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Dissemination and prevalence of polymyxin-resistant bacteria of clinical and environmental origin

Disseminação e prevalência de bactérias resistentes à polimixina de origem clínica e ambiental

Diseminación y prevalencia de bacterias resistentes a la polimixina de origen clínico y ambiental

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Abstract
Polymyxins were discovered in the 1940s and were used to treat infections caused by gram-negative bacteria. These molecules act by destroying the cell membrane through the destabilization of phospholipids and lipopolysaccharides (LPS). Due to adverse effects, such as nephrotoxicity and neurotoxicity, this class had seen limited use. However, with the evolution of antimicrobial resistance to commercial drugs, the use of polymyxins has resumed, and over time, strains resistant to this drug have been observed. Currently, resistant bacteria this antimicrobial are found in hospital environments, and non-anthropized environments. This occurrence constitutes a global human and environmental health problem that is of concern to the population, health professionals, and researchers. Thus, this review was conducted with the objective of describing the mechanisms and the occurrence of bacterial resistance to polymyxins, and to demonstrate the relationship between multi-resistant strains of clinical and environmental origins.
Keywords: *Bacillus polymyxa*; Colistin; Bacterial resistance; Public health.

Resumo
As polimixinas foram descobertas na década de 1940 e eram usadas para tratar infecções causadas por bactérias gram-negativas. Essas moléculas atuam destruindo a membrana celular através da desestabilização de fosfolipídios e lipopolissacarídeos (LPS). Devido a efeitos adversos, como nefrotoxicidade e neurotoxicidade, essa classe teve o uso limitado. No entanto, com a evolução da resistência antimicrobiana aos medicamentos comerciais, o uso de polimixinas foi retomado e, com o passar do tempo, foram observadas cepas resistentes a esses medicamentos. Atualmente, bactérias resistentes a estes antimicrobianos, são encontradas em ambientes hospitalares e não antropizados. Essa ocorrência constitui um problema global de saúde humana e ambiental que preocupa a população,

profissionais de saúde e pesquisadores. Assim, esta revisão foi realizada com o objetivo de descrever os mecanismos e a ocorrência de resistência bacteriana às polimixinas, e demonstrar a relação entre cepas multirresistentes de origem clínica e ambiental.
Palavras-chave: *Bacillus polymyxa*; Colistina; Resistência bacteriana; Saúde pública.

Resumen
Las polimixinas se descubrieron en la década de 1940 y se usaron para tratar infecciones causadas por bacterias gramnegativas. Estas moléculas actúan destruyendo la membrana celular mediante la desestabilización de los fosfolípidos y lipopolisacáridos (LPS). Debido a los efectos adversos, como la nefrotoxicidad y la neurotoxicidad, esta clase ha tenido un uso limitado. Sin embargo, con la evolución de la resistencia antimicrobiana a los fármacos comerciales, se ha retomado el uso de polimixinas y con el tiempo se han observado cepas resistentes a este fármaco. Actualmente, las bacterias resistentes a este antimicrobiano se encuentran en ambientes hospitalarios y ambientes no antropizados. Este hecho constituye un problema mundial de salud humana y ambiental que preocupa a la población, profesionales de la salud e investigadores. Por lo tanto, esta revisión se realizó con el objetivo de describir los mecanismos y la aparición de resistencia bacteriana a las polimixinas, y demostrar la relación entre cepas multirresistentes de origen clínico y ambiental.
Palabras clave: *Bacillus polymyxa*; Colistina; Resistencia bacteriana; Salud pública.

1. Introduction

Polymyxins are antibiotics isolated from the microorganism *Paenibacillus polymyxa* (formerly known as *Bacillus polymyxa*). This drugs were introduced in clinical practice to treat infections caused by gram-negative bacteria in the 1950s. However, their use declined in the 1970s due to limitations such as nephrotoxicity and neurotoxicity, low permeability and absorption in the gastrointestinal tract (Dubashynskaya & Skorik, 2020; Li et al., 2019).

These antibiotics are polypeptides that chemically different that exert bactericidal activity by disrupting the cell membrane through electrostatic and hydrophobic interactions (Zavascki et al., 2007). These drugs have a molecular weight of ~1200 Da and are characterized by the presence of a polycationic peptide ring with a peptide attached to a fatty acid tail (Kaye et al., 2016). Your action happens on gram-negative bacteria, since they destabilize phospholipids and lipopolysaccharides (LPS), the main components of the outer membrane these microorganisms (Yu et al., 2015). Among the five existing polymyxins, only polymyxin B and polymyxin E have clinical applications (Dubashynskaya & Skorik, 2020; Trimble et al., 2016).

Because of the antibiotic resistance worldwide, these drugs have become the last therapeutic resource, especially, against multidrug-resistant gram-negative bacilli such as *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacteriaceae* carbapenemic resistant (Baron et al., 2016; Zakuan & Suresh, 2018). As resistance to less toxic antibiotics increased, the use of polymyxins became more frequent (Li et al., 2019).

Because of the limited number of agents available to treat infections caused by these bacteria, the emergence of resistance to polymyxins is a major concern. The main mechanism of resistance to these drugs involves the modification of LPS of the bacterial outer membrane, which reduces the net negative charge or fluidity of the LPS, increases the efflux of the drug, blocks the porin pathway, and enhances capsule formation and hypervesiculation (Trimble et al., 2016; Giamarellou, 2016).

The intensive use of polymyxins in the treatment of infections humans and in agriculture influences the evolution of resistance to this drug, which varies in different parts of the world, according to environment and geographical location (Falagas et al., 2010; Srinivas & Rivard, 2017). The global rates of resistance to polymyxin are presented in different percentages ranging, for example, from 0.4% to 4.8% in *A. baumannii*, 0.1% to 0.6% in *P. aeruginosa*, and 1.3% to 1.8% in *Enterobacteriaceae* (Bradford et al., 2016; Sader et al., 2014).

Resistance to this drug has been reported in microorganisms of hospital and environmental origin, since Antibiotic Resistance Genes (ARGs) can be transferred between species of both origins. The dissemination of ARGs occurs via

Horizontal Gene Transfer (HGT), which is, through mobile genetic elements. The investigation of bacterial transmission pathways between the clinical environment and the extra-hospital environment contributes to controlling the spread of multiresistant pathogens (Lerminiaux & Cameron, 2019).

In this context, different environments can be places of emergence and dissemination of bacteria resistant to polymyxins (Martins et al., 2014). Thus, this review aimed to present the main mechanisms of bacterial resistance to polymyxins, as well as to correlate the resistance in strains of clinical and environmental origin.

2. Methodology

The present study is an integrative literature review that used articles published in the main academic databases: PubMed, Web of Science, Google Scholar, Science Direct and Mendeley. The survey was conducted between February and March 2020 with no restrictions on languages and years of publication. For the selection of articles relevant to the topic of this review, studies that met the following inclusion criteria (descriptors) were considered: Polymyxins, polymyxin B, colistin, polymyxin resistance, polymyxin-resistant hospital bacteria, polymyxin-resistant bacteria in the environment and mcr genes.

3. Polymyxins

These antibiotcs were discovered in the 1940s and introduced into clinical practice in the late 1950s. Of the five types described (A to E), only two (B and E) were used in clinical practice (Ezadi et al., 2019; Moubareck, 2020). Polymyxin B was originally isolated from *B. polymyxa* in 1947, while polymyxin E (colistin) was isolated from *B. polymyxa* var. *colistinus* in 1949, being the most used in the world (Ortwine, 2015). Until the mid-1970s, these drugs were widely used, causing adverse events, mainly at the renal and neurological (Mendes & Burdmann, 2009; Nation et al., 2019; Rabanal & Cajal, 2017; Poirel et al., 2017).

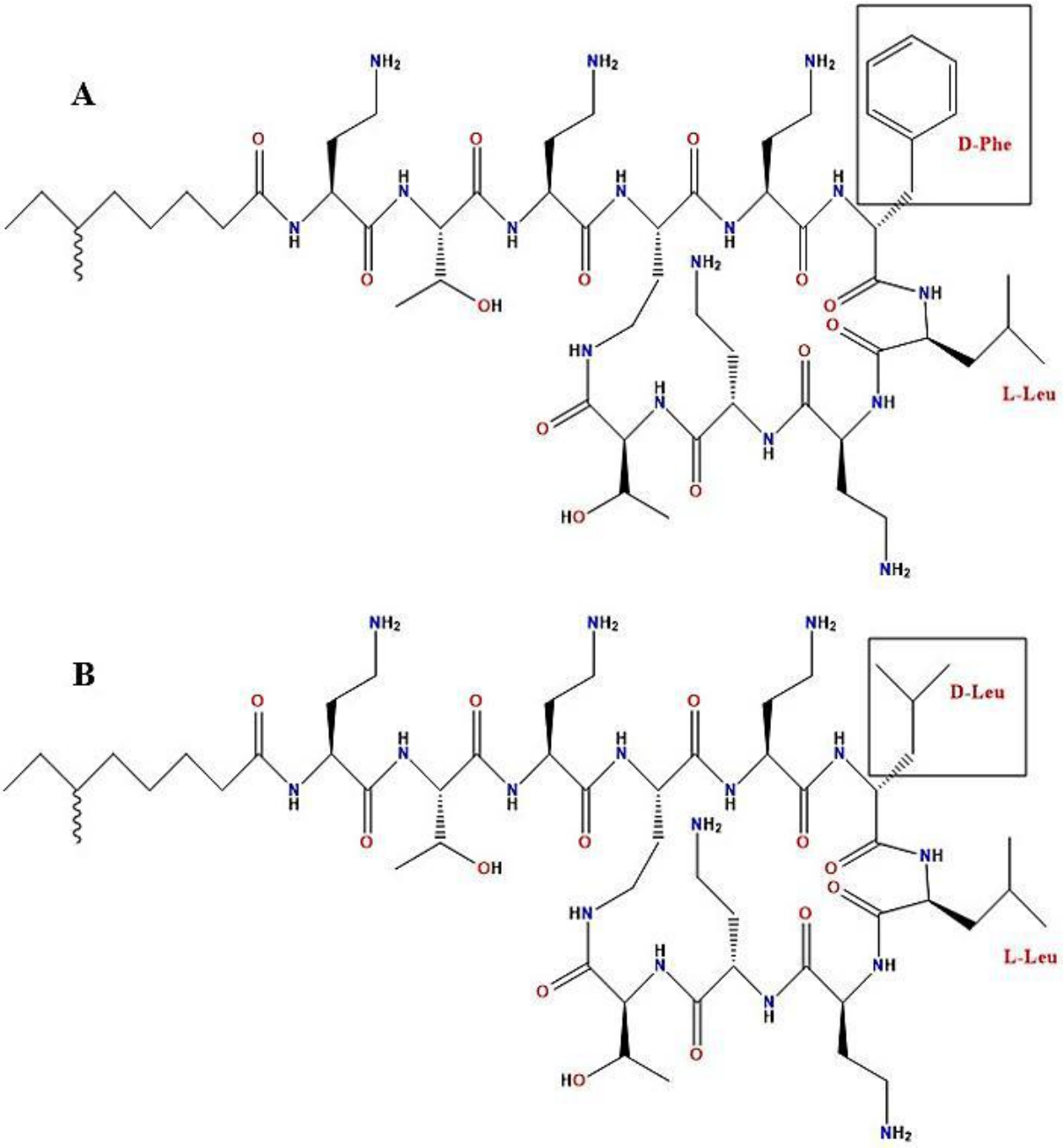
Due to their high toxicity, the use of polymyxins in clinical practice has been discontinued. This was made possible by the introduction of antibiotics with a lower toxicity index, such as third-generation cephalosporins and later carbapenems (Fair & Tor, 2014; Vaara, 2019). However, with the increase in Multidrug-Resistant (MDR) bacteria in the late 20th century and the absence of effective antimicrobials to treat infections caused by these microorganisms, previously discontinued antimicrobials, such as polymyxins B and E, were reconsidered as treatment options (Poirel et al., 2017; Ahmed et al., 2020; Garg et al., 2017).

With the resumption of the use of polymyxins, it is necessary to study the pharmacological characteristics of these drugs, including their pharmacodynamic, pharmacokinetic, and toxicity profiles, to auxiliary the development strategies of minimize adverse effects (Mendes & Burdmann, 2009; Nation et al., 2019; Falagas & Kasiakou, 2006; Tran et al., 2016).

3.1 Chemical structure of polymyxins

Polymyxins B and E are cyclic polycationic polycyclic decapeptide antimicrobials derived from the products of the *P. polymyxa*, which exhibit potent activity against most species of gram-negative bacteria (Moubareck, 2020; Rabanal & Cajal, 2017; Jeong et al., 2019). Structurally, they are cationic polypeptides formed by a heptapeptide ring attached to an acylated fatty acid chain at the N-terminal end. They differ in their chemical structures by the presence of a D-phenylalanine (in polymyxin B) or a D-leucine (in colistin) at carbon 6 (Figure 1) (Yu et al, 2015; Gallardo-Godoy et al., 2019; Gallardo-Godoy et al., 2016).

Figure 1. Chemical structure of the two antibiotics that make up the polymyxins class.



In (A) polymyxin B and (B) colistin, composed of a decapeptide core that contains an intramolecular cycle of heptapeptides linked by amide bonds between the amino group of the side chain of the diaminobutyric acid residue (Dab) in the position 4 and the carboxyl group on the terminal C-threonine residues. Source: Authors

Polymyxin B has the molecular formula $C_{56}H_{98}N_{16}O_{13}$, with a molecular weight of 1203.5 g/mol, melting point >203 ºC and solubility in water of 0.0744 mg/mL. This antibiotic is indicated for the treatment of meningitis, urinary tract infections, and bloodstream. While Polymyxin E has a molecular formula of $C_{52}H_{98}N_{16}O_{13}$, with a molecular weight of 1155.4 g/mol, melting point of 200–220 ºC, solubility in water of 0.238 mg/mL, and is indicated for the treatment of chronic lung infections (Ngamprasertchai et al., 2018; PubChem, 2022; PubChem, 2022).

3.2 Pharmacodynamics and pharmacokinetics

The pharmacokinetic and pharmacodynamic profiles that best describe the action of polymyxins are concerned with the Minimum Inhibitory Concentration (MIC), which is dependent on the concentration of the antimicrobial and the time of exposure (Bergen et al., 2012; Kuti, 2016; Sumi et al., 2019). Thus, the concentration of the antimicrobial should be higher if the bacteria show a higher level of resistance. Colistin is a prodrug used in the form of Colistimethate Sodium (CMS), which after being metabolized is converted to colistin, while polymyxin B is used in the form of sulfated salt. Therefore, despite being similar in spectrum of action, these drugs have different pharmacokinetic profiles (Bialvaei & Kafil, 2015; Wenzler et al., 2016; Qi et al., 2020; Wallace et al., 2010).

Polymyxin B, when administered in active form, quickly reaches its peak plasma concentration. But colistin can take up to 8 h to reach the maximum concentration after the administration of CMS, which is converted to colistin in the renal tubules. This leads to high individual variation in CMS metabolism, especially in individuals with kidney disease (Tran et al., 2016; Couet et al., 2011; Nation et al., 2014). As a result, patients with reduced renal clearance eliminate CMS less efficiently, requiring dose adjustment. Polymyxin B, however, is excreted by other metabolic pathways, thus not requiring dose adjustment even with varying levels of creatinine clearance (Pogue et al., 2017; Zavascki & Nation, 2017).

The conversion rate of CMS to colistin is low, estimated at 30% (Couet et al., 201; Pacheco et al., 2019). One of the advantages of using CMS is that most of the prodrug is eliminated in the urine, and a large part of the newly formed colistin accumulates in the urinary tract, which is advantageous in the treatment of urinary tract infections. This is unlike polymyxin B, in which only a small percentage is eliminated in the urine (Sorlí et al., 2019; Kassamali et al., 2014; Luque et al., 2017).

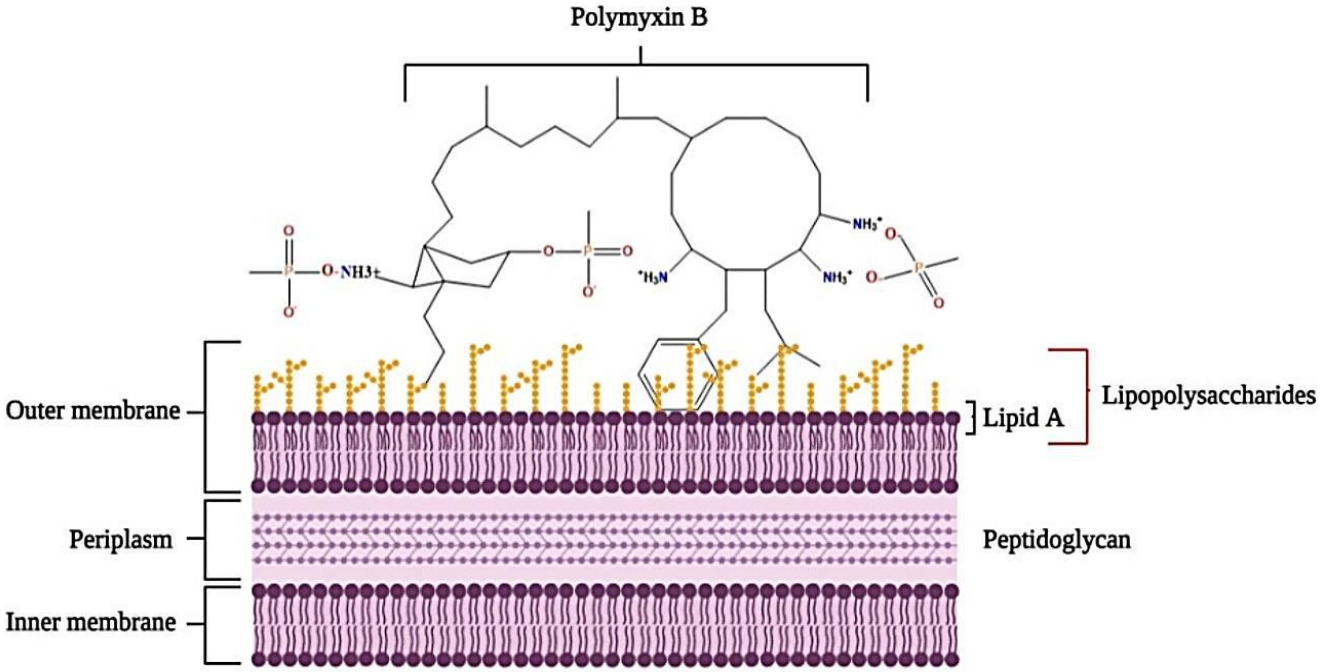
3.3 Mechanism of action and antimicrobial spectrum

The polymyxins at <2 μg/mL concentration show excellent activity against several glucose-fermenting and non-fermenting gram-negative bacilli, including *Klebsiella* spp., *Escherichia coli*, *Enterobacter* spp., *Salmonella* spp., *Shigella* spp., *P. aeruginosa*, and *Acinetobacter* spp., including strains resistant to other classes of antibiotics (Moubareck, 2020; Poirel et al., 2017; Aghapour et al., 2019). The mechanisms of action of these drugs depend on their affinity to LPS, which contribute to the structural integrity of the bacterium and protect its membrane from certain types of chemical attacks, to which the outer membrane of gram-negative bacilli is vulnerable (Yu et al., 2015; Trimble et al., 2016; Telhig et al., 2020).

The positively charged polymyxin molecule interacts with the negatively charged phosphate groups in the lipid A portion of the LPS (Figure 2) (Velkov et al., 2010; Velkov et al., 2013). The insertion of the fatty acid chain and D-Phe-L-Leu (polymyxin B) or D-Leu-L-Leu (colistin), which are hydrophobic domains, destabilize the lipid A fatty acid chain, leading to distention of the single layer of the outer membrane. As a result of this destabilization, the polymyxin molecule can insert its hydrophobic regions in the outer membrane, causing membrane rupture and facilitating the additional uptake of polymyxins by the microorganism. Thus, result in disintegration of the bacterial cell (Moubareck, 2020; Mohamed et al., 2016).

Deris et al., (2014) propose a new secondary mechanism of action of polymyxins, where these drugs act by inhibiting flavoenzyme NDH-2 (menaquinone dehydrogenase type II). This enzyme has plays an essential role in the transport of electrons through bacteria, thereby causing cell death. The authors also demonstrated in their study that polymyxin B has a greater potential for inhibiting NDH-2, when compared to colistin.

Figure 2. Interaction of polymyxin B in the membrane of Gram-negative bacteria.



Polymyxins work by binding to lipopolysaccharide (LPS) and phospholipid molecules present in the outer membrane of gram-negative bacteria. This process results in a change in the bacterial cell wall, leading to extravasation of intracellular content and, consequently, to the death of the bacteria. Source: Created with BioRender.com.

4. Mechanisms of Resistance to Polymyxins

Polymyxins exhibit no activity against anaerobic and gram-positive bacteria, because these microorganisms lack the outer cell membrane that contains LPS. In addition, several gram-negative bacteria are intrinsically resistant to polymyxins, including *Burkholderia cepacia* complex, *Morganella morganii*, *Serratia marcescens Proteus* spp., and *Providencia* spp (Magiorakos et al., 2012). The natural resistance of these microorganisms to this class of antimicrobials is due to constitutive changes in gene expression, which result in the addition of cationic molecules in the outer membrane LPS. As a result, there is a decrease in the binding affinity of polymyxins at the site of action (Baron et al., 2016; Yahav et al., 2012).

The mechanisms of resistance to this drugs are not yet fully understood. So far, it is known that they can occur through mutation or adaptation mechanisms (Girardello & Gales, 2012; Lescat et al., 2018). Studies have found that two polymyxin resistance phenotypes are frequently observed. The first, called natural resistance, occurs through mutations in the bacterial genome and promotes MIC values close to those considered as resistance cutoff points for this class of antimicrobials. While the second is due to adaptive mechanisms of bacteria and occurs after exposure of bacterial strains to subinhibitory concentrations of the antimicrobial. In the case of the phenotype resulting from bacterial adaptation, MIC values may be higher, with MICs above 128 µg/mL described in some studies (Srinivas & Rivard, 2017; Girardello & Gales, 2012).

The development of resistance to polymyxins because of the change in LPS was discovered through studies on strains of *Salmonella enterica*. It was observed that the addition of 4-amino-arabinose to the lipid A portion of LPS, one of the components of the external membrane of gram-negative bacteria, was associated with changes in the susceptibility to polymyxins in these microorganisms (Srinivas & Rivard, 2017).

In *P. aeruginosa*, the resistance to polymyxins involves a complex network of three systems (PmrAB, PhoPQ, and ParRS) with two components. The PhoPQ system is involved in the modification of LPS lipid A of gram-negative bacteria, and mutations in it lead to loss of function of the phoQ gene, resulting in high levels of resistance to polymyxins. In addition,

the PmrAB and PhoPQ systems promote changes in the expression of the operon responsible for the addition of 4-amino-arabinose to lipid A, causing alterations in the polymyxin susceptibility phenotype in strains of this species. While the two-component ParRS system is associated with the mechanism of adaptive resistance of *P. aeruginosa* strains to polymyxins (Baron et al., 2016; Girardello & Gales, 2012).

For *Acinetobacter* spp., the pmrCAB operon is associated with polymyxin resistance. The genes in this operon form a two-component system, in which pmrB functions as a histidine kinase sensor and pmrA is the response regulatory protein. This system controls the expression of the pmrC gene, which is responsible for adding phosphoethanolamine to LPS lipid A. The addition of phosphoethanolamine to lipid A reduces the negative charge on the bacterial surface and limits the interaction with polymyxins. In addition, mutations in the pmrB gene are associated with decreased susceptibility to polymyxins (Lescat et al., 2018; Mlynarcik & Kolar, 2019).

In other species such as *K. pneumoniae* strains, the activation of the PhoPQ system is associated with the alteration of the permeability properties of the outer membrane through stimulation of the expression of the *PagP* gene involved in lipid acylation. In *Legionella pneumophila* strains, the *rcp* gene has a *PagP*-like function, providing resistance to polymyxin B. In addition, missense mutations in the *CrrB* gene are associated with colistin resistance in *K. pneumoniae* isolates (Storey et al., 2020; Robey et al., 2001).

Studies indicate that resistance to polymyxins in some isolates of *Neisseria meningitidis* and *K. pneumoniae* due to increased production of capsular polysaccharides, which decreases the interaction of the drug with the bacterial surface. Thus, changes in the expression of genes involved in the regulation of polysaccharide capsule synthesis (*siaD*, *OmpA*, and the operon *cps*) may be associated with associated decreased susceptibility to polymyxins (Ahmed et al., 2020; Mlynarcik & Kolar, 2019).

According to an epidemiological surveillance study, an increase in colistin resistance was observed in *E. coli* strains isolated from animals. In further analysis, the researchers discovered a resistance mechanism that was transmissible between the strains, involving the plasmidial gene *mcr-1* (Liu et al., 2015). To date, seven different *mcr* genes and their variants have been described in the literature. The *mcr* gene encodes a phosphoethanolamine transferase involved in the modification of the LPS lipid A phosphate group (Srinivas & Rivard, 2017; Mlynarcik & Kolar, 2019; Moffatt et al., 2019).

The prevalence of strains resistant to polymyxins and the carriers of the *mcr-1* gene, varies between locations around the world. In addition, time is also a factor influencing the profile of bacterial resistance, especially in gram-negative bacteria, in which the conjugation process is capable of transferring genetic information between microorganisms of different species.

4.1 Antimicrobial resistance in strains of clinical origin

The increased use of therapeutic agents of last choice, such as colistin, has resulted in the emergence of new mechanisms in target pathogens in clinical settings. Some strains of *P. aeruginosa*, *A. baumannii*, and species of the family *Enterobacteriaceae* Resistance to colistin (CoR) have already been identified in hospitalized patients (Sherry & Howden, 2018; Cannatelli et al., 2014; Lee et al., 2011). Since the first clinical CoR strain of *K. pneumoniae* was reported, species of the *Enterobacteriaceae* that carry the CoR spread globally (Antoniadou et al., 2007). Increased rate of colistin resistance in *K. pneumoniae* has been reported in several countries like Tunisia (from 3.57% in 2002 to 9.68% in 2013) and Romania (25.8%) (Battikh et al., 2017; Maalej et al., 2012). While the clinical CoR isolates of *A. baumannii* have also increased over the last few decades, polymyxin resistance rates are extremely variable between *A. baumannii* isolates across the world (Li et al., 2019).

In 2013, the European Antimicrobial Resistance Surveillance Network (EARS-Net) collected annual data from 17 countries, showing high levels of CoR strains (>80%) in Greece and Italy (Giamarellou, 2016). While studies in other countries, such as Iran and Bulgaria, did not report the occurrence of CoR (Mahmoudi et al., 2017; Strateva et al., 2018). In case of *P. aeruginosa*, the rate of CoR has remained relatively low (0.3–1.4%) in comparison with other *Enterobacteriaceae*

and *A. baumannii*. The exception was a national surveillance study from China in 2013, where 22.2% of *P. aeruginosa* Extensively Drug-Resistant (XDR) isolates were resistant to polymyxin B (Sherry & Howden, 2018; Xu et al., 2016).

Some studies have shown that several factors, including polymyxin subtherapy, prolonged monotherapy, association with steroid and high colonization pressure, are directly linked to the rise resistance (Li et al., 2019; Ah et al., 2014; Papadimitriou-Olivgeris et al., 2014). Huang et al., (2020) showed that the resistance to colistin increased in *Enterobacteriaceae* isolates in China during the period 2014-2019, after the introduction of polymyxin in clinical use. Prim et al., (2017), showed that patients infected with *Enterobacteriaceae* CoR with a record of colistin administration, had more previous hospital admissions and comorbidities, and presented with hospital-acquired infections.

The main factor responsible for the mechanism of resistance to polymyxins are chromosomal mutations in several genes. For example, *MgrB* and *CrrB* gene, are directly involved in LPS modifications that prevent the interaction between the polymyxins and LPS; and also provide resistance to this antimicrobial agent (Gunn, 2008; Olaitan et al., 2014; Wright et al., 2015). Cannatelli et al., (2014), demonstrated the relationship between the inactivation of *MgrB* by mutations or insertion sequences, and polymyxin resistance in clinical *K. pneumoniae* isolates. Other chromosomal mutations included the alteration of the negative charge on LPS in the gram-negative bacteria cell wall. In the two-component systems (TCSs), *PhoPq* and *PmrAB*, are responsible for the addition of cationic groups to LPS. Mutations in these systems or their regulators result in their upregulation, such that more cationic groups are added to LPS, decreasing the negative charge, and thus preventing the action of colistin (Sirijatuphat & Thamlikitkul, 2014; Jeannot et al., 2017). This was observed in the study by Poirel et al., (2017) which detected mutations in *PmrAB* in clinical isolates of *K. pneumoniae* and *E. coli*.

In addition to chromosomal mutations, the emergence of the first plasmid-mediated mobile colistin resistance (*mcr*) gene, *mcr-1*, raised the alarm worldwide for the possibility of horizontal spread. This gene is responsible for the production of a phosphoethanolamine transferase that catalyzes the addition of cationic groups to LPS, as well as chromosomal mutations, thus decreasing the action and effect of colistin (Liu et al., 2015; Moffatt et al., 2019; Sherry & Howden, 2018). Despite being more common in environmental bacteria, *mcr-1* has been reported in *E. coli* isolates clinical origin, as well as *Salmonella* spp. and *K. pneumonia* (Prim et al., 2016; Shen et al., 2018; Lu et al., 2019; Strepis et al., 2021). The discovery of many other *mcr* genes, including *mcr-2* and *mcr-3*, and their presence being reported in many different plasmids, can provide new insights into horizontal and cross dissemination of colistin resistance between clinical isolates.

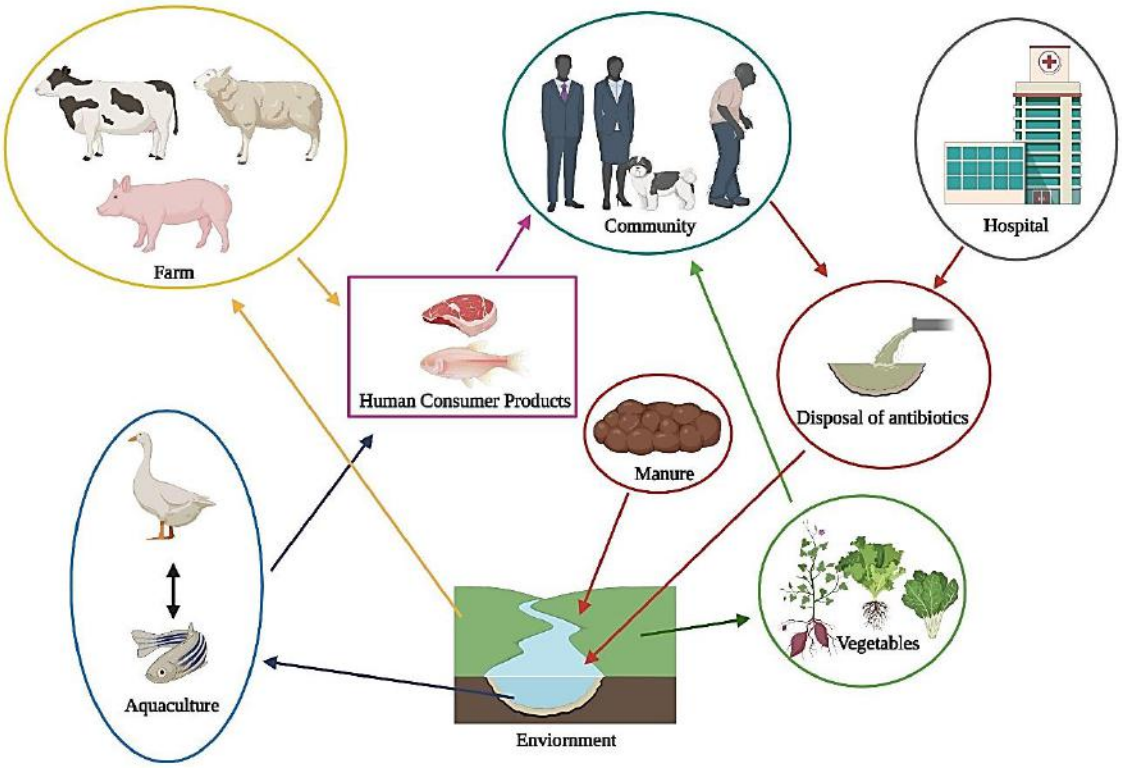
4.2 Bacterial resistance in strains of environmental origin

Bacterial resistance in the clinical environment is a public health problem that requires considerable attention. Bacteria resistant to antibiotics, especially to polymyxins, originating from the clinic, whether for humans or veterinary use, can easily spread to the environment (Balsalobre et al., 2014; Meirelles-Pereira et al., 2002). Unchanged bioactive forms of drugs can be excreted from human patients and enter the environment owing to the inefficiency of wastewater treatment. In addition, owing to their use in veterinary medicine, they are also present in animal excreta used as manure in agriculture (Figure 3) (Manyi-Loh et al., 2018; Serwecinska, 2020).

The environment has been shown to be a significant reservoir of ARGs. Frequently, ARGs are detected in cities, communities, farms, and natural environments (Xiaomin et al., 2020). Colistin resistance genes such as *mcr-1*, *mcr-2*, and *mcr-9* have been identified in recent years, and act by causing changes in lipid A in liposaccharide membranes (Carroll et al., 2019). Sun et al., (2018) showed the presence of these genes in pig manure through environmental samples, with a wide geographical distribution in Asian countries, in Australia, Europe, Africa, North America and South America. In other studies, it was observed rates of occurrence of positive isolates for *mcr-1* of 9.90% and 29.40%, in environmental samples collected from farms in China and Germany, respectively. This investigation showed that 25% and 100% of the samples were positive for

mcr-1, respectively, in these two countries (Guenther et al., 2017; Hille et al., 2018; Roschanski et al., 2017; Wang et al., 2018; Wang et al., 2018).

Figure 3. Cycle of transmission of antibiotic-resistant bacteria in the environment.



Representation of different ways of spreading resistant microorganisms between humans, animals and the environment, especially water sources, which are recipients of residual effluents. Source: Created with BioRender.com.

On farms, bacteria of the *Enterobacteriaceae* family carrying mcr-1 are more frequent, such as, for example, *Providencia alcalifaciens*, *Raoultella planticola*, and *Enterobacter cloacae* (Wang et al., 2018). Bacterial conjugation assays showed that *mcr-1* could be transferred from *P. alcalifaciens* and *E. cloacae* to *E. coli*. This suggests that *mcr-1* can be naturally spread among species in this family and can be transferred from clinical to environmental isolates (Wang et al., 2018).

The agricultural environments are considered important for the storage and dissemination of *mcr-1*. The highest prevalence rates of *mcr-1* were observed in wastewater from hospitals and sewage treatment plants (Jin et al., 2018; Ovejero et al., 2017). The presence of *mcr-1* in different municipal wastewater treatment indicates that conventional sewage treatment processes cannot completely eliminate *mcr-1* (Hembach et al., 2017). Thus, isolates carrying this gene can further contaminate aquatic environments. The *mcr-1* has been detected not only in wastewater, but also in well water (Sun et al., 2018; Caltagirone et al., 2017), source water (Zhou et al., 2017), rivers (Zurfuh et al., 2016; Yang et al., 2017; Tuo et al., 2018), oceans and beaches in different countries as Algiers, Norway, China, and Switzerland (Drali et al., 2018; Jørgensen et al., 2017). Therefore, are necessary and urgent effective models or technologies to remove *mcr-1* from wastewater and also from other environments to prevent spread.

According to previous studies, it is evident that the *mcr-1* gene has prevalence in environments different. The data demonstrate the importance of understanding the destination of antimicrobials in the environment, since these sites can harbor and enable the emergence of resistant bacteria (Hurst et al., 2019; Menz et al., 2019), causing public health problems.

5. Conclusion

Studies have been conducted to identify strains with a profile of reistance to polymyxins in hospital, community, and non-anthropized environments. This indicates the emergence of global problems associated with the reduction in the effectiveness of antibiotics, especially this category used as a last therapeutic option, which results in an increase in extremely resistant bacterial pathogens. In this sense, approaches that seek to emphasize the mechanisms of gene transmission between pathogenic bacteria of clinical and environmental origin are essential. The present study contributes to alerting about the growing increase in microbial resistance to drugs routinely used in clinical practice, and how this resistance extends to other environments and can be disseminated in natural ecosystems.

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