 2020.Available at: http://portal.lns.gob.gt/media/attachments/2021/09/14/circular-17-2020-alerta-carbapenemasas-oxa-48.pdf
26. Levy Hara G, Gould I, Endimiani A, Ramón Pardo P, Daikos G, Hsueh P-R, Mehtar S, Petrikkos G, Casellas JM, Daciuk L, Paciel D, Novelli A, Saginur R, Pryluka D, Medina J, Savio E. 2013. Detection, treatment, and prevention of carbapenemase-producing *Enterobacteriaceae*: recommendations from an International Working Group. J Chemother. 25(3):129-40
27. Facility Guidance for Control of Carbapenem- Resistant *Enterobacteriaceae* (CRE): November 2015 Update. National Center for Emerging and Zoonotic Infectious Diseases, Division of Healthcare Quality Promotion. CDC 2015. Available at: https://stacks.cdc.gov/view/cdc/79104
28. Guidelines for the prevention and control of carbapenem-resistant *Enterobacteriaceae*, *Acinetobacter baumannii* and *Pseudomonas aeruginosa* in health care facilities. Geneva: World Health Organization; 2017. Licence: CC BY-NC-SA 3.0 IGO. Available at: https://www.who.int/publications/i/item/9789241550178.
29. Implementation manual to prevent and control the spread of carbapenem-resistant organisms at the national and health care facility level. Geneva: World Health Organization; 2019 (WHO/UHC/SDS/2019.6). Licence: CC BY-NC-SA 3.0 IGO. Available at: https://www.who.int/publications/i/item/WHO-UHC-SDS-2019-6.