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Bacterial resistance: A narrative review on *Staphylococcus aureus*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*

Resistência bacteriana: Uma revisão narrativa sobre *Staphylococcus aureus*, *Klebsiella pneumoniae* E *Pseudomonas aeruginosa*

Resistencia bacteriana: Una revisión narrativa sobre Staphylococcus aureus, *Klebsiella pneumoniae* y *Pseudomonas aeruginosa*

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Abstract
The aim of this article is to present a narrative review of the bacteria *Staphylococcus aureus*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*, addressing their resistance mechanisms, peculiarities and characteristics. Bacterial resistance has become a public health issue of worldwide relevance. Due to the misuse of antibiotics or even their prolonged use, many species of bacteria have become increasingly resistant to antimicrobial agents. The nosocomial environment, especially intensive care units, where patients undergoing treatment use antibiotics for prolonged periods of time, is the environment in which the emergence of these bacteria is most commonly detected, including *Staphylococcus aureus*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*. Many actions have been taken by the governments of various countries, the pharmaceutical industry, international organizations and researchers, both to raise awareness about the correct use of antimicrobials and in the search for new molecules to combat these pathogens. Given the relevance of the subject, this study will present a narrative review of the mechanisms of resistance of the bacteria *S. aureus*, *K. pneumoniae* and *P. aeruginosa*, strains that are highly resistant to available antimicrobials, in an attempt to understand the role of these pathogens.
Keywords: Bacterial resistance; *Staphylococcus aureus; Klebsiella pneumoniae; Pseudomonas aeruginosa.*

Resumo
O objetivo deste estudo é apresentar uma revisão narrativa sobre as bactérias *Staphylococcus aureus*, *Klebsiella pneumoniae* e *Pseudomonas aeruginosa*, abordando seus mecanismos de resistência, peculiaridades e características. A resistência bacteriana se tornou uma questão de saúde pública de relevância mundial. Devido ao uso indevido de antibióticos ou mesmo pelo seu uso prolongado, muitas espécies de bactérias têm se tornado cada vez mais resistentes aos agentes antimicrobianos. O ambiente hospitalar, principalmente nas unidades de terapia intensiva, local no qual pacientes em tratamentos, fazem uso de antibióticos por tempo prolongado, é o ambiente no qual mais se detecta o surgimento destas bactérias, dentre as quais se destacam *Staphylococcus aureus*, *Klebsiella pneumoniae* e *Pseudomonas aeruginosa*. Muitas ações vêm sendo tomadas por parte dos governos de diversos países, indústria farmacêutica, organizações internacionais e pesquisadores, tanto no sentido de conscientização quanto ao uso correto dos antimicrobianos, como na pesquisa na busca de novas moléculas para o combate destes patógenos. Visto a relevância do tema, neste estudo será apresentada uma revisão narrativa acerca dos mecanismos de resistência das bactérias *S. aureus*, a *K. pneumoniae* e a *P. aeruginosa*, cepas que apresentam elevada resistência aos antimicrobianos disponíveis, buscando compreender o papel destes patógenos.
Palavras-chave: Resistência bacteriana; *Staphylococcus aureus*; *Klebsiella pneumoniae*; *Pseudomonas aeruginosa*.

Resumen
El objetivo de este estudio es presentar una revisión narrativa de las bacterias *Staphylococcus aureus*, *Klebsiella pneumoniae* y *Pseudomonas aeruginosa*, abordando sus mecanismos de resistencia, peculiaridades y característicasLa resistencia bacteriana se ha convertido en un problema de salud pública de relevancia mundial. Debido al mal uso de los antibióticos o incluso a su uso prolongado, muchas especies de bacterias se han vuelto cada vez más resistentes a los agentes antimicrobianos. El ambiente hospitalario, especialmente en las unidades de cuidados intensivos, donde los pacientes en tratamiento utilizan antibióticos durante un período prolongado, es el ambiente en el que con mayor frecuencia se detecta la aparición de estas bacterias, entre las que destacan *Staphylococcus aureus*, *Klebsiella pneumoniae* y *Pseudomonas aeruginosa*. Muchas acciones han sido tomadas por los gobiernos de diferentes países, la industria farmacéutica, organismos internacionales e investigadores, tanto en materia de concientización sobre el uso correcto de los antimicrobianos, como en investigación en la búsqueda de nuevas moléculas para combatir estos patógenos. Dada la relevancia del tema, este estudio presentará una revisión narrativa de los mecanismos de resistencia de las bacterias *S. aureus, K. pneumoniae* y *P. aeruginosa*, cepas que presentan alta resistencia a los antimicrobianos disponibles, buscando comprender el papel de estos patógenos.
Palabras clave: Resistencia bacteriana; *Staphylococcus aureus; Klebsiella pneumoniae; Pseudomonas aeruginosa.*

1. Introduction

Bacterial resistance has become a public health problem of worldwide relevance. This issue has been discussed in several countries around the world, with the aim of developing strategies such as raising awareness about the rational use of antimicrobials, the production of new drugs, among others. To this end, the commitment of various government bodies, the pharmaceutical industry and international organizations is necessary in order to try to alleviate and solve this issue (Miethke *et al*., 2021).

Depending on the environment and the way antimicrobials are used, some bacteria end up developing internal mechanisms that result in the resistance of these microorganisms. This resistance can come from a genetic mutation caused by the need for environmental adaptation or exposure to prolonged use of antimicrobials (Founou *et al*., 2017). Among the main mechanisms of bacterial resistance are efflux pumps, enzymatic modification, target alteration, acquisition of new genes and biofilm formation (Zhang & Cheng, 2022).

The nosocomial environment, especially in intensive care units, ends up being an environment conducive to the development of resistance, mainly due to the prolonged use of antibiotics by patients being treated for persistent infections (Edwardson; Cairns, 2019), as well as the indiscriminate use of antimicrobials contributing even more to this problem. Several bacteria are resistant to antimicrobials and in this narrative review three were selected: *Staphylococcus aureus, Klebsiella pneumoniae* and *Pseudomonas aeruginosa*.

Staphylococcus aureus is a gram-positive bacterium, well known for being an opportunistic pathogen, due to its high level of adaptability to the main antibiotics used in the treatment of pathogens, leading to a genetic alteration in its structure, providing resistance to these antimicrobials (Chang *et al*., 2020). *Klebsiella pneumoniae* is a gram-negative bacterium responsible for a large proportion of hospital infections. Due to the inappropriate and often prolonged use of antibiotics in the clinical and intensive care areas, it has led to the emergence of hypervirulent multidrug-resistant strains, putting the most immunocompromised patients at risk (Yang *et al*., 2020). *Pseudomonas aeruginosa* is no different. It is a gram-negative bacterium capable of producing various enzymes and toxins that allow it to invade host tissues, causing various cellular damages, with the ability to resist many antibiotics, due to both its innate resistance mechanism and its ability to produce biofilm (Reynolds & Kollef, 2021).

A common characteristic among these bacteria is the formation of a powerful biofilm, which hinders the action of antimicrobials, as well as their genetic resistance characteristics, acquired or developed through the need to adapt to the environment or exposure to antimicrobials (Edwardson & Cairns, 2019).

The search for the development of new antimicrobials, as well as raising awareness about the correct use of these drugs, is a goal to be achieved with the support of governments, the pharmaceutical industry and international organizations are essential to overcome this problem for global public health (Miethke *et al*., 2021).

The aim of this article is to present a narrative review of the bacteria *Staphylococcus aureus, Klebsiella pneumoniae* and *Pseudomonas aeruginosa*, addressing their resistance mechanisms, peculiarities and characteristics.

2. Methodology

This study was prepared in the form of a narrative review, which takes a broad approach to a given topic, based on a selection of literature published in books, articles and magazines, basically a theoretical description of a specific topic, with the aim of providing the reader with material in which they can quickly find current information on the subject (Rother, 2007).

In general terms, when the purpose of the review study is to provide speed in the assimilation of information, as well as facilitating learning, it is desirable to use graphic schemes that speed up the process, such as the use of concept maps. However, this narrative review opted to use synoptic tables to summarize the main concepts on the subject, in order to organize and facilitate the assimilation of the content (Pereira et al., 2018; Prodanov & Freitas, 2013).

This narrative review article used the Google Scholar search engine, as well as platforms such as PubMed, MPDI (Publisher of Open Access Journals) and Scielo (Scientific Electronic Library Online), preferably selecting those published in the last five years, from 2018 to 2023, in English. The search was focused on the topics covered in this work, which are bacterial resistance as a public health problem worldwide, bacterial resistance mechanisms and directly by the names of the bacteria *S. aureus, K. pneumoniae, P. aeruginosa*, to track their specific characteristics, as well as the virulence potential and resistance mechanisms peculiar to each of them.

3. Results

After searching the platforms, 28 articles were selected as the basis for this review, using the following keywords: "bacterial resistance", "bacterial resistance mechanisms", "antimicrobial resistance", "antimicrobial resistance mechanisms", "antibiotic resistance mechanisms", "Virulence factors", "Quorum sensing", "Biofilms", "*Staphylococcus aureus", "Klebsiella pneumoniae"* and *"Pseudomonas aeruginosa*". Below is a table (Table 1) of the main articles:

Table 1 - Articles selected for the narrative review within the themes covered in alphabetical order.

Author	Keywords	Title
Abushaeen et al., 2020	Antibiotics; Antimicrobial resistance (AMR); Mechanisms of antimicrobial action	*"Antimicrobial resistance, mechanisms and its clinical significance"*
Ahmad-Mansour et al.,2021	*Staphylococcus aureus*; pathogenicity toxins anti-toxin strategies; virulence	*"Staphylococcus aureus Toxins: An Update on Their Pathogenic Properties and Potential Treatments"*
Brindhadevi et al., 2020	Biofilm; Quorum sensing; *Pseudomonas aeruginosa;*Autoinducers;Extracellular polymeric substances	*"Biofilm and Quorum sensing mediated pathogenicity in Pseudomonas aeruginosa"*
Butrico; Cassat, 2020	osteomyelitis; *Staphylococcus aureus*; toxin; accessory gene regulator; quorum; virulence; infectious; pathogenesis; bone	*"Quorum Sensing and Toxin Production in Staphylococcus aureus Osteomyelitis: Pathogenesis and Paradox"*
Reygaert, 2018	antimicrobial resistance; β-lactamase; MRSA; ESBL; CRE	*"An overview of the antimicrobial resistance mechanisms of bactéria"*
Chadha et al., 2022	*Pseudomonas aeruginosa; Quorum sensing*	*"Revisiting the virulence hallmarks of Pseudomonas aeruginosa: a chronicle through the perspective of quorum sensing"*

Chang et al., 2020	*Staphylococcus aureus;* Persister cells Antibiotics ; Mechanism; Genetics	*"A pursuit of Staphylococcus aureus continues: a role of persister cells"*
Guerra et al.,2022	Biofilm; *Klebsiella pneumoniae; quorum sensing;* pathogenesis; virulence factors	*"Klebsiella pneumoniae Biofilms and Their Role in Disease Pathogenesis"*
Guo et al., 2020	*Staphylococcus aureus*, molecular mechanisms, acquired antibiotic resistance, antibiotic resistance, therapy, cell membrane	*"Prevalence and Therapies of Antibiotic-Resistance in Staphylococcus aureus"*
Howden et al.,2023	*Staphylococcus aureus*	*"Staphylococcus aureus host interactions and adaptation"*
Huemer et al.,2020	persistence; persistent infections; persisters; resistance; tolerance	*"Antibiotic resistance and persistence implications for human health and treatment perspectives"*
Idrees et al., 2021	*Staphylococcus aureus*; biofilm formation; gene expression; quorum sensing; antimicrobial resistance; pathogenesis; antibiofilm agents	*"Staphylococcus aureus Biofilm: Morphology, Genetics, Pathogenesis and Treatment strategies"*
Jindal et al., 2015	Antimicrobial resistance (AMR);Public health; Microorganisms;Health care expenditure	*"Antimicrobial resistance: A public health challenge"*
Jurado-Martín et al., 2021	*Pseudomonas aeruginosa*; virulence factors; adaptation; cystic fibrosis; diversity; genomics; lung environment	*"Pseudomonas aeruginosa: An Audacious Pathogen with an Adaptable Arsenal of Virulence Factors"*
Kakoullis et al.,2021	*Escherichia coli; Staphylococcus aureus; Pseudomonas aeruginosa; Enterococcus faecalis; Enterococcus faecium; Acinetobacter baumannii; Klebsiella pneumoniae;* MRSA; VRE; multi-drug resistant infections	*"Mechanisms of Antibiotic Resistance in Important Gram-Positive and Gram-Negative Pathogens and Novel Antibiotic Solutions"*
Lam et al., 202	*Klebsiella pneumoniae*	*"A genomic surveillance framework and genotyping tool for Klebsiella pneumoniae and its related species complex"*
Lamut et al, 2018	AcrAB-TolC; bacterial resistance, efflux pump inhibitor;MexAB-OprM; multidrug efflux systems; NorA, structure-activity relationship	*"Efflux pump inhibitors of clinically relevant multidrug resistant bacteria"*
Miethke et al., 2021	Antibiotics	*"Towards the sustainable discovery and development of new antibiotics"*
Nishino et al., 2021	Inhibitor; regulation; drug resistance, Gram-negative bactéria; multidrug efflux pumps	*"Function and Inhibitory Mechanisms of Multidrug Efflux Pumps"*
Pachori et al., 2019	Antibiotics;Blood stream; infections;Infection;Pathogen;Resistance; Urinary tract; infections	*"Emergence of antibiotic resistance Pseudomonas aeruginosa in intensive care unit; a critical review"*
Reynolds; Kollef, 2021	*Pseudomonas aeruginosa*	*"The Epidemiology and Pathogenesis and Treatment of Pseudomonas aeruginosa Infections: An Update"*
Turner et al., 2019	*Staphylococcus aureus*	*"Methicillin-resistant Staphylococcus aureus: an overview of basic and clinical research"*
Uruén et al., 2020	biofilms; antibiotic resistance; antibiotic tolerance; multidrug-resistant bacteria; biofilm control	*"Biofilms as Promoters of Bacterial Antibiotic Resistance and Tolerance"*
Van Duijkeren et al., 2017	Bacterial Resistance mechanisms	*"Mechanisms of Bacterial Resistance to Antimicrobial Agents"*
Wang et al.,2021	*K. pneumoniae*; pathogenicity; biofilm; multidrug-resistant	*"The Characteristic of Virulence, Biofilm and Antibiotic Resistance of Klebsiella pneumoniae"*
Zhang; Cheng, 2022	bacterial drug resistance; new antibacterial compounds; phage therapy; CRISPER-Cas; precision therapy	*"The Mechanism of Bacterial Resistance and Potential Bacteriostatic Strategies"*
Zhao et al., 2020	quorum sensing; microbial resistance; biofilm; quorum quenching	*"Quorum-Sensing Regulation of Antimicrobial Resistance in Bacteria"*

Source: Authors.

4. Discussion

Bacterial resistance is an event arising from mutations that occur in bacteria due to a response of the bacteria to the use of antibiotics and environmental conditions that favor these genetic and epigenetic changes (Guimarães *et al*., 2010). It is considered a global public health problem that has been increasing and causing a great deal of concern in recent decades (Jindal *et al*., 2015).

A really worrying fact is when bacterial resistance occurs in cases of nosocomial-acquired infections, in which patients are exposed to various types of multidrug-resistant bacteria (Edwardson; Cairns, 2018). Due to the inappropriate and often excessive use of antimicrobials as a therapeutic measure, bacteria can quickly develop resistance, making infections increasingly costly and difficult to treat (Founou *et al*., 2017). According to the World Health Organization WHO, by 2050, bacterial resistance could cause up to 10 million deaths a year worldwide (Iacg-who, 2019). Raising awareness about the responsible use of antibiotics, as well as the search for the development of new drugs with the support of governments, the pharmaceutical industry and international organizations are essential to tackle this major global public health challenge (Miethke *et al*., 2021).

Bacterial resistance mechanisms are the strategies developed by bacteria for survival and growth, as well as in the presence of antimicrobials (Abushaheen *et al*, 2020), as can be seen in the table (Table 2) below:

Table 2 - Main bacterial resistance mechanisms summarized.

Quorum sensing	Quorum sensing is a signaling mechanism that promotes communication between bacteria, with the function of regulating gene expression in the face of changes in population density (Lang *et al*. 2022), as well as regulating various cellular processes, such as the production of toxins, the process of pumping antimicrobials (efflux pumps) and the formation of biofilms, among others (Zhao, *et al*., 2020).
Biofilms	Extracellular matrix produced by bacteria and attached to a biotic or abiotic surface, creating an environment of tolerance and resistance to antibiotics through different mechanisms that depend on factors such as the composition of the biofilm and the conditions for its growth (Uruén *et al*., 2021). It is basically composed of proteins, polysaccharides and DNA from the forming bacteria, whose main function is to make it difficult for antimicrobial agents to enter the bacteria (Reygaert, 2018).
Mutations	They occur through transformation, which is the absorption of genetic material from the surface of the bacteria into its interior through channels in the cytoplasmic membrane; Transduction, which is the transmission of a sequence of resistance genes through a bacteriophage between bacteria; Conjugation, which is the transfer of resistant genes through plasmids and transposons (Abushaheen *et al*., 2020). An example of mutation is what occurs in the target's protective proteins, modifying the site of action of antimicrobials (Van Duijkeren *et al*., 2018).
Reducing permeability	These are changes in the bacterial plasma membrane that alter porin channels and reduce the permeability of antimicrobial agents, either by reducing the number of porins in the membranes due to exposure to antimicrobials or by genetic changes (Zhang; Cheng, 2022); (Van Duijkeren *et al*., 2018).
Efflux pumps	They are a method of active transport that provides a mechanism of resistance to bacteria (Abushaheen *et al*., 2020), present in the bacterial plasma membrane, with the function of expelling antimicrobials and other types of substrates present in the cytoplasm, functioning as a protective mechanism, preserving the cell from the accumulation of toxins (Zhang; Cheng, 2022).
Enzyme modification	It consists of the production of enzymes by some bacteria in order to inactivate antimicrobial agents (Nishino *et al*, 2021). The ability to modify or hydrolyze molecules that may enter the cell, rendering them inactive before they reach their target (Zhang; Cheng, 2022).
Target protective proteins	These are proteins produced by bacteria that protect certain antibiotic targets, suppressing their bacteriostatic effects and basically have three types: Type I in which ribosomal protection proteins bind, preventing the binding of some antimicrobials (tetracyclines); Type II, antibiotics are prevented from binding by changes in the conformation of the target; Type III reverses the binding of the antibiotic with the target, as well as rescuing the function of the target, even after binding with the antimicrobial (Zhang; Cheng, 2022); (Wilson *et al*. , 2020).

Source: Authors (2023).

Antibiotics are a remarkable achievement of modern medicine, enabling the effective treatment of a wide variety of infectious diseases and are fundamental in advanced surgical procedures, such as organ transplants, as well as in the treatment of varied medical illnesses, including rheumatology and oncology. The availability of effective antibiotic therapies has also contributed significantly to the reduction of infant mortality, raising life expectancy in general. However, due to the scarcity of

new antimicrobial drugs and the increased prevalence of multidrug-resistant bacteria, failures in treatments for infections are becoming increasingly frequent, making antibiotic-resistant bacteria a major threat to public health (Huemer *et al*., 2020).

There are many bacteria that acquire resistance to different classes of antimicrobials, and this is the subject of study in several publications around the world. In this work, due to the wide range of bacteria that could be addressed within this topic, three strains were chosen, which are *Staphylococcus aureus*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*. The following table (Table 3) summarizes and simplifies the antimicrobial resistance mechanisms present in these three bacteria:

Table 3 – Resistance mechanisms to simplified antimicrobials *S. aureus*, *K. pneumoniae* and *P. aeruginosa*.

Antimicrobial	**Resistance Mechanisms**		
	S. aureus	***K. pneumoniae***	***P. aeruginosa***
Penicillins	Enzyme modification and *Penicilin-binding protein 2a*	Enzyme modification	Enzyme modification
1st, 2nd, 3rd and 4th cephalosporins; *Carbapenems;* *Beta-lactamase inhibitors*	*Penicilin-binding protein 2a*	Enzyme modification	Enzyme modification
Tetracyclines	Efflux pumps and ribosomal methylation of the binding sites	Efflux pumps	Efflux pumps
Tigecyclines	Efflux pumps	Efflux pumps	Efflux pumps
Macrolides and Clindamycin	Ribosomal methylation of binding sites and Efflux pumps		Efflux pumps
Fluoroquinolones	Mutations and Efflux pumps	Mutations, Target protective proteins, Enzyme modification and Efflux pumps	Mutations and Efflux pumps
Linzolid	Mutations		
Rifampicin	Mutations	Enzyme modification	Mutations
Sulfamethoxazole-trimethoprim (TMP-SMX)	Mutations		Efflux pumps
Aminoglycosides	Enzyme modification	Enzyme modification	Enzyme modification
Daptomycin	Electrostatic repulsion: increase in cell surface charge		
Vancomycin	VRSA (vancomycin-resistant *S. aureus*) due to mutations; Thicker cell wall (peptidoglycan)		
Colistin		Reducing the membrane's negative charge by adding phosphoethalonamine A	Reduction of the membrane's negative charge by N4-aminoarabinose to lipid A
Aztreonam		Enzyme modification	Enzyme modification

Source: Adapted from Kakoullis *et al*. (2021).

4.1 *Staphylococcus aureus*

Staphylococcus aureus belongs to the cocci group, measuring around 1µm in diameter, forming medium-sized colonies and, when in culture media, causing hemolysis on blood agar plates. They come from the *Staphylococcaceae* family and are normally found on the skin, in the oral cavity, respiratory system and intestines. They are facultative anaerobes, using oxygen for cellular respiration, but in its absence they use other means. They are catalase, oxidase and coagulase positive (Guo *et al*., 2020; Brabb *et al*., 2012). It is known for being an opportunistic pathogen, which is frequently diagnosed in medical care and due to its high level of resistance and adaptability to the main antibiotics that are used to treat pathogens, altering its genetics. This resistance has become a significant threat to public health, resulting in countless deaths for those infected by it over the years (Chang *et al*., 2020).

4.1.1 Virulence factors and resistance mechanisms of *S. aureus*

S. aureus infections occur due to the production of proteins on its surface, which allows it to adhere to tissues, as well as causing the secretion of toxins and enzymes that destroy the host's cells, promoting its growth and expansion. Some of the enzymes produced by *S. aureus*, such as coagulase, hyaluronidase, deoxyribonuclease and lipase, increase its pathogenicity and help it spread within the host. There are also enterotoxins, such as TSST 1, which causes toxic shock syndrome, exfoliative toxins, hemolysins, inhibitors of epidermal cell differentiation, all known as toxins that increase pathogenicity (Ahmad-Mansour *et al*., 2021). Its genome has a single chromosome that can be associated with one or more plasmids, in which the resistance genes are found, as well as in transposons (Howden *et al*., 2023).

The quorum sensing system of *S. aureus* allows it to detect population density in a given niche through the production of an autoinducer peptide (AIP) and this peptide in turn activates Agr (accessory regulatory gene), which is responsible not only for quorum activation but also for the production of toxins, binding proteins and those involved in the process of bacterial adhesion and aggregation, this Agr being an item responsible for inducing the virulence factors of *S. aureus* (Butrico; Cassat, 2020). Another resource that amplifies the pathogenic potential of *S. aureus* is its biofilm, which is basically composed of 97% water and organic matter that includes EPS (exopolysaccharides) and microcolonies, making up 50% to 90% of total organic matter. The main component of EPS is PIA (polysaccharide intercellular adhesin), which is one of the *S. aureus* genes responsible for the formation of its biofilm (Idrees *et al*., 2021).

4.1.2 Clinical diseases provocated by *S. aureus*

Staphylococcus aureus infections can develop a wide range of diseases from moderately severe skin infections to bloodstream infections causing critical illnesses such as pneumonia, endocarditis and bacteremia. Gaining access to the host's bloodstream increases the risk of it becoming fatal (Chang *et al*., 2020).

There are mainly three types of *S. aureus* infections such as superficial lesions (for example, folliculitis, furuncle, carbuncle and impetigo), toxinosis and systemic and fatal conditions. Infections resulting from food poisoning (presence of toxins in food and not due to infection), toxic shock syndrome (TSST-1 superantigen produced by *S. aureus*), endocarditis, osteomyelitis and pneumonia appear as some diseases caused by this pathogen (Turner *et al*., 2019).

4.2 *Klebsiella pneumoniae*

It was described by Carl Friedlander in 1882 as a bacterium isolated from the lungs of patients who died of pneumonia. It is classified as an opportunistic, hypervirulent and multidrug-resistant pathogen. *K. pneumoniae* is a lactose fermenter, its characteristic being mucoid when present in agar media (Guerra *et al*., 2022). It consists of adhesins, pili type 1 and 3, its bacterial adhesion is through epithelial cells, immune and abiotic surfaces, located ubiquitously in the environment such as water, soil and on mucosal surfaces of animals (Wang *et al*., 2020). It is a gram-negative bacterium with a rod shape (Yang *et al*., 2020).

4.2.1 Virulence factors and resistance mechanisms in *K. pneumoniae*

K. pneumoniae strains are recognized for being opportunistic, hypervirulent and multidrug-resistant. Most infections have been generated by the classic strains of *K. pneumoniae* that are present in hospitals and cause infections in the most debilitated patients. The genetic factors for the high virulence characteristics are found in a large virulence plasmid, and there may be integration of conjugated elements. Its antibiotic resistance genes are encoded by the plasmid, and it benefits from plasmids and transferable genetic elements, becoming resistant with the improper use of antibiotics, thus emerging a new extremely resistant strain (Wang *et al*., 2020).

K. pneumoniae quorum sensing is responsible for signaling various events, including the expression of virulence genes. In the process of *K.pneumoniae* biofilm formation, its capsule, fimbriae, LPS (lipopolysaccharides), quorum sensing, as well as some genes associated with these items are involved. Biofilm is an important characteristic of this bacteria, as it increases resistance against external agents, promoting a favorable environment for dissemination and genetic exchange associated with antimicrobial resistance (Guerra *et al*., 2022).

4.2.2 Clinical diseases provocated by *K. pneumoniae*

K. Pneumoniae causes frequent colonization of the gut, and this leads to the development of chronic diseases of the gastrointestinal tract, such as inflammatory bowel disease and colorectal cancer. It also causes infections such as urinary tract infections, pneumonia, wound or surgical site infections, sepsis, and generally affects more susceptible individuals, such as neonates, the elderly, immunocompromised and hospitalized patients (Lam *et al*., 2021).

Because it is a bacterium that frequently colonizes abiotic surfaces and human mucous membranes, especially in the oropharynx and gastrointestinal tract, and has the ability to invade other tissues in the human body, it is also commonly associated with urinary tract infections and bloodstream infections (Martin; Bachman, 2018). Treatment of infections is often limited due to its resistance to various antimicrobials, which is the result of the number of genes acquired horizontally by mutation (Wang *et al*., 2020).

The hypervirulent strain has a k1, k2 and k5 polysaccharide capsule, these capsules are horizontally acquired, the virulence factors that encode arerobactin and salmochelin siderophores, colobactin and a hypermucoid phenotype. The hypervirulent strain is rarely multidrug-resistant and is generally susceptible to antimicrobials, except ampicillin because it intrinsically possesses beta-lactamases. Some genomic studies associated with community-acquired infections have revealed several strains with a high virulence gene load. Tests have revealed the existence of subspecies which, when joined together, form a *K. pneumoniae* species complex, of which two subspecies cause an infection called rhinoscleroma, triggering atrophic rhinitis or ozena. Due to the increase in resistant strains, this bacterium requires more and more molecular epidemiology studies (Lam *et al*, 2021).

4.3 *Pseudomonas aeruginosa*

Pseudomonas aeruginosa is a gram-negative, rod-shaped, aerobic bacterium from the *Pseudomonadaceae* family, which has 12 other types in its group. It can vary in size from 0.5 to 0.8 ÿm by 1.5-3.0 ÿm and survives at 37-42 °C. It produces a pigment called pyoverdine, a yellowish-green fluorescent substance that is visible when sown on agar. Due to its low nutritional requirements, it can survive in environments with dry surfaces, such as operating theatres and hospital rooms, on medical equipment, making it a very common bacterium in resistant infections in hospital environments. It has a complex electron transport system, which allows it to use different energy sources, including ammonia, nitrite, nitrite and hydrogen (Iglewski, 1996); (Pachori *et al*., 2019; Reynolds & Kollef,2021).

4.3.1 Virulence factors and resistance mechanisms *P. aeruginosa*

The virulence factors of *Pseudomonas aeruginosa* allow it to grow and survive, causing devastating damage to the host such as necrosis, evasion and impairment of the immune system. The production of these defense systems demands a high metabolic cost on the pathogen, requiring synchronicity between its bacterial population in order to adapt its functions. Thus, quorum sensing plays a key role in this bacterium's system (Chadha *et al*., 2022).

Through quorum sensing, basic cellular mechanisms are coordinated through this signaling such as sporulation, synthesis of antimicrobial peptides, plasmid conjugation, virulence factor and biofilm formation. The biofilm it produces prevents the action of conventional antimicrobials and the reaction of the host's immune system, through the production of

alginate. The production of pioquelin, pyocyanin and pioverdin helps its metabolism, regulating virulence factors such as endoprotease and exotoxin A. In *Pseudomonas aeruginosa*, biofilm is an important characteristic that contributes to virulence and antibiotic resistance. There are three main types of exopolysaccharides that enable the stability of the *Pseudomonas* biofilm, which are alginate, Pel and Psl (polysaccharides) (Brindhadevi *et al*., 2020).

The high virulence that the *Pseudomonas aeruginosa* biofilm provides is an important characteristic in chronic lung infection in patients with cystic fibrosis, as it makes it very difficult for antibiotics to permeate through it. They also showed that the cells in the biofilm expressed genes involved in the production of virulence factors, such as elastase and pyocyanin (Jurado-Martín *et al*.,2021).

The outer membrane of *P. aeruginosa*, unlike other gram-negative bacteria, is much less permeable and its efflux pumps are able to expel antibiotics more effectively than *Escherichia coli*, because its main membrane porin is twice as small as that of *E. coli*, which is why the resistance base of this bacterium is higher, making it a challenge to combat. *Pseudomonas* efflux pumps have the ability to extrude their own physiological compounds, such as N-acylmoserine lactone, from within themselves and diffuse them to other cell populations, activating many processes, including serving as quorum-sensing beacons (Lamut *et al*., 2018).

4.3.2 Clinical diseases provocated by *P. aeruginosa*

As a potential pathogen in the nosocomial environment, *Pseudomonas aeruginosa* can infect the host by disrupting its immune system, causing bacteremia, bone and joint infections, gastrointestinal infections, dermatitis, respiratory infections, urinary infections and soft tissue infections. It can also infect patients with burns, cystic fibrosis and cancer. This bacterium has a high capacity to form biofilm and this barrier formed by the biofilm prevents the penetration of antibiotics (Brindhadevi *et al*., 2020), making *Pseudomonas aeruginosa* a difficult bacterium to treat.

5. Closing Remarks

This narrative literature review presented a panorama of publications on bacterial resistance, in an analysis of the characteristics that make *S. aureus, K. pneumoniae* and *P. aeruginosa*, which are so common in nosocomial infections, such as the ability to form biofilm and other morphological characteristics and genetic structure that enable their virulence potential, thus demonstrating the importance of a more didactic approach to each one.

The literature analyzed is emphatic in showing the importance of understanding the resistance mechanisms for research and the creation of new antimicrobial drugs, as well as the search for new strategies to prevent contagion, such as by developing medical equipment with manufacturing materials that prevent the formation of biofilms, among others. It is therefore hoped that new studies on this subject will be encouraged in order to broaden the range of solutions to this worldwide problem of bacterial resistance to antibiotics.

Therefore, the next steps are to expand research into other resistant bacterial strains such as *Acinetobacter baumannii*, *Clostridium difficile*, as well as resistant fungi such as *Candida auris* and *Cryptococcus neoformans*, in order to contribute to the academic and scientific environment with new reviews on this important and extremely relevant topic of antimicrobial resistance.

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