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Resistencia a los antimicrobianos por enterobacterias a nivel de américa latina y el caribe 2013-2023

Antimicrobial resistance by Enterobacteriaceae in Latin America and the Caribbean 2013-2023

[1] Ary Sebastian Sarango Berru https://orcid.org/0009-0001-3135-0519
Faculty of Biochemistry and Pharmacy, Catholic University of Cuenca, Cuenca, Ecuador.
assarangob22@est.ucacue.edu.ec

[2] Jonathan Gerardo Ortiz Tejedor https://orcid.org/0000-0001-6770-2144
Faculty of Biochemistry and Pharmacy - Master's Degree in Clinical and Molecular Laboratory Diagnostics. Catholic University of Cuenca. Cuenca - Ecuador.
jonnathan.ortiz@ucacue.edu.ec

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Palabras claves:
América Latina, Infecciones por Enterobacteriaceae, Betalactámicos, Resistencia a los betalactámicos.

Resumen

Introducción. La resistencia a los antimicrobianos es un problema a nivel mundial, también denominado la pandemia silenciosa, debido al creciente índice de bacterias multirresistentes y panresistentes. Siendo las enterobacterias una parte importante de este problema, debido a que son las más comunes a nivel hospitalario y comunitario, y tienen la capacidad de producir enzimas betalactamasas inhibidoras de los antibióticos betalactámicos. **Objetivo.** Reportar los antibióticos betalactámicos con mayor eficacia contra enterobacterias productoras de enzimas betalactamasas, y la incidencia de dichas enterobacterias en Latinoamérica, desde el año 2013 al 2023. **Metodología.** Se realizó una revisión sistemática empleando el método PRISMA y utilizando fuentes como son PAOH, Scielo, Redalyc, PubMed, y el metabuscador Google Académico, recopilando 69 documentos, y manteniendo 7 en base a los criterios de inclusión y exclusión planteados. **Resultados.** En base a los diferentes estudios se obtuvo que las enterobacterias con resistencia antimicrobiana y mayor incidencia intrahospitalariamente son*:* *E. coli*, *K. pneumoniae*, y *Enterobacter spp.*, y los antibióticos betalactámicos con mayor eficiencia frente a enzimas betalactamasas son: Imipenem y Meropenem, pero, también han empezado a perder su eficacia, causando que se recomiende un tratamiento alternativo más drásticos, como es el caso de la colistina. **Conclusión.** En los hospitales de Latinoamérica se puede observar un gran número de casos de infecciones bacterianas producidas por enterobacterias con multirresistencia a betalactámicos, principalmente causado por una automedicación del paciente, que, a pesar de los esfuerzos de controlar la venta de estos medicamentos, sigue existiendo un alto índice de enterobacterias con RAM. **Área de estudio general:** Bioquímica y Farmacia. **Área de estudio específica:** Microbiología. **Tipo de estudio:** Revisión bibliográfica.

Keywords:
Latin America, Enterobacteriaceae infections, Beta-

Abstract

Introduction: Antimicrobial resistance is a global problem, also known as the silent pandemic, due to the increasing rate of multi-resistant and pan-resistant bacteria. Enterobacteria are

lactams, Resistance to beta-lactams.

important to this problem because they are the most common at the hospital and community level and can produce beta-lactamase enzymes that inhibit beta-lactam antibiotics. Objective: To report the beta-lactam antibiotics with the highest efficacy against beta-lactamase enzyme-producing enterobacteria and the incidence of these enterobacteria in Latin America from 2013 to 2023. Methodology: A systematic review was conducted using the PRISMA method and sources such as PAHO, SciELO, Redalyc, PubMed, and the Google Scholar metasearch engine, collecting 69 documents and maintaining seven based on the inclusion and exclusion criteria. Results: Based on the different studies, it was found that the enterobacteria with antimicrobial resistance and the highest incidence in hospitals are E. coli, K. pneumoniae, and Enterobacter spp., and the beta-lactam antibiotics with higher efficacy against beta-lactamase enzymes are Imipenem and Meropenem; However, it has also begun to lose its effectiveness, causing a more drastic alternative treatment to be recommended, such as colistin. Conclusion: In Latin American hospitals, a large number of cases of bacterial infections produced by enterobacteria with multi-resistance to beta-lactams can be observed, caused by patient self-medication, which, despite efforts to control the release of these medications, continues to exist a high rate of enterobacteria with antimicrobial resistance (AMR).**General study area:**Biochemistry and Pharmacy. Specific area of study: Microbiology. Type of study: Literature review.

Introduction

Antimicrobial resistance is a global health problem, which has caused a reduction in the pharmacological efficiency of antimicrobial drugs and, together with the uncontrolled dissemination of antibiotic-resistant genes in non-clinical environments, generates the emergence of multi-resistant bacteria, where the main causes are the inappropriate prescription of antimicrobials and self-medication.(1).

Due to the great geographic, climatic and biological diversity that Latin America possesses, several challenges have been raised, specifically in the monitoring of antimicrobial resistance. The fact that a large portion of the population lives in poverty and that antimicrobials are available without a prescription in many countries in the region, shows that the production and regulation of sales of these drugs is inconsistent, which is visible mainly in the area of human health, but is also emphasized in the agricultural and veterinary areas.(2–4).

The indiscriminate use of antibiotics in livestock and agriculture for treatment and accelerated growth, together with the fact that coliforms (E. coli) with antibiotic-resistant genes have been recorded in drinking water supply systems in several countries in the region, promotes the creation and spread of resistant strains transmitted by food.(5, 6).

Among bacteria, the Enterobacteriaceae family is the largest and most clinically important group that causes a wide variety of pathologies in humans, of which the clinically important species are the primary pathogenic enterobacteria (Klebsiella pneumoniae, Enterobacter spp, Salmonella enterica spp, Shigella spp, Yersinia spp, and some strains of Escherichia coli) and the opportunistic enterobacteria.(5, 6).

Being the largest group of bacteria, it also makes them one of the major causes of bacterial infections, which consequently makes them the most likely to acquire resistance to specifically beta-lactam antibiotics, which, like enterobacteria, are the largest family of antimicrobials and the most clinically used. The present work aims to report the beta-lactam antibiotics with the greatest efficacy against enterobacteria that produce beta-lactamase enzymes, and the incidence of said enterobacteria in Latin America, from 2013 to 2023, through a systematic review of the literature.

Bacterial resistance to antimicrobials

Antimicrobials are drugs used to treat diseases caused by microorganisms such as viruses, bacteria, fungi and parasites. Antimicrobials include antibiotics, a large and heterogeneous group of widely distributed drugs intended to treat bacterial infections (considered one of the main causes of mortality in developed countries), thereby reducing the high rate of deaths that bacteria can cause. However, because every microorganism has the ability to neutralize or resist antimicrobial action either naturally (specific to each organism) or acquired (as a result of defense mechanisms developed when exposed to antimicrobial agents), and together with the indiscriminate and uncontrolled use of these drugs, a new problem has arisen worldwide, called Antimicrobial Resistance (AMR).(7, 8).

AMR is one of the main current public health problems, which began in 1940-1944 with the report of bacterial strains resistant to penicillin, through the production of hydrolytic enzymes called penicillinases, which are part of beta-lactamases (a group of enzymes capable of inactivating beta-lactam drugs).(7, 9).

Beta-lactams

These drugs have the same mechanism of action, which is to prevent transpeptidation (the last step in the synthesis of the bacterial wall) leaving the membrane exposed, which, thanks to osmotic pressure or the activation of autolysins, generates cell lysis.(10).

They form the largest family of bactericidal antibiotics, with the beta-lactam ring defining them chemically. They occupy the predominant place in the treatment of bacterial infections both at outpatient and hospital level and are divided into four groups: penicillin and its derivatives, cephalosporins, monobactams and carbapenems, mentioned in table 1.(6, 10).

*Penicillins:*Penicillin was the first antibiotic discovered by Dr. Alexander Fleming in 1928, from which numerous drugs were derived. They are considered the most effective and least toxic drugs against gram-positive and gram-negative microorganisms, but have come to have limited use due to the low resistance they present against beta-lactamases.(11).

*Cephalosporins:*They are antibiotics discovered by Dr. Giusseppe Brotzu in 1948, which are affected by the same resistance mechanisms as penicillins, but they have a slight advantage, because they tend to be more resistant to certain beta-lactamases.(12).

Carbapenems: They are synthetic antibiotics discovered by Alberts-Shonberg and collaborators in 1976, considered of great importance due to their broad spectrum of activity in gram-positive and gram-negative microorganisms that produce beta-lactamases.(13).

Monobactams: Currently, it contains only one antibiotic, discovered in 1981 by two independent teams: Imeda and colleagues, and the Squibb Institute for Medical Research. The antibacterial activity of this group is directed especially at gram-negative microorganisms and has no action against gram-positive and anaerobic microorganisms. It is resistant to the action of beta-lactamases, with the exception of ESBLs.(14).

Table 1. Beta-lactam antimicrobials*(7, 10, 11, 15)*

Cluster	Representative antimicrobials
Penicillins	Penicillin G, Penicillin V, Ampicillin, Amoxicillin, Carbenicillin, Ticarcillin, Piperacillin, Mezlocillin
Cephalosporins	First Generation: Cefazolin, Cephalotin
	Second Generation: Cefuroxime, Cefoxitin, Cefotetan, Cefaclor, Cefamandole.
	Third Generation: Cefotaxime, Ceftriaxone, Ceftazidime, Cefixime, Cefpodoxime.
	Fourth Generation: Cefepime, Cefpirome.
	Fifth Generation: Ceftaroline Fosamil, Ceftobiprole Medocaril, Ceftolozane
Monobactams	Aztreonam
Carbapenems	Imipenem, Meropenem, Ertapenem, Doripenem

Beta-lactamases

It is the group of enzymes with the ability to hydrolyze the beta-lactam ring, generated by bacteria capable of resisting these drugs. These enzymes were first identified in 1940, but they really came to represent a public health problem after an indiscriminate use of penicillin in 1941, giving rise to the first beta-lactamase, penicillinase, resulting in the need for new antimicrobials with a broader spectrum.(16).

Main bacteria with antimicrobial resistance in Latin America

Bacteria are able to survive in extreme environments and in Latin American countries, the warm and humid environment is perfect for their proliferation. Among all the bacteria that can grow in this environment, there are three bacterial groups with greater clinical importance.(17):

Gram positive bacteria

- *Staphylococcus aureus*
- *Streptococci: Streptococcus pneumoniae, Beta-hemolytic streptococci*
- *Enterococcus*

Gram negative bacilli

- *Enterobacteriaceae*

Non-fermenting Gram-negative bacilli

- *Acinetobacter spp: Acinetobacter baumannii*
- *Pseudomonas aeruginosa*

Among these three bacterial groups, the Enterobacteriaceae family is considered the largest and most clinically important.

Enterobacteriaceae

The Enterobacteriaceae family, also commonly known as enterobacteria, are gram-negative bacteria found in soil, water, or vegetation, and some are part of the intestinal flora of humans and animals. It constitutes about 50% of the isolates made in patients with nosocomial infections and 80% of the isolates of gram-negative bacilli, and a main cause of enteric infections and urinary tract infections.(18, 19).

In Latin America, the enterobacteria with the highest incidence and clinical importance are: Escherichia coli, Klebsiella pneumoniae, Salmonella spp, and Shigella spp.

Methodology

A systematic review was carried out following the PRISMA 2020 guide, with keywords and search strategy, which are: <Bacterial infections>, <Incidence of enterobacteria>, <Resistant genes in hospitals>, <Intrahospital Enterobacteriaceae>, <Antimicrobial resistance>, <Bacterial resistance and Enterobacteriaceae>, and <Registry and Enterobacteriaceae and Latin America>, with a filter for a period of 10 years, starting in 2013 until 2023 in Latin American countries, mainly those that have Antimicrobial Resistance Surveillance, using Boolean operators such as: "And, and Or" and as a bibliographic manager: "Zotero".

The search for the study began on May 15, 2023, and ended on December 12 of the same year, in scientific databases such as: PAOH, Scielo, Redalyc, PubMed, and the Google Scholar metasearch engine.

*Inclusion Criteria:*Articles and records published between 2013-2023, original articles in Spanish, Portuguese or English, national and international articles and records, longitudinal and cross-sectional articles.

*Exclusion Criteria:*Articles published outside the study period, letters to the editor, articles with unreliable scientific bases, articles with insufficient data, duplicate documents.

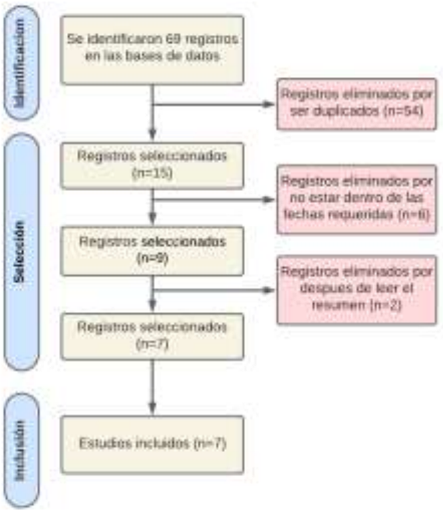

Figure 1. Flowchart of the PRISMA Methodology for article selection

Results

Table 2, with data from 2013, shows the most common enterobacteria of hospital origin in Latin American countries, where E. coli is the predominant bacteria, followed by K. pneumoniae and Enterobacter spp. Ampicillin is the antibiotic to which these bacteria are most resistant. Then there is Cefepime, the antibiotic that is available in all countries and

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has varying efficacy, indicating that it should be used with greater care. Finally, there are Imipenem and Meropenem, which are the most efficient antibiotics against these beta-lactamase-producing enterobacteria.

In table 3, data from articles written in the same countries as in table 2 are found, showing that the E. coli bacteria still predominates at the hospital level followed by K. pneumoniae despite the years that have passed. It also highlights the fact that all the articles present resistance mechanisms belonging to beta-lactamases, which degrade the beta-lactam ring, rendering this group of antibiotics ineffective. The most important of these are carbapenems (the last line of treatment for these bacteria), but the dissemination of genes such as bla KPC, bla NDM, bla OXA-48, cause this drug to become increasingly ineffective.

Table 2. Enterobacteriaceae resistant to beta-lactam antibiotics in Latin American countries

Qualification	Author	Year of publication	Country	Bacterium	Isolated	Beta-lactam resistant
Annual Report of the Antibiotic Resistance Monitoring/Surveillance Network;	Pan American Health Organization	2014	Argentina	*E. coli*	1857	AMP (77%), AMC (28%), CEP (42%), TZP (5%), C3G (25%), FOX (3%), FEP (10%), IMP (0.1%), MEM (0.1%)
				K. pneumoniae	1773	AMC (53%), CEP (69%), TZP (28%), C3G (59%), FOX (9%), FEP (35%), IMP (9%), MEM (8%)
				E. cloacae	481	TZP (21%), CTX (53%), CAZ (47%), FEP (16%), IMP (1%), MEM (1%)
			Bolivia	*E. coli*	202	AMP (96%), AMC (83%), CEP (91%), CTX (82%), FOX (16%), CAZ (82%), FEP (22%)
				K. pneumoniae	171	AMC (88%), CEP (88%), CTX (84%), FOX (15%), CAZ (84%), TZP (10%), IMP (3%), FEP (60%)
				Enterobacter spp	106	CTX (83%), FOX (87%), CAZ (85%), IMP (3%), MEM (5%), FEP (50%)
			El Salvador	*E. coli*	7726	AMP (84%), AMC (14%), CTX (44%), CAZ (45%), TZP (6%), IMP (0.3%), MEM (0.3%), FEP (44%)
				K. pneumoniae	2771	AMC (22%), CTX (53%), CAZ (52%), TZP (23%), IMP (0.4%), MEM (0.5%), FEP (54%)
				Enterobacter spp	835	CTX (75%), CAZ (75%), TZP (9%), IMP (2%), MEM (2.3%), FEP (54%)
			Brazil	*E. coli*	580	AMP (69%), AMC (55%), CEP (30%), CTX (3%), FOX (20%), CAZ (56%), TZP (10%), IMP (13%), MEM (8%), FEP (64%)
				K. pneumoniae	2497	AMP (72%), AMC (61%), CEP (29%), CTX (54.5%), FOX (55%), CAZ (47%), TZP (58%), IMP (46%), MEM (42%), FEP (85%)

	Enterobacter spp	1161	AMP (70%), AMC (64%), CEP (24.5%), CTX (39%), FOX (64%), CAZ (43%), TZP (36%), IMP (32%), MEM (20%), FEP (60%)
	E. coli	619	AMP (80%), AMC (31%), CEP (50%), CTX (55%), FOX (42%), CAZ (45%), TZP (13%), IMP (1%), MEM (2%), FEP (50%)
Ecuador	*K. pneumoniae*	353	AMP (97%), AMC (40%), CEP (70%), CTX (76%), FOX (70%), CAZ (74%), TZP (40%), IMP (15%), MEM (14%), FEP (79%)
	Enterobacter spp	94	CTX (35%) FOX (93%), CAZ (43%), TZP (16%), IMP (2%), MEM (2%), FEP (30%)

Fountain: Institute of Tropical Pathology and Public Health (20)

Amoxicillin-Clavulanic Acid (AMC); Ampicillin (AMP); Cephalothin (CEP); Third-generation cephalosporins (C3G); Cefepime (FEP); Cefotaxime (CTX); Ceftazidime (CAZ); Cefoxitin (FOX); Imipenem (IPM); Meropenem (MEM); Piperacillin-tazobactam (TZP).

Table 3. Beta-lactamase-containing enterobacteria with the highest incidence in Latin America

Qualification	Author	Year of publication	Type of study	Isolated	Bacterium	Resistance mechanism	Country	Bibliographic citation
Community-acquired urinary tract infection by Escherichia coli in the era of antibiotic resistance in Ecuador	Maria Belen Solis	2022	Longitudinal and prospective	3341	*E. coli*	BLEE	Ecuador	(21)
Genes involved in antimicrobial resistance in Ecuadorian hospitals.	Victor Rafael Tamayo Trujillo	2022	Non-experimental retrospective description	-	*K. pneumoniae* *E. coli*	blah KPC bla NDM	Ecuador	(22)
Molecular characterization of extended-spectrum β-lactamase in Escherichia coli strains causing urinary tract infection in immunocompromised patients.	Pereyra Marcia	2019	Longitudinal and prospective	35	*E. coli*	bla CTX-M	Bolivia	(23)
Molecular characterization of multi-resistant Klebsiella pneumoniae belonging to CC258 isolated from outpatients with urinary tract infection in Brazil	Paola Aparecida	2019	Experimental	48	*K. pneumoniae*	blah KPC	Brazil	(24)
Identification of bacteria resistant to carbapenem antibiotics in hospitals in El Salvador.	Villatoro Esmeralda	2018	Transversal and prospective	97	*K. pneumoniae*	bla OXA-48	El Salvador	(25)
Clinical, epidemiological and microbiological characterization of bacteremias caused by carbapenem-resistant enterobacteria in a university hospital in Córdoba, Argentina.	Flavio G. Lipari	2020	Retrospective, observational and descriptive	84	*K. pneumoniae*	blah KPC	Argentina	(26)

Discussion

In Latin America, problems such as geography, climate, biological diversity and, above all, poverty have made it difficult to control the sale and distribution of antibiotics correctly, leading to people without a prescription self-medicating, causing the emergence of mainly resistant, multi-resistant and pan-resistant enterobacteria, which spread their genes through horizontal transfer mechanisms.(2, 27, 28).

Enterobacteriaceae are one of the main bacterial families that cause pathologies globally, with Latin America being one of the regions with the highest clinical incidence of these bacteria, mainly E. coli and K. pneumoniae, which are also the most common globally, followed by Salmonella spp. and Shigella spp., which are more common in community settings, and rare in sterile environments such as hospitals.(2, 20).

The analysis is based on data obtained from sources such as PAOH, the Ministry of Public Health of Ecuador, Scielo, Redalyc, PubMed, and the Google Scholar metasearch engine, which provided epidemiological information on bacteria with AMR. In this work, five Latin American countries were chosen: Ecuador, Bolivia, Brazil, El Salvador and Argentina. In these four countries chosen in the present study, the enterobacteria that presented more strains with AMR were: First, E. coli; Second, K. pneumoniae; Third, Enterobacter spp.; Fourth, Salmonella spp.; and Fifth, Shigella spp. The last two bacteria, although not mentioned in the work, are almost as important as E. coli, but are mainly limited to the community.(20).

Based on the data in the documents analyzed, it can be said that in Latin America antibiotics such as Ampicillin, Amoxacillin-Clavulanic Acid, Cephalotin, among others, have come to lose their effectiveness against the main intrahospital enterobacteria, and Meropenem and Imipenem, despite being part of the latest line to treat these bacteria, have begun to lose their therapeutic action and in some cases are 50% less effective than normal.(20).

To control bacteria from becoming more resistant to these antibiotics, it is necessary to find new treatments, such as Colistin, a polymyxin antibiotic that was kept as a reserve due to problems of nephrotoxicity and neurotoxicity, but with the increase in AMR, specifically to carbapenems, it is used as a valid therapeutic option for patients in critical condition. Due to its toxicity, it is administered in combination therapy with other drugs, however, with the use of the drug, AMR has also appeared, such as the mcr-1 gene, capable of providing resistance to bacteria against this drug.(29, 30).

Conclusions

- Antimicrobial resistance (AMR) occurs when patients self-medicate with the wrong antibiotics, which gives the bacteria causing their symptoms the opportunity to develop the ability to fight the administered medications, mainly through beta-lactamase enzymes, which are capable of inhibiting the pharmacological action of the medication. The patient, unable to treat the infection, goes to a health center, but already has AMR to the previously administered medications.
- In Latin America, a large number of cases of bacterial infections with this type of pattern mentioned above can be observed, which prevents the rapid treatment of the patient. Among these infections are those produced by enterobacteria, which present numerous cases of multi-resistance mainly to beta-lactam antibiotics, especially within the hospital environment, where bacteria can be opportunistic in immunosuppressed patients, thus causing Health Care Associated Infections (HAIs).
- Based on different studies of hospitals in Latin America, it can be analyzed that the enterobacteria that present the highest number of cases of AMR are six subgroups of Escherichia coli, Klebsiella pneumoniae, Enterobacter spp., Salmonella spp. and Shigella spp.

Conflict of interest

The authors declare that there is no conflict of interest for the publication of this article.

Authors' contribution statement

Ary Sebastian Sarango Berru designed the study, analyzed the data and drafted the paper.

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