RESISTANCE TO ANTIBIOTIC AGENTS: PERSPECTIVE AND REALITY.

RESISTENCIA A LOS AGENTES ANTIBIÓTICOS: PERSPECTIVA Y REALIDAD.

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Acosta España Jaime David [1,2*]

1 Hospital Vozandes Quito – HVQ SA. Servicio de Microbiología. Quito – Ecuador.
2. Universidad de las Américas. Escuela de Medicina. Quito - Ecuador

ORCID ID:
Acosta España Jaime
orcid.org/ orcid.org/0000-0001-5299-2732

***Corresponding author:** Acosta España David
E-mail: jdacosta@hospitalvozandes.com

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Microorganisms have infected humans since time immemorial and in this context, we have lived through an endless war that has produced increasingly complex adaptation and selection pressure. Although antibiotics marked a new era beginning in 1928, it is interesting to mention that traces of tetracycline were found in human bone samples from ancient Sudanese Nubia dating from 350–550 AD. C **(1)**.

Paul Erlich, by his staining methods, already deduced at the end of the 19th century and the beginning of the 20th century, that there may be a magic bullet that acts on microorganisms to eliminate them, without affecting other cell types. This molecule is currently known as an antibiotic or antimicrobial in relation to its natural or synthetic origin. Of this interest, in 1910 the first molecule with studies in rabbits infected with syphilis to demonstrate antimicrobial activity was described **(2,3)**.

After this discovery, an antimicrobial revolution began with drugs from neosalvartan, penicillin, sulfonamidochrysoidine (prontosil) to complex molecules such as fifth-generation cephalosporins (ceftobiprole,ceftaroline,and ceftolozane) and even the association with new beta-lactamase inhibitors that include ceftazidime/avibactam,meropenem/vaborbactam,ceftolozane/tazobactam, imipenem- cilastatin- relebactam, among others **(4–6)**.

So, it is essential to highlight that microorganisms have been exposed to various molecules: bactericides,bacteriostats, fungicides,antiprotozoa, anthelmintics, antivirals, etc. And going back to the past again, as mentioned in his book "... The Origin of Species ..." by Charles Darwin, in which he referred that biological adaptation, is essential for the survival of biological organism, microorganisms will continue to adapt and only the best prepared for this adverse environment will be left **(3)**.

Thus, microorganisms have developed various mechanisms to evade the action of these antimicrobial substances since time immemorial, which is currently known as antimicrobial resistance (AMR), among these, one of the best known is bacterial resistance **(7)**. In which natural resistance is included: which is specific and intrinsic to microorganisms, for example ampicillin in *Klebsiella pneumoniae*; and acquired resistance: which is the one that microorganisms gain by various mechanisms, such as the production of extended spectrum beta-lactamases (ESBL) from *Klebsiella pneumoniae* by plasmids **(8)**.

In our daily clinical practice, it is currently common to find cultures of patients with resistant, multidrug resistant (MDR), extremely resistant (XDR) or pandemic resistant (PDR) microorganisms. Which in certain cases can result in a complicated work even for infectologists to find the best therapeutic option. In fact, it has become a priority for the World Health Organization (WHO), which has declared AMR as one of the 10 priority public health threats facing humanity, associated with higher mortality, increased health costs and therefore the government budget **(9)**.

Keys Words: SARS-Cov2, Pandemia, Aprendizajes

WHO prioritized pathogens of importance for the surveillance and research of new antibiotics, for priority one were considered: Acinetobacter baumannii resistant to carbapenems, *Pseudomonas aeruginosa* resistant to carbapenems, *Enterobacteriaceae* resistant to carbapenems and third generation cephalosporins. Priority two describes: vancomycin-resistant *Enterococcus faecium*, methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-intermediate (VISA), clarithromycin-resistant *Helicobacter pylori*, fluoroquinolone-resistant *Campylobacter* sp, *Salmonella* spp. resistant to fluoroquinolone and *Neisseria gonorrhoeae* resistant to fluoroquinolones and third generation cephalosporins. Finally, as priority 3: *Streptococcus pneumoniae* not susceptible to penicillin, *Haemophilus influenzae* resistant to ampicillin and *Shigella* spp. resistant to fluoroquinolone **(10)**.

These and other microorganisms are of special importance and it is advisable to know the biology, virulence factors, intrinsic or extrinsic resistance mechanisms, as well as the most frequent infections related to them. Indeed, the international bibliography asks to pay attention to the microorganisms ESKAPE, which is an acronym used to refer to *Enterobacter* sp., *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii, Pseudomonas aeruginosa*, and *Enterococcus faecium*. Since they lead the infections associated with health care worldwide due to their resistance mechanisms such as production of beta-lactamases, carbapenemases, efflux pumps, impermeability, etc. **(11)**.

This appearance of AMR is multifactorial and has been related to the indiscriminate use of antibiotics by human and veterinary health professionals, pharmacological waste in sewage with antibiotic residues, and untreated water produced by health services, farms, among others. It is important to analyze the veterinary use in food and water of various types of antibiotics to enhance the growth of animals and prevent infections, which has led several governments to prohibit the use of certain antibiotics used in humans in the production of animals or to control their levels and promote rational use. And this holistic approach to fighting AMR is known as "ONE HEALTH" or one health **(12–14)**.

In Ecuador, the reality is very similar to the world panorama and the surveillance faculty is carried out through the National Reference Center for Antimicrobial Resistance (CRN-RAM), which receives mandatory surveillance strains based on WHO recommendations. The Ministry of Public Health of Ecuador (MSP) in the document "Data Report On Antimicrobial Resistance In Ecuador 2014-2018" that the microorganisms subject to surveillance most frequently reported were in descending order: *Escherichia coli, Klebsiella pneumoniae, Staphylococcus aureus* and *Pseudomonas aeruginosa* **(15)**.

In the report document of the data analysis of antimicrobial resistance in Ecuador, it is described in *E. coli* was observed resistant to carbapenems (KPC and NDM type) and highlights the resistance to colistin through the micro-1 gene, among others. For *Klebsiella pneumoniae*, the production of carbapenemase (KPC, NDM, VIM, OXA) was observed and also with the presence of the mrc-1 gene. On the other hand, *Pseudomonas aeruginosa* resistant to carbapenems through impermeability, efflux pumps, carbapenemases (VIM, IMP) and even ESBL producers. Finally, *Staphylococcus aureus* with 87% of isolates resistant to penicillins, resistance to methicillin (MRSA) with a mean for the years studied of 46% and even with production of methylases that confer resistance to macrolides **(15)**.

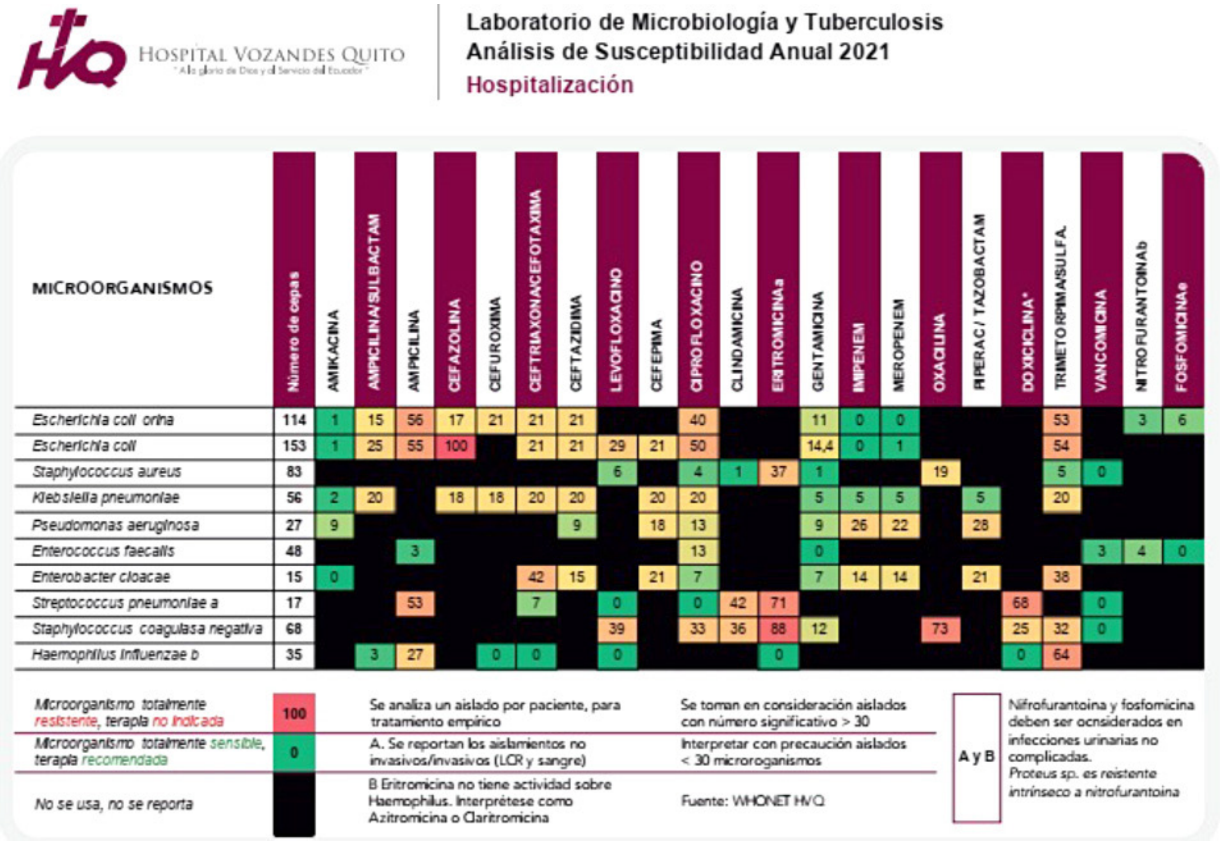
Unfortunately, at the time of writing this article, no updated published data was found for this problem in relation to AMR in Ecuador. In any case, Ecuador in November 2019 launched the National Plan for the prevention and control of antimicrobial resistance (AMR) 2019-2023 of Ecuador. In which a multisectoral intervention is considered that includes the MSP, Ministry of Agriculture and Livestock, Ministry of the Environment, among others. And this focuses on 4 objectives that range from improving the understanding of AMR, strengthening surveillance, preventing and controlling HAIs, to strengthening the rational use of drugs in human, animal and plant health **(16)**.

Finally, the picture was complex adverse projections, like those of the UN referred to the RAM 2050 will cause increased morbidity and mortality compared with other diseases worldwide. But this reality is much closer due to the effects of the pandemic by "Coronavirus Disease 2019" (COVID-19) produced by SARS-CoV-2, where the indiscriminate use of antibiotics has exceeded all expectations. The appearance of this new betacoranavirus at the end of 2019 led to the use of antimicrobials such as azithromycin, ivermectin, nitazoxanide, etc. based on studies carried out in monkey kidney cell cultures or small populations **(17–21)**.

In addition to the use of broad-spectrum antibiotics in patients hospitalized for their critical condition associated with COVID-19, for example, Langford et al. report that 71.8% of patients infected with SARS-CoV-2 received antibiotics **(22)**. These interventions are generating selective pressure on microorganisms and this can be evidenced by the superinfection of MDR microorganisms in various studies by *E. Coli, K. pneumoniae, Pseudomonas aeruginosa*, etc **(23–25)**. Another example is the Gonzalez-Zorn study that shows the abuse of azithromycin in Spain, with an increase of 400% in March 2020 compared to February of the same year **(26)**.

Although the limit between the clinical features of a coinfection or a bacterial superinfection in a COVID-19 patient is complex to define from the clinical point of view, the concern for possible infections with resistant pathogens could lead to unnecessary empirical prescription, inducing that only microorganisms more resistant remain in the patients, hospital services in even the environment. Which can lead to an antimicrobial resistance pathogen crisis sooner than expected. Therefore, we must focus on multidisciplinary and multidimensional actions for the prevention of infections, rational use of antibiotics, adequate microbiological diagnosis, antimicrobial analysis charts (**Figure 1**), strict use of standard precautions, hand hygiene, etc.

Figure 1 Example of antimicrobial analysis booklet from Hospital Vozandes Quito S.A.



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Laboratorio de Microbiología y Tuberculosis
Análisis de Susceptibilidad Anual 2021
Hospitalización

MICROORGANISMOS	Número de cepas	AMIKACINA	AMPICILINA/SULBACTAM	AMPICILINA	CEFAZOLINA	CEFUROXIMA	CEFTRIAXONA/CEFOTAXIMA	CEFTAZIDIMA	LEVOFLOXACINO	CEFEPIMA	CIPROFLOXACINO	CLINDAMICINA	ERITROMICINAa	GENTAMICINA	IMIPENEM	MEROPENEM	OXACILINA	PIPERAC / TAZOBACTAM	DOXICICLINA*	TRIMETORPIMA/SULFA.	VANCOMICINA	NITROFURANTOINAb	FOSFOMICINAe
Escherichia coli orina	114	1	15	56	17	21	21	21			40			11	0	0				53		3	6
Escherichia coli	153	1	25	55	100		21	21	29	21	50			14,4	0	1				54			
Staphylococcus aureus	83								6		4	1	37	1			19			5	0		
Klebsiella pneumoniae	56	2	20		18	18	20	20		20	20			5	5	5		5		20			
Pseudomonas aeruginosa	27	9						9		18	13			9	26	22		28					
Enterococcus faecalis	48			3							13			0							3	4	0
Enterobacter cloacae	15	0					42	15		21	7			7	14	14		21		38			
Streptococcus pneumoniae a	17			53			7		0		0	42	71						68		0		
Staphylococcus coagulasa negativa	68								39		33	36	88	12			73		25	32	0		
Haemophilus influenzae b	35		3	27		0	0		0				0						0	64			

Microorganismo totalmente resistente, terapia no indicada	100	Se analiza un aislado por paciente, para tratamiento empírico	Se toman en consideración aislados con número significativo > 30	A y B	Nifrofurantoina y fosfomicina deben ser ocnsiderados en infecciones urinarias no complicadas. *Proteus sp. es reistente intrínseco a nitrofurantoina*
Microorganismo totalmente sensible, terapia recomendada	0	A. Se reportan los aislamientos no invasivos/invasivos (LCR y sangre)	Interpretar con precaución aislados < 30 microroganismos		
No se usa, no se reporta	■	B Eritromicina no tiene actividad sobre Haemophilus. Interprétese como Azitromicina o Claritromicina	Fuente: WHONET HVQ		

Source: Hospital Vozandes Quito, Microbiology Laboratory.

Pathogen susceptibility analysis table, this tool can be used to establish an empirical therapy based on the usual hospital epidemiology. Resistant microorganisms are shown in red and sensitive microorganisms are shown in green. This table does not replace the indication for culture in patients who require it, since certain patients may present antimicrobial resistant microorganisms.

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