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ARTICLE REVIEW

Antimicrobial resistance profile of the main microorganisms subject to surveillance in Ecuador

Perfil de resistencia antimicrobiana de los principales microorganismos sujetos a vigilancia en el Ecuador

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ABSTRACT

Introduction: Infectious diseases are one of the most important causes of death in the world, with the introduction of antibiotics being one of the most important interventions for their control and increasing the life expectancy of the population by several years. However, a growing threat is undermining the effectiveness of these drugs: "Bacterial resistance to antibiotics".
Objective: to describe the antimicrobial resistance profile of the main microorganisms subject to surveillance in Ecuador.
Methods: the search and selection of information was carried out on several open access platforms: Digital Library (SciELO), Search Engine (Google Scholar), Database (Science Direct, Scopus), Search Engine (PubMed), as well as texts from specialized medical literature. The following were included:articles with access to their abstract or full content, articles published in high-impact scientific journals, written in Spanish and English.
Development: The microorganisms subject to antimicrobial resistance (AMR) surveillance that have been reported in the highest percentage are: Escherichia coli (>50%), followed by Klebsiella pneumoniae, Staphylococcus aureus and Pseudomonas aeruginosa. The main resistance genes are: CTX-M (BLEE, most common and of greatest importance in public health), followed by NDM, VIM, IMP, KPC, VAN-B and MCR-1.
Conclusions: Antimicrobial resistance represents a serious public health problem, from antibiotic resistance in bacteria responsible for common infections to resistance to last-resort antibiotics.

Keywords: Infectious Disease Incubation Period Resistance; Bacteria; Antibiotics; Antimicrobial.

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RESUMEN

Introducción: las enfermedades infecciosas son una de las causas más importantes de muerte en el mundo, siendo la introducción de los antibióticos una de las intervenciones más importantes para su control y aumento en varios años la esperanza de vida de la población. Sin embargo, una amenaza creciente deteriora la eficacia de estos fármacos: "La resistencia bacteriana a los antibióticos".
Objetivo: describir el perfil de resistencia antimicrobiana de los principales microorganismos sujetos a vigilancia en el Ecuador.
Métodos: se llevó a cabo la búsqueda y selección de la información en varias plataformas de acceso abierto: Biblioteca digital (SciELO), Buscador (Google Académico), Base de datos (Science Direct, Scopus), Motor de búsqueda (PubMed), así como textos de literatura médica especializada. Se incluyeron artículos con acceso a su resumen o todo el contenido, artículos publicados en revistas científicas de alto impacto, redactados en español e inglés.
Desarrollo: los microorganismos sujetos a vigilancia de resistencia antimicrobiana (RAM) que se han reportado en mayor porcentaje son: *Escherichia coli* (>50 %), seguido de *Klebsiella pneumoniae*, *Staphylococcus aureus* y *Pseudomonas aeruginosa.* Los principales genes de resistencia son: CTX-M (BLEE, más común y de mayor importancia en salud pública), seguido de NDM, VIM, IMP, KPC, VAN-B y MCR-1.
Conclusiones: la resistencia a los antimicrobianos representa un grave problema para la salud pública, desde la resistencia a antibióticos en bacterias responsables de infecciones comunes, hasta la resistencia a antibióticos de último recurso.

Palabras clave: Periodo De Incubación De Enfermedades Infecciosas; Resistencia; Bacterias; Antibióticos; Antimicrobianos.

INTRODUCTION

An antibiotic is any chemical substance produced by a microorganism and used to kill or inhibit the growth of other infectious microorganisms.[1,2] In 1929, British bacteriologist Alexander Fleming accidentally discovered penicillin (a derivative of the fungus Penicillium notatum). This discovery led to the development of other antibacterial compounds produced by microorganisms.[2]

Since the widespread use of antibiotics in the 1950s, the landscape of infectious diseases has changed radically. Diseases that were once the leading cause of death, such as tuberculosis, pneumonia or sepsis, are now much less serious. The use of antibiotics has also meant a spectacular advance in the surgical field, allowing complex and prolonged surgeries to be performed without excessive risk of infection.[2]

Antimicrobial resistance has been defined as a silent pandemic, which manifests itself much more rapidly than the time required for the development of new drugs, so that there are almost no new types of antibiotics in the development phase. In addition, existing antibiotics lose effectiveness due to antimicrobial resistance.[3,4,5,6]

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Antibiotic resistance is one of the major health problems we face today, and is considered as such by the World Health Organization, which even refers to a possible "post-antibiotic era." A recent report predicts that nearly 300 million people will die in the coming decades as a direct result of antimicrobial resistance. More specifically, by 2050, it is estimated that 3 million people will die from infections caused by multi-resistant E. coli and that infections will be the leading cause of death, above cancer.[7]

The COVID-19 pandemic produced, among many other consequences, a marked increase in the frequency of healthcare-associated infections (HAIs), just as antimicrobial resistance (AMR) has accelerated to unsuspected levels.[8]

This review highlights the antimicrobial resistance profile of the main microorganisms subject to surveillance in Ecuador, and recommendations based on the literature, as a tool in decision-making when instituting a treatment.

METHODS

Narrative type bibliographic review to describe the antimicrobial resistance profile of the main microorganisms subject to surveillance in Ecuador. The search and selection of information was carried out on several open access platforms: Digital Library (SciELO), Search Engine (Google Scholar), Database (Science Direct, Scopus), Search Engine (PubMed), as well as texts from specialized medical literature. The following were included: articles with access to their abstract or full content, articles published in high-impact scientific journals, written in Spanish and English. They were excluded. Articles that are not relevant or useful for the research topic and that do not meet the criteria estimated for the review.

DEVELOPMENT

Resistance is a growing public health problem worldwide and is a consequence of the process of natural selection, as a result of random mutations in the bacterial population or the acquisition of resistance mechanisms by transfer from other resistant bacteria due to the selective pressure of the antibiotic. In practice, a bacterium is sensitive to an antibiotic when it is effective against it and a cure of the infection can be expected. On the contrary, bacteria are resistant when their growth can only be inhibited with concentrations higher than those that the drug can reach at the site of infection. Antibiotics are not mutagenic; they only create selection pressure.[9,10,11]

When a bacterium resistant to an antibacterial drug is selected, its descendants usually inherit that characteristic and over time, under pressure from the drug, the population of resistant strains becomes dominant in the environmental niche in which it develops. On other occasions, microorganisms use mechanisms of genetic material transfer, known as transmissible resistance, with which they can transmit their resistance to their own species or to others.[11,12]

The resistance mechanisms developed by bacteria could be summarized as follows:

1. Expulsion of the antibiotic from the interior of the bacterial cell, by means of efflux pumps.[13]

2. Neutralization of the antibacterial agent by enzymes that render it inactive. Among Gram-negative bacteria, the production of beta-lactamases is the main mechanism of resistance to beta-lactam antimicrobials. They are excreted and concentrated in the periplasmic space, between the bacterial wall and the outer membrane, unlike Gram-positive bacteria, which,

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lacking an outer membrane, are excreted outside the cell, which makes this mechanism not very efficient. Regarding their spectrum of action, they can be divided into:[14,15]

- Extended spectrum beta-lactamases (Example: TEM-1, SHV-1): Can hydrolyze first generation penicillins and cephalosporins.
- Extended spectrum beta-lactamases – ESBL (Example: CTX-M): They can hydrolyze penicillins, monobactams and first to fourth generation cephalosporins, but not carbapenems.
- AmpC-type beta-lactamases: Resistance to cephalosporins and, to a lesser extent, to carbapenems.
- Carbapenemases (Example: KPC, NDM, VIM, IMP): Can hydrolyze carbapenems.

3. Alteration or modification of the binding site of the antimicrobial drug or its protection (as is the case with certain quinolone resistance mechanisms [Qnr]) results in a loss of affinity and, therefore, prevents the action of the drug.[16]

4. The alteration of bacterial permeability, which limits the entry of the antibacterial. This is an important mechanism in gram-negative bacteria, since they have protein channels called porins that allow or prevent the passage of hydrophobic molecules.[17,18]

5. Biofilms. Biofilm-forming bacteria are protected from ultraviolet light, dehydration, the action of antibiotics, the body's defense mechanisms, such as phagocytosis, and other environmental threats.[19]

The World Health Organization (WHO) Global Antimicrobial Resistance and Use Surveillance System (GLASS) reports high rates of antimicrobial resistance against common bacterial infections. (Table 1)

Table 1. Time series of antibacterial resistance reported by WHO worldwide (2017-2020).

Bacterium	Antibiotic	Median	
		2017	2020
Blood			
S. aureus	Methicillin-resistant bacteria (MRSA)	16,6	18,3
E. coli	Ampicillin	79,2	73,9
	Ciprofloxacin	42,2	44
	Cephalosporin (3rd generation)	20,2	24
	Meropenem	0,5	0,9
	Colistin	0,9	1,5
K. pneumoniae	Ceftriaxone	50,2	70,3
	Cefepime	42,8	55,3
	Meropenem	12,3	12,5
	Colistin	5,4	3,7
Acinetobacter spp.	Amikacin	64,2	58,9
	Meropenem	73,1	72,9
Urinary tract			
E. coli	Ampicillin	70	70,8
	Ciprofloxacin	39	37,5
	Ceftriaxone	44,7	45,2
	Meropenem	0,4	0,6

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	Colistin	0,7	1
K. pneumoniae	Ciprofloxacin	31,3	33,2
	Ceftriaxone	43,3	43,2
	Meropenem	5,2	4,2
	Colistin	5,1	8,4
Gastrointestinal			
Salmonella spp.	Ciprofloxacin	8	6,9
Shigella spp.	Ciprofloxacin	16,9	22,7
Gonorrhea			
Neisseria Gonorrhoeae	Azithromycin	7,2	8,8
	Ceftriaxone	0	0

Fountain: Global AMC data. Time series of resistance to antibacterials (2017-2020). World Health Organization.[20]

When consulting the countries, territories or areas (CTA) in the Americas region, enrolled in the WHO GLASS-AMR (Antimicrobial Resistance) program, there is no data available for Ecuador. [21]

In Ecuador, the surveillance of antimicrobial resistance is led by the National Directorate of Epidemiological Surveillance, with the support of the National Institute of Public Health Research-INSPI.[22]

In Ecuador between 2010 and 2017, the main resistance genes found in health facilities are:

- KPC (so named because it was first found in Klebsiella pneumoniae).
- NDM (New Delhi metallo-beta-lactamase), VIM (Verona integron-encoded metallo-beta lactamase), IMP (resistant to the antibiotic Imipenem).
- VAN-B confers resistance to Vancomycin.
- MCR-1 allows the bacteria to resist Colistin.
- CTX-M (ESBL), which is the most common and important microbial resistance in public health.

Thus, the microorganism subject to AMR surveillance that has been reported in the highest percentage from the isolates from hospital services registered by INSPI is Escherichia coli with more than 50 %, followed by Klebsiella pneumoniae, Staphylococcus aureus and Pseudomonas aeruginosa.[22]

In relation to the antimicrobial resistance profile of the main microorganisms subject to surveillance in Ecuador:

- *Escherichia coli:*

Expressed resistance genes (KPC, NDM, MCR-1). Cephalosporins present resistance percentages of up to 50 %, compared to carbapenem-type antibiotics that present lower resistance percentages. [22]

In a study on urinary tract infection (UTI) caused by community-acquired E. coli, during the period between January and December 2020, with 4209 urine cultures, 3341/4209 were obtained where Escherichia coli (79,38 %) was isolated, with resistance greater than 60 % to ampicillin/sulbactam, greater than 40 % to Ciprofloxacin, less than 20 % to cephalosporins, and being E. coli ESBL (18,4 %), being in these cases alternative treatment: Nitrofurantoin, Fosfomycin, Amoxicillin/Clavulanic acid, Gentamicin, Amikacin and Ertapenem.[23]

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- *Klebsiella pneumoniae:*

Expressed resistance genes (KPC, NDM, IMP, MCR-1). Considered an opportunistic pathogen causing a large number of Health Care Associated Infections (HAIs). The resistance percentages for carbapenems such as Imipenem and Meropenem are similar, both in patients hospitalized with hospital infections (20-35 % resistance), and in the ICU with 40-55 % resistance.[22]

In a study on the annual prevalence of multi-resistant bacteria in patients admitted to the ICU, the sensitivity profile of Klebsiella pneumoniae was reported, showing resistance of 60 % to Ceftazidime, Ceftriaxone, and Cefepime, 40 % to Imipenem and Meropenem, being lower in Amikacin and Gentamicin with 22,2 %.[24]

- *Pseudomonas aeruginosa:*

Expressed resistance genes (VIM, IMP). Opportunistic pathogen of major importance, due to its high relationship with IAAS. In hospitalized patients (2014 to 2017) with hospital infections, resistance percentages of up to 30 % are evident for carbapenems such as Imipenem and Meropenem. In the case of Ceftazidime, it shows high resistance percentages of 23,7 % and 18,5 %, in 2016 and 2017 respectively. Regarding piperacillin-Tazobactam and Cefepime, resistance levels range between 15 % and 23 %.[22]

- *Staphylococcus aureus*MRSA (methicillin resistant):

In hospitalized patients with a percentage of resistance to penicillin of 87 %, followed by Cefazolin with 60 %. The same high percentages of resistance are present in patients coming from the ICU with 87 % resistance to penicillin. In the case of Oxacillin, the percentage of resistance has decreased from 46 % in 2014 to 35 % in 2017.[22]

DISCUSSION

In the World Health Organization (WHO) Global Antimicrobial Resistance and Use Surveillance System (GLASS) reports for 2022, high rates of antimicrobial resistance against common bacterial infections are reported. Globally, the proportion of Methicillin-resistant S. aureus (MRSA) is variable, with a median of 18,3 % for 2020.[20]

In Ecuador there is more than 30 % resistance to Cefoxitin and Oxacillin, indicating a significant proportion of MRSA, for which the therapeutic options are: Vancomycin, linezolid.[7] Globally, E. coli in blood shows significant resistance to Ampicillin (> 70 %) and Ciprofloxacin (> 40 %), and less than 20 % for Cephalosporin (3rd generation). In the case of E. coli in urine, it presents significant resistance to Ampicillin (> 70 %), 3rd generation Cephalosporin (> 40 %) and Ciprofloxacin (37,5 %), and less than 1 % for carbapenems.[20]

In Ecuador, in a study on urinary tract infection (UTI) caused by community-acquired E. coli, during the period between January and December 2020, significant resistance was found to Ampicillin/sulbactam (>60 %), Ciprofloxacin (>40 %) and cephalosporins (<20 %), with E. coli being ESBL (18,4 %), with the following therapeutic alternatives: Nitrofurantoin, Fosfomycin, Amoxicillin/Clavulanic acid, Gentamicin, Amikacin and Ertapenem.[24]

At global level, for K. pneumoniae in blood there is significant resistance to 3rd generation cephalosporins (70,3 %) and 4th generation (>50 %), as well as to carbapenems (12,5 %) and Colistin (3,7 %). Regarding K. pneumoniae in urine, it presents significant resistance to 3rd generation cephalosporins (>40 %), Ciprofloxacin (33,2 %), as well as resistance to carbapenems (4,2 %) and Colistin (8,4 %).[20]

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In Ecuador, significant resistance to carbapenems (20-35 %) is reported for K. pneumoniae, which is even higher in patients admitted to intensive care (>40 %), as well as to 3rd and 4th generation cephalosporins (60 %), being lower for Amikacin and Gentamicin (22,2 %).[25] Like the figures reported worldwide, it presents levels of resistance to antibiotics considered as a last resort, which are alarming.

The study carried out by Álvarez Lerma et al,[26] in Spain, offers a detailed analysis of antibiotic resistance trends in Pseudomonas aeruginosa strains isolated from invasive device-related infections in ICU patients, reporting resistance to antibiotics: Piperacillin-Tazobactam (40,2 %), Imipenem (46,1 %), Meropenem (46,5 %), Ceftazidime (39,1%) and Cefepime (37,2 %).

In relation to Pseudomonas aeruginosa in Ecuador, it represents the most important opportunistic pathogen, due to its high relationship with health care-associated infections (HAI), with resistance to carbapenems (30 %), 3rd generation cephalosporin (18,5 %), 4th generation cephalosporin and Piperacillin-Tazobactam (15-23 %).[22]

In this context, the use of synergistic combinations of antimicrobial drugs to treat infections caused by resistant microorganisms is attractive. Combinations of penicillins against Pseudomonas, such as: Piperacillin with Gentamicin, Tobramycin or Amikacin also show synergy against many strains of Pseudomonas aeruginosa, with a mechanism similar to that described for Enterococci (i.e. increased uptake of the aminoglycoside in the presence of the antipseudomonal penicillin). The current FDA-approved package insert for piperacillin-tazobactam indicates that this (3-lactam) should be used in combination with an aminoglycoside for the treatment of P. aeruginosa pneumonia.[11]

CONCLUSIONS

Antimicrobial resistance is a serious threat to public health worldwide. Antibiotic resistance is present in bacteria responsible for common, serious infections that have been treatable for decades and that could become life-threatening. Resistance exists to antibiotics that are used as a "last resort." Antimicrobial resistance is no longer a prediction for the future, but is now a reality in all regions of the world, complicating the course of diseases and increasing the cost of health care, as it lengthens hospital stays and requires more care.

RECOMMENDATIONS

Some widely recognized recommendations for addressing antibiotic resistance, which are often endorsed by public health organizations such as the World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC):[27,28,29,30]

- Limit antibiotic use to only when strictly necessary and as prescribed by a healthcare professional, to reduce the selection pressure that promotes resistance.
- Establish and improve surveillance systems to monitor antibiotic resistance and antimicrobial consumption.
- Implement rigorous infection control measures in healthcare settings, as well as promote personal hygiene.
- Promote awareness of antibiotic resistance among the public, healthcare professionals and policy makers to encourage responsible antibiotic prescribing and use practices.
- Invest in research and development of new antibiotics and diagnostic technologies to stay ahead in the race against resistant bacteria.

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- Promote cooperation and information exchange between countries and organizations to address antibiotic resistance globally.
- Regulate and limit the use of antibiotics in agriculture.

As measures that can be applied in clinical practice, to promote the rational use of antibiotics, we have:[11,12]

- Before starting antibiotics, clinical parameters (thermal curve, signs and symptoms suggestive of infectious disease) and laboratory parameters (white blood cell count, procalcitonin and other markers of infection) should be considered to justify their use.
- Laboratory data should be interpreted taking into account the clinical picture, since the findings may be due to colonization or contamination of the sample and not to an infection.
- Sampling for microbiological diagnosis is always required before starting and before changing due to failure.
- Dose optimization: by weight, hepatic or renal insufficiency or interactions. Improves efficacy. Reduces toxicity.
- Duration of treatment taking clinical practice guidelines as a reference (Example: Sanford Guide)
- There are non-infectious clinical situations that can cause fever and simulate an infectious condition: chemical phlebitis, pulmonary thromboembolism, immune diseases, among others.
- Not all infections warrant antibiotic treatment. Examples include asymptomatic bacteriuria (except in pregnant women or urologic procedures), superficial abscesses that can be drained, and nonbloody diarrhea.
- Avoid prescribing antibiotics for upper respiratory infections.
- Antibiotics should not be used to treat stasis dermatitis of the lower extremities.
- On the third day of treatment, there is usually sufficient microbiological data to assess modifications (switching to oral route, de-escalation, increase in spectrum, etc.).
- The seventh day of prescription allows for the assessment of the possibility of discontinuing treatment in numerous infectious syndromes.

When there is more than one antimicrobial capable of combating the causal agent, the following should be selected:[19]

- Less toxic and fewer side effects.
- Have the most appropriate route of administration and dosage.
- Induce less resistance (WHO AWARE classification)
- Be of lower cost.
- Have the most limited spectrum with respect to the infecting pathogen.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

Authorship Contribution

GJSV: Conceptualization, Data Curation, Formal Analysis, Research, Methodology, Project Management, Resources, Software, Supervision, Validation, Visualization, Writing - original draft, Writing - review and editing.
GAVS: Conceptualization, Data Curation, Formal Analysis, Research, Methodology, Project Management, Resources, Software, Supervision, Validation, Visualization, Writing - original draft, Writing - review and editing.
GLEA: Conceptualization, Data Curation, Formal Analysis, Research, Methodology, Project Management, Resources, Software, Supervision, Validation, Visualization, Writing - original draft, Writing - review and editing.

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