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Letter to the Editor

Unmasking carbapenemases molecular patterns in Ecuador: An analysis of Gram-negative bacteria, 2014–2022

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Dear Editor,

Carbapenem resistance in healthcare-associated infections is a significant health problem in multiple countries. With the worsening antimicrobial resistance crisis, resistance to carbapenems in Gram-negative pathogens is a major clinical challenge. Carbapenems have long been considered the most active and effective agents against multidrug resistant Gram-negative bacteria (MDR).

In the World Health Organisation's (WHO) 2017 global priority list for antibiotic-resistant bacteria, three of the four pathogens are ranked as critically important for research and developing new antibiotics. These include carbapenem-resistant Enterobacterales (CRE), carbapenem-resistant *Pseudomonas aeruginosa* (CRPA) and carbapenem-resistant *Acinetobacter baumannii* (CRAB) [1]. However, despite projections from WHO, predicting a critical situation of high morbidity and mortality associated with MDR in 2050, we have observed an acceleration of this problem, especially in Latin America, where an increase in carbapenemase-producing microorganisms was observed during the pandemic COVID -19 [2]. Several countries have reported data on carbapenem resistance patterns, but Ecuador lacks comprehensive reports.

Carbapenem resistance can arise through several mechanisms, including porin-mediated resistance, efflux pump overproduction and enzyme-mediated resistance. A single microorganism may express one or more of these mechanisms. Class A carbapenemases, known as serin-β-lactamases (SBLs), such as the carbapenemases of *K. pneumoniae* (bla_{KPC}), bla$_{IMI}$, bla_{GES}, the carbapenemase of *Serratia fonticola*, the enzyme of *Serratia marcescens* and non-metallo-carbapenemase-A, can hydrolyse β-lactams and confer resistance to multiple antimicrobials. bla_{KPC}, with variants such as bla_{KPC-2} and bla_{KPC-3}, are frequently reported and horizontally transmitted via plasmids. bla_{IMI} carbapenemases, although rarely detected, show resistance to imipenem and intermediate resistance to ertapenem and are not clinically relevant. Reports of bla_{GES} carbapenemases with a mutation in the bla_{GES} gene are increasing and are transmitted via plasmids [3].

Class B carbapenemases, known as metallo-*β*-lactamases (MBLs), are diverse and can inactivate most β-lactams except monobactams. New Delhi metallo-*β*-lactamase 1 (bla_{NDM}) confers resistance to enteric pathogens, Verona integron-encoded MBL (bla_{VIM}) hydrolyses most β-lactams except aztreonam and specific MBLs like German imipenemase and Sao Paulo MBL have been detected in clinical isolates of particular bacteria. Bacteria co-expressing MBLs and SBLs can hydrolyse aztreonam, a clinically relevant monobactam [3].

To shed light on the situation in Ecuador, we obtained information on molecular patterns of carbapenemases resistance in Gram-negative bacteria from the open database of the National Institute of Public Health Research of Ecuador (INSPI). Data collected by the National Reference Centre for Antimicrobial Resistance (CRN-RAM) between 2014 and 2022 revealed a total of 7356 enzymatically carbapenem-resistant isolates. The predominant microorganism was *Klebsiella pneumoniae* ss. *pneumoniae*, with a cumulative count of 6244 bla_{KPC} and 125 bla_{NDM} isolates, and 16 bla_{OXA48}, 4 bla_{IMP}, and 3 bla_{VIM} isolates. *Pseudomonas aeruginosa* ranked second with 572 bla_{VIM} and 39 bla_{IMP} isolates, along with 8 bla_{KPC} and 5 bla_{NDM} isolates. The *Enterobacter cloacae* complex exhibited 39 bla_{IMP} and 24 bla_{NDM} isolates, while the *Acinetobacter calcoaceticus/baumannii* complex showed 11 bla_{NDM} and 1 bla_{IMP} isolate (Table 1).

For infections caused by microorganisms that produce bla_{KPC}, the following treatment alternatives can be considered: meropenem-vaborbactam, ceftazidime-avibactam and imipenem-cilastatin-relebactam. In addition, in the case of MBLs such as bla_{NMD}, a combination of ceftazidime-avibactam with aztreonam or cefiderocol can be used as monotherapy [4].

In the treatment of $bla_{OXA-48-like}$ infections, ceftazidime-avibactam is the preferred treatment option. It is worth noting that in 2023 the Infectious Diseases Society of America (IDSA) recommended that cefiderocol be reserved for the treatment of metal-β-lactamase-producing Enterobacterales (e.g. bla_{NDM}, bla_{VIM}, bla_{IMP} producers) or in selected cases with glucose non-fermenting Gram-negative organisms [4].

The appropriate antibiotic selection should consider the individual

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Table 1
Molecular mechanisms of carbapenem resistance in Gram-negative isolates processed by the National Center for Antibiotic Resistance between 2014 and 2022.

	*bla*KPC						*bla*VIM		*bla*IMP				*bla*NDM				*bla*OXA48		
Year	*Klebsiella pneumoniae ss. pneumoniae*	*Enterobacter cloacae complex*	*Pseudomonas aeruginosa*	*Enterobacter amnigenus*	*Enterobacter asburiae*	*Enterobacter sp.*	*Pseudomonas aeruginosa*	*Klebsiella pneumoniae ss. Pneumoniae*	*Pseudomonas aeruginosa*	*Enterobacter cloacae complex*	*Klebsiella pneumoniae ss. pneumoniae*	*Acinetobacter calcoaceticus/baumannii complex*	*Klebsiella pneumoniae ss. pneumoniae*	*Enterobacter cloacae complex*	*Acinetobacter calcoaceticus/baumannii complex*	*Pseudomonas aeruginosa*	*Klebsiella pneumoniae ss. pneumoniae*	*Enterobacter cloacae*	*Name of the microorganism*
2014	405	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	Number of isolates
2015	673	1	0	0	0	0	10	0	6	6	0	0	1	0	1	0	0	0	
2016	514	8	2	0	0	0	38	0	5	5	0	0	9	0	0	0	0	0	
2017	461	18	0	0	0	1	100	0	6	6	1	0	6	1	3	1	0	0	
2018	496	24	0	0	0	1	55	0	11	11	0	0	1	1	3	0	0	0	
2019	708	48	1	0	3	0	73	0	0	0	0	0	4	1	1	0	4	1	
2020	1065	45	2	1	0	0	64	1	4	4	3	1	28	6	1	2	6	0	
2021	1273	68	2	2	0	0	118	2	5	5	0	0	40	7	0	1	3	0	
2022	649	40	1	0	0	0	114	0	2	2	0	0	36	8	2	1	3	0	

susceptibility profile of each bacterial isolate, the particular conditions of each patient, the specific identification of the carbapenemase type and the local availability of antibiotics [4]. When the above antibiotics are unavailable, alternative options such as tetracyclines, polymyxins, aminoglycosides, folate inhibitors or quinolones may be used according to the above recommendations [4].

To address the urgent problem of carbapenem resistance. Comprehensive strategies are essential: responsible use of antimicrobials based on the "One Health" approach, strict infection control, molecular tools at the point of care, and efforts by local authorities to provide new antibiotics that are not available in all hospitals [2]. Surveillance controls resistance patterns and new mechanisms. International cooperation, education campaigns and awareness raising are needed to prevent resistance. Urgent action is needed to contain carbapenem-resistant bacteria.

Ethical approval

Not required. Data were extracted from the open database of the National Institute for Public Health Research of Ecuador (INSPI).

Consent for publication

Not applicable.

Availability of data and materials

The data are available on request from the National Institute of Public Health of Ecuador.

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Authors' contributions

J.D.A-E requested the data from INSPI, wrote the initial manuscript and carefully reviewed and approved all subsequent versions. C.S.S. contributed by doing the initial data extraction and carefully reviewing and approving all iterations. K.S. and C.L. enriched the manuscript by contributing their insightful views on the clinical management of infections based on the reported molecular mechanism. A.J.R-M made a significant contribution by actively participating in the drafting of the manuscript and providing invaluable critical assessments of the content.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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