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Pseudomonas aeruginosa: Mechanisms of resistance to antibiotics and case analysis

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Abstract

Pseudomonas aeruginosa is an opportunistic pathogen, causing great concern due to the rapid increase in its resistance to antibiotics. The objective of the research was to describe the resistance mechanisms that *P. aeruginosa* possesses, as well as to report its behavior against antibiotics in the years 2003 to 2018 in Mexico. A retrospective and longitudinal documentary research was carried out in different digital resources referring to antibiotic resistance in *P. aeruginosa*. The results showed that the main resistance mechanisms of *P. aeruginosa* are β-lactamases, ejection pumps, mutations in porins, acquisition of plasmids, low permeability, formation of biofilms, alterations in penicillin-binding proteins, modifying enzymes of aminoglycosides and mutations in the active site. The antibiotics with the highest percentage of resistance presented between the years 2003 to 2018 were imipenen IMP, gentamicin GEN, ticarcillin / clavulanate TIC, trimethoprim / sulfamethoxazole TMS, ticarcillin TC, ceftriaxone CRO, aztreonam AZT, ceftazidime CAZ, cefepime FEP, levofloxacin LEV, chloramphenicol CL, tigecilcin TIG and ciprofloxacin CIP, with a peak of resistance between the years 2007 to 2008 and a possible downward trend in 2018. The behavior of resistance between the years 2003 to 2018 report a downward trend in the last two years.

Keywords: *Pseudomonas aeruginosa*; Mechanisms; Resistance; Antibiotics

1. Introduction

Pseudomonas aeruginosa is a bacterium belonging to the genus *Pseudomonas*, which includes microorganisms characterized by being aerobic, Gram-negative, non-glucose-fermenting, catalase-positive bacilli, with polar flagella and non-spore-forming [1]. Their cultures have a color similar to oxidized copper, between blue-green, given by the pigment pyocyanin [2]. Being a facultative aerobic bacterium, it has the ability to survive in low oxygen conditions, at low levels of nutrients and even able to tolerate temperature ranges between 4 to 42 ° C, with the ease of adhering and surviving on hospital surfaces [3].

The *P. aeruginosa* species is known to be one of the most frequent opportunistic pathogens in nosocomial infections [4]. Among the diseases caused by *P. aeruginosa* are nosocomial pneumonia, infections in the urinary tract, in surgical wounds and in the bloodstream [5] in addition to causing other serious infections such as meningitis, external otitis, endophthalmitis and endocarditis. Immunocompromised neutropenic cancer patients, burn patients, cystic fibrosis, and bone marrow transplantation are the most susceptible to *P. aeruginosa* infections [5, 2].

Antibiotic resistance is a natural and inevitable phenomenon, given by the same bacterial evolution [6]. But the indiscriminate or inappropriate use of antibiotics has expanded and accelerated the process. Resistance to antibiotics

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has been considered one of the major public health problems worldwide since 2011 [7]. *P. aeruginosa* has reported an increase in resistance to antibiotics in recent decades, according to the Surveillance Network Database, it was considered multi-resistant as it was registered with resistance to more than 3 antibiotics that were previously effective against them, between 1996 and 2000 [8]. Its eradication has become increasingly difficult due to its great physiological adaptability, its metabolic potential, its virulence mechanisms and its remarkable ability to resist antibiotics [9], *P. aeruginosa* use resistance mechanisms against antibiotics as an adaptive response recently characterized [10].

For all of the above, it is relevant to pay more attention to the research carried out on this pathogen to understand its development and evolution, in order to create new strategies to control and eradicate *P. aeruginosa* infections. This review seeks to evaluate the resistance to antibiotics that *P. aeruginosa* possesses, through the description of its main resistance mechanisms throughout the years 2003 to 2018 in Mexico.

2. Material and methods

A retrospective and longitudinal documentary investigation was carried out regarding antibiotic resistance in *P. aeruginosa*. The information was consulted in libraries, publishers, magazines and electronic search engines such as SciELO, Google Scholar, PubMed, Elsevier, Permanyer, Medigraphic, and NCBI and Open Journal Systems, for the search of scientific journals, medical records, research articles, scientific data and official pages such as the World Health Organization (WHO) and the Mexican Institute of Social Security (IMSS), to collect all the necessary information and address the important points in the investigation.

3. Results and discussion

P. aeruginosa is resistant to a large number of antibiotics such as cephalosporins, tetracyclines, chloramphenicol and macrolides, its resistance mechanisms [11] are described below in a list according to their level of clinical relevance.

3.1. The β-lactamases

They are enzymes that catalyze the hydrolysis of the β-lactam ring of antibiotics, destroying its active site and preventing its effectiveness. These β-lactamases are a constitutive part of the periplasmic space of the bacterium [12]. The *P. aeruginosa* species has two classes of β-lactamases, Amp-C, which are encoded on the bacterial chromosome and are capable of being induced in a few days by β-lactam antibiotic, especially cephalothin and ampicillin, and β -spread spectrum lactamases (ESBL), which are encoded by plasmids that confer resistance against penicillins, cephalosporins and carbapenems [11]. In this class there is an important group of β-lactamases known generically as carbapanemases that have become very concerned due to the spread of this mechanism among Gram-negative bacilli, making them more resistant to carbapenems [13]. The most important group of carbapanemase enzymes are the metalloenzymes called metallo-β-lactamases, which have the ability to hydrolyze the aforementioned antibiotics, but not monobactams such as aztreonam, and require a cofactor such as Zn to be able to act [14].

3.2. Active expulsion pumps

Also known as efflux pumps, they are enzymatic complexes that generate alterations in the permeability of the membrane, expelling substances from within the cell that would damage the bacteria. The complex consists of a pump protein in the cytoplasmic membrane, plus a binding lipoprotein in the periplasmic space and an exit channel in the outer membrane [11]. *P. aeruginosa* uses several ejection pumps of the resistance to nodulation division (RND) family, among which are the MexAB-OprM, MexXY-OprM, MexCD-OprJ and MexEF-OprN pumps, which expel a large amount of antibiotics such as β-lactams, chloramphenicol, quinolones, macrolides, novobiocin, sulfonamides, tetracyclines and trimethoprim, in addition to other types of substances such as acriflavin, ethidium bromide and some organic solvents, giving it the high impermeability it has against antibiotics and making it much more resistant [15].

3.3. Mutations in transmembrane porins

Transmembrane porins have the primitive function of allowing the passive uptake of dibasic amino acids through the membrane, and also allowing the entry of carbapenems, but this mechanism is based on the appearance of a mutation in a gene that codes for the porin OprD, where there is an absence of this, giving it great resistance to carbapenemic antibiotics such as imipenem and a reduced susceptibility to meropenem, reducing the transport and affinity of these through the protein [11].

3.4. Acquisition of plasmids

This is an important intrinsic mechanism typical of almost all bacterial species. Plasmids are double-stranded, circular, extrachromosomal genetic material that does not provide essential genetic information for the life of the cell, but does provide many advantageous genes for adaptation in different environments, such as conferring resistance to various antibiotics. The transfer of plasmids from one bacterial strain to another is carried out in a process called conjugation, it is based on the horizontal and unidirectional exchange of genetic elements such as plasmids, from a donor bacterium to a recipient bacterium through direct contact through the sexual pili [16]. In strains of *P. aeruginosa* it is very common for the exchange of plasmids that contain resistance genes to occur, such as those that code for the production of some β-lactamases and for the hyperproduction of the Mex AB-OprM ejection pump system [17].

3.5. Low permeability

This mechanism gives *P. aeruginosa* a low permeability to hydrophilic compounds of high functional capacity by the main porin OprF, which significantly limits the passage of antibiotics, but despite its great functionality, the three mechanisms mentioned above they tend to outweigh clinical importance [18].

3.6. Biofilm formation

Biofilms are colonies of bacteria that grow in aggregates and are surrounded by an extracellular matrix that the same colony produces, made up of proteins, extracellular DNA and exopolysaccharides (EPS), the latter together with type IV pili (T4P), are responsible for giving them considerable resistance against antimicrobials, both antibiotics and antiseptics [3]. This biofilm is generated when the aggregate secretes secondary metabolites useful for microbial communication by quorum sensing. The EPS contained in the matrix are important, since they participate in the transfer of resistance genes between the microorganisms of the colony, which facilitates the survival of the group, in addition to allowing the formation of persistent bacterial cells, which have an inactive metabolism and morphological changes that impede the action of antimicrobials [19].

3.7. Alterations of PBPs

Penicillin-binding proteins (PBPs) are β-lactam binding proteins, which are present in the cytoplasmic membrane and are involved in the synthesis of peptidoglycan in bacteria. A normal PBP facilitates the affinity with β-lactams, so its modification generates a reduced sensitivity against these AB, for example, modifying PBP3 in *P. aeruginosa* causes it to lose affinity to bind to marked penicillins, therefore which has been related to the increasing resistance of *P. aeruginosa* during treatments [20]. It is important to consider that the conditional elimination of PBP3 in *P. aeruginosa* can also cause a defect in the bacterial cell division and a greater susceptibility to β-lactams, which is why it is a possible objective to find more effective drugs [21].

3.8. Aminoglycoside modifying enzymes (EMA)

Aminoglycosides are antibiotics that act by attacking the ribosomes of the bacteria, causing abnormal proteins to be produced that affect the growth of the bacteria. Resistance is created thanks to enzymes encoded in plasmids, which modify aminoglycosides, inactivating them by acetylation, adenylation and phosphorylation, being capable of producing at least 14 different modifying enzymes. Inactivation of aminoglycosides produces poor binding of the binding site with the ribosome, preventing drug function from taking place [22].

3.9. Mutations in antibiotic target sites

It is one of the least documented resistance mechanisms in the literature. An example of this is the mutation in the target site of quinolones, an antibiotic that inhibits the enzymes DNA topoisomerase II and topoisomerase IV, key enzymes for the mechanisms of replication, transcription and DNA repair, but within *P. aeruginosa* it is finds a mutation in topoisomerase II, which prevents the DNA-Topoisomerase-Quinolone complex from being formed, destabilizing the binding of the antibiotic with its target site, losing its activity [23].

3.10. Reports of the resistance behavior of *P. aeruginosa* between the years 2003-2018 in Mexico

In order to analyze how antimicrobial resistance in *P. aeruginosa* has developed in our country, 11 investigations carried out in Mexican hospitals or laboratories were reviewed in which the behavior of this resistance among the years 2003 to 2018.

Table 1 Glossary of antibiotic abbreviations

Antibiotic	**Abb.**	**Antibiotic**	**Abb.**	**Antibiotic**	**Abb.**	**Antibiotic**	**Abb.**
Amikacin	AMK	Amoxicillin / clavulanic acid	AMC	Ampicillin	AMP	Ampicillin /sulbactam	SAM
Aztreonam	AZT	Cefazolin	CZO	Cefepime	FEP	Cefotaxime	CTX
Ceftazidime	CAZ	Ceftriaxone	CRO	Cefuroxime	CXM	Ciprofloxacin	CIP
Chloramphenicol	CL	Gentamicin	GEN	Imipenem	IMP	Levofloxacin	LEV
Meropenem	MEM	Moxifloxacin	MOX	Nitrofurantoin	NIT	Norfloxacin	NORF
Ofloxacin	OFX	Ticarcillin / clavulanate	TIC	Ticarcillin	TC	Tigecycline	TIG
Trimethoprim / sulfamethoxazole	TMS	Tobramycin	TOB	Piperacillin	PIP	Piperacillin / tazobactam	TZP

Year 2003. This study was carried out by Ruiz, I., *et al* [24]. Data were obtained from the Hospital de Pediatría del Centro Médico Nacional Siglo XXI, in Mexico City, Mexico. The objective of the research was to compare the differences in the resistance profiles of the microorganisms that cause Nosocomial Infections. The results on *P. aeruginosa* indicate that due to the frequent use of carbapenems in the hospital, there was an increase in resistance, with imipenem (IMP) being the antibiotic with the highest resistance, with a percentage of 41.93% (Table 2).

Table 2 Percentage of resistance for *P. aeruginosa*, year 2003.

Antibiotic	AMK	FEP	CTX	CAZ	IMP	MEM	NORF
Resistance %	35.48	12.90	38.70	29.03	41.93	09.67	19.35

[24].

Years 2004-2006. The research carried out by Camacho, A., *et al* [25], was carried out at the "Dr. José E. González", in Monterrey, Nuevo León, Mexico. There, a review of bacterial cultures of *P. aeruginosa* was made during the years 2004, 2005 and 2006. Its results conclude that antimicrobial resistance showed an increase from 2004 to 2005, but there was a decrease from 2005 to 2006, finding some level resistance in all antibiotics tested except gentamicin (GEN) and ticarcillin / clavulanate (TIC). Of the 8 antibiotics analyzed, the 5 with the highest reported resistance in the 3 years were TIC, GEN, amikacin (AMK), ciprofloxacin (CIP) and ceftazidime, being GEN the one with the highest resistance in 2004, TIC in 2005 and 2006 (Table 3) with a percentage of 56.10%, 54% and 60.40, respectively.

Table 3 Percentage of resistance for *P. aeruginosa*, year 2004-2006

Year 2004								
Antibiotic	AMK	FEP	CAZ	CIP	GEN	IMP	TIC	TZP
Resistance %	40.40	32.20	33.60	33.30	56.10	23.00	55.50	28.80
Year 2005								
Antibiotic	AMK	FEP	CAZ	CIP	GEN	IMP	TIC	TZP
Resistance %	49.10	42.30	47.75	53.40	33.50	31.00	54.00	46.50
Year 2006								
Antibiotic	AMK	FEP	CAZ	CIP	GEN	IMP	TIC	TZP
Resistance %	44.20	41.17	45.70	46.10	54.10	28.50	60.40	46.50

[25]

Year 2007. Carried out by Murillo-Llanes, J., *et al* [26], in the General Hospital of Culiacan, Sinaloa, Mexico. The objective was to determine the resistance in *P. aeruginosa* to the antibiotics most used in the Hospital. The results of the 1,511 positive cultures of *P. aeruginosa* showed trimethoprim / sulfamethoxazole (TMS) and cefotaxime (CTX) as the antibiotics with the highest resistance, with a percentage of 96.30% and 90.79% respectively (Table 4). Something important to highlight in the study was the difference in the general antimicrobial resistance of *P. aeruginosa* in the 4 years studied, in which there was an increase between 2005 (23.04%) and 2006 (23.07%) with respect to 2004 (20.49%) and a decrease compared to all in 2007 (12.9%), which can be contrasted with the research of Camacho, A., *et al*, [25].

Table 4 Percentage of resistance for *P. aeruginosa*, year 2004-2007.

Antibiotic	AMK	CTX	CAZ	CRO	CIP	GEN	IMP	TMS	TPZ
Resistance %	62.90	90.79	62.60	87.40	60.70	33.50	54.14	96.30	19.20

[26]

Year 2008. In the investigation of Ortiz, M., Mora, J., & Aguilera, A., [27] it was proposed to determine the bacterial colonization and antibacterial susceptibility of *P. aeruginosa* in isolates of burned patients of the Regional Hospital of Alta Specialty from Veracruz, Mexico. The resistance profile of 13 antibiotics was determined in 43 bacterial strains of *P. aeruginosa*. The antibiotics with the highest resistance were ticarcillin (TC) and chloramphenicol (CL) with a percentage of 98% and 95%, respectively, followed by tobramycin with 81% (Table 5).

Table 5 Percentage of resistance for *P. aeruginosa*, year 2008

Antibiotic	AMK	AZT	FEP	CTX	CAZ	CIP	CL
Resistance %	79.00	35.00	48.00	71.00	70.00	37.00	95.00
Antibiotic	GEN	IMP	LEV	MEM	TC	TOB	
Resistance %	70.00	74.00	40.00	44.00	98.00	81.00	

[27]

Table 6 Percentage of resistance for *P. aeruginosa*, year 2009-2012.

Year 2009										
Antibiotic	AMK	AZT	FEP	CAZ	CRO	CIP	IMP	LEV	MEM	TZP
Resistance %	25.00	60.00	36.00	48.00	100.0	36.00	41.70	52.00	44.00	-
Year 2010										
Antibiotic	AMK	AZT	FEP	CAZ	CRO	CIP	IMP	LEV	MEM	TZP
Resistance %	47.10	52.90	51.40	55.70	97.10	41.80	47.10	46.30	44.40	40.00
Year 2011										
Antibiotic	AMK	AZT	FEP	CAZ	CRO	CIP	IMP	LEV	MEM	TZP
Resistance %	57.50	70.00	70.00	62.50	100.0	38.50	57.50	42.50	63.60	25.00
Year 2012										
Antibiotic	AMK	AZT	FEP	CAZ	CRO	CIP	IMP	LEV	MEM	TZP
Resistance %	50.00	63.60	63.60	65.90	97.60	46.50	60.50	48.80	55.30	25.60

[28]

Years 2009-2012. The research by Rincón-León, H., & Navarro-Fuentes, R., [28] was carried out at the Ciudad Salud Regional High Specialty Hospital (HRAECS), in Tapachula, Chiapas, Mexico. The objective of the research was to evaluate the antimicrobial resistance trends in pathogens isolated from this hospital. Among the four years reported, *P. aeruginosa* was found as the most frequent and most important microorganism during the years 2011 and 2012. The

results of this study reflect that in 2009 the antibiotics with the highest resistance was ceftriaxone (CRO), followed of aztreonam (AZT), with a percentage of 100% and 60%, respectively. For 2010, the highest resistance was for CRO and ceftazidime (CAZ), with percentages of 97.1% and 55.7%. In 2011 we found CRO as the antibiotic with the highest resistance with a percentage of 100%, followed by AZT and cefepime (FEP), both with a percentage of 70%. Finally, in 2012, we again find CRO with the highest resistance, followed by CAZ, with 97.6% and 65.9%, respectively (table 6). In general, most AB show a stable trend in resistance levels, with the exception of Imipenem (IMP) which was the one that showed an alarming increase, starting with 41.7% in 2009 and reaching a percentage of 60.5% in 2009. 2012. Finally, concluding that the *P. aeruginosa* strains during these years showed high percentages of resistance to cephalosporins, especially to ceftriaxone.

Year 2013. The study carried out by Ochoa, S., *et al* [3], is located at the Hospital Infantil de México Federico Gómez, Mexico City, Mexico. The objective of this research was to evaluate the formation of biofilms in 92 strains of *P. aeruginosa* resistant to carbapenems. The results indicated that 50% of the strains were resistant to the 12 antibiotics that were tested. The antibiotics with the highest reported resistance were cefotaxime (CTX), ticarcillin / clavulanic acid (TIC) and levofloxacin (LEV) with a percentage of 75%, 73.9% and 66.3%, respectively (Table 7).

Table 7 Percentage of resistance for *P. aeruginosa*, year 2013

Antibiotic	AZT	FEP	CTX	CAZ	CRO	CIP
Resistance %	63.00	63.00	75.00	64.10	66.10	64.10
Antibiotic	GEN	IMP	LEV	MEM	TIC	TZP
Resistance %	64.10	63.00	66.30	60.80	73.90	63.00

[3]

Year 2014. The study carried out by Salazar-Holguín, H., & Cisneros-Robledo, M., [29], focused on the detection of intrahospital infections, the identification of the causative agent and its resistance to antibiotics. It was carried out at the IMSS Regional General Hospital No. 1 in Chihuahua, Mexico, with a collection of 300 cases of these infections within the hospital, where *P. aeruginosa* was the third most frequent species, at 15.3%. The results were divided according to the hospital infections evaluated, showing a high resistance of *P. aeruginosa* to chloramphenicol (CL), with a percentage of 95.8% in vascular lines, followed by Ticarcillin / clavulanate (TIC) and aztreonam (AZT) with 91.7 % in surgical sites and, in third place, gentamicin (GEN) with 69.6% in pneumonia (Table 8).

Table 8 Percentage of resistance for *P. aeruginosa*, year 2014.

Antibiotic	AMK	AMC	AZT	CIP	CL	GEN	TIC	PIP	TZP
Resistance %	45.80	56.50	91.70	73.70	95.80	69.60	91.70	66.70	58.30

* Data were taken regarding their highest percentages of resistance among the three hospital infections in the original study. [29]

Year 2015. The research by Galván-Meléndez, M., *et al* [30], aimed to identify the infections associated with health care and their antimicrobial resistance, specifically in the clinical file of the General Hospital Dr. Santiago Ramón y Cajal from ISSSTE in Durango, Mexico. 100 confirmed cases of hospital-acquired infections were reviewed in 2015, isolating a total of 26 bacterial species. It was concluded that *P. aeruginosa* was the third species with the most presence in the isolates. The results show that *P. aeruginosa* had greater resistance to ampicillin (AMP), ampicillin/sulbactam (SAM), ceftriaxone CRO, and trimethoprim/sulfamethoxazole (TMS) with a percentage of 100%, something expected due to its intrinsic resistance, therefore that, when omitted, the antibiotics with the highest resistance are imipenem (IMP) and tigecilcin TIG, both with a percentage of 65% (Table 9).

Table 9 Percentage of resistance for *P. aeruginosa*, year 2015

Antibiotic	AMP	SAM	FEP	CAZ	CRO	CIP	GEN
Resistance %	100.0	100.0	24.00	29.00	100.0	41.00	24.00
Antibiotic	IMP	MEM	MOX	TIG	TMS	TOB	TZP
Resistance %	65.00	24.00	35.00	65.00	100.0	30.00	24.00

[30]

Year 2016. In this year, the investigation by Garza-Montúfar, M., *et al* [31] was carried out, in which urine cultures were reviewed in patients of the General Hospital of the Zone of the Mexican Social Security Institute (IMSS) of Monterrey, Nuevo León, Mexico, to identify patterns of bacterial resistance. The results provided for *P. aeruginosa* indicate that it had a high resistance to most of the antibiotics tested, with a higher resistance against levofloxacin (LEV) with 75%, followed by ciprofloxacin (CIP) and meropenem (MEM) with 70%. % (table 10).

Table 10 Percentage of resistance for *P. aeruginosa*, year 2016

Antibiotic	AMK	FEP	CAZ	CIP	GEN	IMP
Resistance %	65.00	55.00	50.00	70.00	65.00	65.00
Antibiotic	LEV	MEM	NORF	OFX	TZP	
Resistance %	75.00	70.00	69.00	69.00	38.00	

[31]

Year 2017. This research comes from a multicenter study of nosocomial bacterial resistance in 14 Mexican hospitals, carried out by Gutiérrez, J., *et al* [32]. The objective of this research was to evaluate the resistance of the microorganisms that cause infections of epidemiological interest. The results of *P. aeruginosa* indicated that the antibiotics with the highest resistance were ceftriaxone (CRO) with a percentage of 62.5, followed by cefepime (FEP) and ceftazidime (CAZ) with 38.10% for both (table 11). The high resistance of *P. aeruginosa* to antibiotics is highlighted, especially to 3rd generation cephalosporins, carbapenems and quinolones.

Table 11 Percentage of resistance for *P. aeruginosa*, year 2017.

Antibiotic	AMK	FEP	CTX	CAZ	CRO	CIP
Resistance %	30.95	38.10	0.00	38.10	62.50	25.00
Antibiotic	GEN	IMP	MEM	MOX	PIP	TZP
Resistance %	29.33	33.85	25.93	0.00	41.94	26.67

[32]

Year 2018. In the investigation by Barlandas-Rendón, N., *et al* [33], isolates from the General Hospital Dr. Raymundo Abarca Alarcón and the BIOCLIN laboratory of Chilpancingo, Guerrero, Mexico were analyzed, the objective of which was to identify the profile resistance to antimicrobials in three critical priority microorganisms (Table 12). In these results, omitting the antibiotics with intrinsic resistance (CZO, AMP, CRO, SAM, AMC, TMS and CTX), levofloxacin (LEV), a 3rd generation quinolone and a ciprofloxacin (CIP), a 2nd generation quinolone were observed. generation as the two most resistant antibiotics, followed by meropenem (MEM), a carbapenem; the three with a percentage of 46.2%, 23.4% and 20.8% respectively.

Table 12 Percentage of resistance for *P. aeruginosa*, year 2018

Antibiotic	AMK	AMC	AMP	SAM	CZO	FEP	CTX
Resistance %	16.40	92.30	99.2	93.8	100.0	10.2	84.60
Antibiotic	CAZ	CRO	CXM	CIP	GEN	IMP	LEV
Resistance %	7.70	97.60	100.0	23.4	70.0	7.70	46.2
Antibiotic	MEM	NIT	TMS	TOB	TZP		
Resistance %	20.80	98.20	89.5	18.5	14.5		

[33]

Regarding the registration of the percentages of antibiotic resistance of the studies carried out in Mexico during the last two decades, we can obtain the following graph (figure 1), in which the flow of growth or decrease of the percentages of resistance in the different years studied. For the graph, 5 of the antibiotics most tested in research between 2003 and 2018 were chosen.

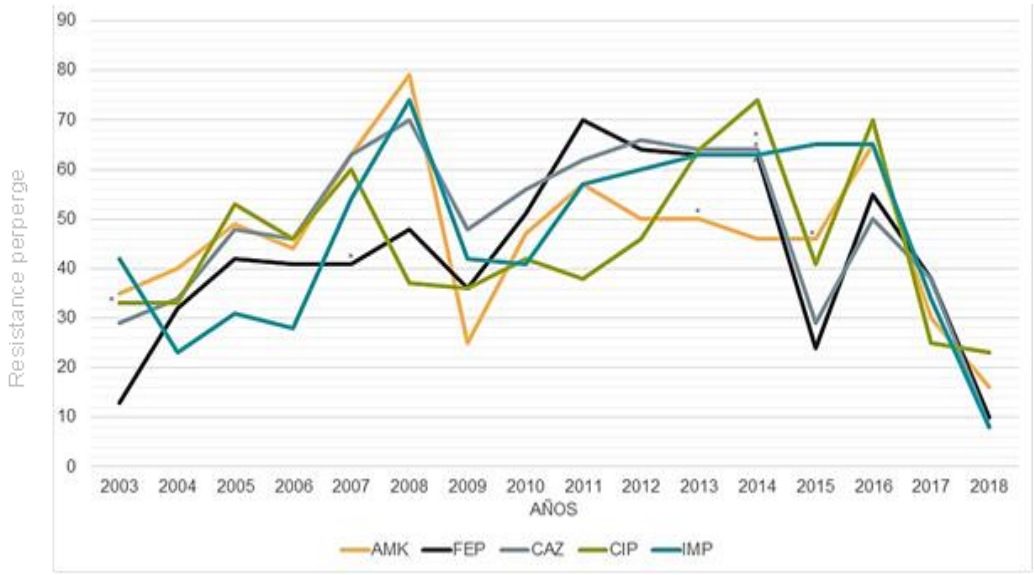

Figure 1 Graph of the behavior of antibiotic resistance of *P. aeruginosa* based on the results of the years 2003-2018.

It can be seen that the antibiotic with the highest amikacin resistance (AMK) with 79% in 2008[27], but having a significant decrease of 25% in 2009[28], which may have been influenced by many factors, since strains that had not yet been found acquired the resistance in the hospital that was evaluated, the levels of resistance according to the geographical area where the study was carried out (in 2008 it was in Veracruz and 2009 in Chiapas), the type of sample (blood, urinary tract, etc.), as well as the controls and techniques used by the researchers in the study[29].

Another interesting observation is how most antibiotics show a prominent peak in 2016 [31], and a notable decline as 2018 approaches, in which there were percentages of 16.4% for AMK, 7.7% for CAZ and IMP, 23.4% for CIP and 10.2% for FEP, which would be interesting to contrast with future research published with respect to the percentages of 2019 and 2020 in Mexico, to suppose if the resistance is actually decreasing or was only presented with the samples of the study carried out in 2017 and 2018 [33], although it should be noted that although the percentages of resistance in these years have decreased, they do not indicate that they have completely ceased to be resistant to these antibiotics.

Among the possible reasons why we can see a decrease in the percentage of resistance of some antibiotics in recent years, it is because the use of certain antibiotics for the control of *P. aeruginosa* was reduced compared to others, for example, among the carbapenems most consumed for its treatment is MEM, which, in 2018, registered a higher percentage (20.8%) than IMP (7.7%) which is consumed in less proportion [34]. It should be noted how in each of the 11 studies on *P. aeruginosa* the antibiotics used to evaluate resistance vary, with AMK, FEP, CAZ, CIP and IMP being the most common among them, since they are the most used antibiotics for treat nosocomial infections and still had anti-pseudomonas effect [8]. It is interesting to note how some antibiotics that were widely used in the first years of treatment against pseudomonas, with the passage of time, began to be obsolete due to the great resistance that was acquiring, for example, AZT, which in 2009 had a percentage of resistance of 25% [28], but in 2014 it reached a percentage of 91.72% [29] and being discontinued in the rest of the subsequent studies. Percentages similar to those presented in AZT are those presented by CTX, which in 2003 had 38.7% [24], in 2018 it reached 84.6% [33]; GEN with 56.10 in 2004 [25], and reaching 70% in 2018 [33], TIC with 55.5 in 2004 [25] and reaching 91.7% in 2014[29].

4. Conclusion

The main mechanisms of resistance to antibiotics that P. aeruginosa possesses are nine. It is resistant to more than 3 antibiotics, among which stand out especially against Imipenem and Gentamicin; It has been classified as a multi-resistant bacterium because it has shown an increase in resistance in most of the antibiotics used today. This work contributes to the understanding of the behavior of resistance to antibiotics throughout the years 2003 to 2018 of this bacterial species.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare that they have no conflicts of interest.

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