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A Review of Biofilm Formation and Antibiotic Resistance in Klebsiella Pneumoniae

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Abstract
Infections caused by the Gram-negative, opportunistic bacteria Klebsiella pneumoniae are common in healthcare settings and include pneumonia, bloodstream infections, urinary tract infections (UTIs), and wound infections. The primary objective of this study was to determine the prevalence of biofilm-forming gram-negative bacteria Klebsiella pneumoniae and their potential association with multidrug resistance. Multicellular microbial communities, such biofilms, vary from planktonic cells in many ways. Biofilm former frequency and correlation between biofilm formation capacity and multi-drug resistance were determined using a one-arm meta-analysis and a two-arm meta-analysis, respectively. Previous findings from other meta-analyses including various microbes are consistent with this prevalence rate. Modern approaches to treating infections need to be revised in light of the widespread presence of biofilm formers. Both biofilm formers and non-biofilm formers had the same risk of developing multidrug resistance, according to the two-arm meta-analysis. This finding casts doubt on planktonic cells' inherent ability to develop multi-drug resistance. It is crucial to do additional study in order to revise the profiles of biofilm formation and to comprehend the mechanism of resistance in frequently encountered bacterial diseases.

Keywords: Klebsiella pneumoniae, Biofilm formation, Antibiotic resistance, Multidrug resistance (MDR), Pan-drug resistance (PDR), Extended-spectrum beta-lactamases (ESBLs), Carbapenem-resistant Klebsiella pneumoniae (CRKP), Quorum sensing, Efflux pumps, Extracellular polymeric substances (EPS)

1. INTRODUCTION

Biofilms (BF) and antibiotic resistance are two of the most contentious and essential topics in modern medicine. Many new diseases and antibiotic-resistant variations of old ones have arisen in recent years, therefore the scientific community should keep these concerns in the forefront of their minds at all times. Combating the development of resistance to antibiotics is a pressing issue in public health around the world. Antibiotic resistance mechanisms in BFs have recently come into sharp focus due to the finding that standard explanations for antibiotic resistance do not account for them. (1) Several studies have assessed the antibiotic resistance profiles and BF-forming capability of various bacterial species' isolates, including those that generate BFs and those that do not.

1.1 Antibiotic resistance

Bacteria will develop resistance to antimicrobials as time goes on. The ability of bacteria and other germs to resist antibiotics produced by other animals develops with time. When germs develop mechanisms to

resist or eliminate the effects of antibiotics, this phenomenon is known as antimicrobial resistance (AMR). Antibiotics are very helpful in chemotherapy, but the development of bacteria that are immune to them is a major threat to global health. The medical industry and other sectors, like the food and agricultural industries, have an excess of them, which contributes to this. Antibiotic resistance is on the rise, making it harder to treat infectious diseases. One of the top ten global public health problems is antimicrobial resistance (AMR), according to a paper in Clinical Medicine. The World Health Organization (WHO) has just recognized this (2). Bacterial resistance to antibiotics is the result of a complicated process. Antibiotic resistance can develop for a variety of causes, some of which are linked to the bacteria's normal evolutionary process and others to poor healthcare environments.(3)(4) The mechanism by which a bacterial strain develops antibiotic resistance is fundamentally intricate. Bacterial variables linked to their natural evolutionary process and unfavourable healthcare environments are two of the many causes of antibiotic resistance. (5) Inadequate, incorrect, or excessive antibiotic usage, as well as a bad hospital environment, fall under the second category, while genetic mutation and natural selection are examples of the former (6). The ability to withstand antibiotics is passed on from one generation of bacteria to the next. Transferable genetic components, such as plasmids or transposons, provide a more involved mechanism for the horizontal transfer of resistance characteristics between strains, species, or genera (7). Clinical breakpoints to therapy offer the parameters for evaluating antibiotic resistance. (8), Internationally recognized standards are provided by three of the most prominent organizations: the Food and Drug Administration (FDA), the Clinical and Laboratory Standards Institute (CLSI), and the European Committee on Antimicrobial Susceptibility Testing (EUCAST).

When a bacterium shows resistance to numerous antibiotics, this phenomenon is known as multi-drug resistance (MDR). The literature makes use of a variety of definitions for MDR. For some bacterial infections, specialists from the CDC and the ECDC came up with a common definition of multidrug-resistant (MDR) in the context of acquired resistance. The term "multi drug-resistant" was used to describe bacteria that could withstand three or more types of antibiotics.(9)

Biofilm microbes attach polysaccharides and extracellular polymeric substances (EPS) to both living and nonliving surfaces; these compounds form the basis of bacterial films (BFs). A bacterial BF may originate from a single species of bacteria or from a combination of species. A variety of surfaces, both living and nonliving, can harbor BFs; these include tissues, medical devices, and more. Differences in gene expression between planktonic cells and BFs contribute to antimicrobial resistance and other characteristics. As a line of defense against drugs and immune cells, bacterial BFs are quite effective.(10) Because of their ability to withstand antibiotics and host immunity, BFs pose a serious risk to public health. Unlike isolated planktonic microbes, BFs have their own unique defence mechanisms.

Among the many hypotheses advanced by BFs is the idea that they limit the antibiotics' ability to penetrate, slow growth, set off an adaptive stress response, and lead to the emergence of antibiotic resistance genes (11). An additional layer of protection, the EPS matrix binds to or physically blocks the antibiotic.

1.2 The pathogen: Klebsiella Pneumoniae

One common gram-negative bacillus found in many environments and animal mucosas is Klebsiella pneumoniae (K. pneumoniae), which is a member of the Enterobacteriaceae family. In humans, it is a typical and essential component of the gut flora. It is well-known that K. pneumoniae can cause infections both in the community and in healthcare facilities. Immunocompromised people are more vulnerable to Klebsiella pneumoniae infections because the bacteria are opportunistic pathogens. New research suggests that Klebsiella pneumoniae can cause serious illnesses in the community (12). The most common

complications of a nosocomial infection with Klebsiella pneumoniae include UTIs, pneumonia, and septicaemia. More than 600,000 people died in 2019 as a result of antibiotic resistance (AMR) caused by Klebsiella pneumoniae, making it the third most deadly infection in the world. Over time, K. pneumoniae has demonstrated resistance to an array of medicines, starting with β-Lactam drugs. The bacteria in question manufacture β-lactamases, which break down the antibiotics' β-Lactam ring. (13), the inherent resistance to penicillin and other β-Lactam antibiotics in K. pneumoniae is caused by the ubiquitous SHV-1 penicillinase gene. The bacterium has also developed resistance to carbapenem and colistin, two families of antibiotics that are typically used to treat K. pneumoniae infections. In their 1988 study on the parameters that promote bacterial survival in chlorinated water supplies, LeChevallier et al. explained how K. pneumoniae could make BFs (Leche Vallier et al., 1988). Multiple investigations have shown that BFs produced by Klebsiella pneumoniae may be isolated from a variety of bodily fluids, including blood, wound swabs, and urine. It has been shown that structural phenotypes such as type 1 and 3 fimbriae and capsules are crucial for K. pneumoniae BF development.(14)

2. Literature Review

The Enterobacteriaceae family includes the gram-negative bacillus Klebsiella pneumoniae (K. pneumoniae), which can be found in both the environment and animal mucosa. In humans, it is a common and important part of the microbiome. It is well-known that Klebsiella pneumoniae can cause both hospital- and community-acquired pneumonia. Because Klebsiella pneumoniae are opportunistic pathogens, they can more easily infect individuals with impaired immune systems. However, recent studies have shown that Klebsiella pneumoniae can infect humans and cause severe infections. (15) (16)
Because of its dynamic resistance, pathophysiology, and transmission patterns, K. pneumoniae is one of six recognised "ESKAPE bugs" that constitute the biggest risk of nosocomial infections. (17)
In 2017, the World Health Organization (WHO) ranked this specific infection as one of the top three antibiotic-resistant bacteria on their Global Priority List. The Enterobacteriaceae family includes the other two diseases mentioned here as well. (18)
K. pneumoniae gradually became resistant to a wide range of treatments after initially being resistant to β-Lactam antibiotics. The bacterial enzymes that cause the breakdown of antibiotics' β-Lactam ring are called β-lactamases. K. pneumoniae naturally becomes resistant to many β-Lactam antibiotics, including penicillin, since SHV-1 penicillinase is present in every one of their chromosomes.(19) (20)
In 1988, LeChevallier et al. demonstrated that K. pneumoniae could produce BFs as part of an attempt to find out how bacteria survive in chlorinated water sources.(21)
Klebsiella pneumoniae (K. pneumoniae) is an antibiotic-resistant strain of a common healthcare-associated infection (HAI). Bacteria with the ability to create biofilms have gained a lot of attention. The purpose of this study was to identify Klebsiella pneumoniae biofilm-producing capabilities and drug resistance pattern.(22)(23)
In addition to making the ensuing disease more difficult to cure, biofilms can increase drug resistance and the bacterium's survivability by shielding it from host immune responses and the antipathogenic effects of drugs.(24)
Bacteria enhance their chances of surviving on hospital surfaces by forming biofilms.This makes it challenging for doctors to treat infected biomaterials and tissue surfaces with desiccation, benzalkonium chloride disinfection, or UV radiation, as these surfaces are resistant to these treatments. (25)
Researching the genes and regulatory mechanisms involved in biofilm formation is essential for

developing new approaches to control and prevention of biofilm-related illnesses.(26)(27)

One of the main reasons why K. pneumoniae can cause persistent nosocomial infections is because it forms BF and is resistant to antibiotics.(28) Research on antibiotic resistance profiles and BF development, as well as studies that evaluate the relationship between the two (29).There are two variables.(30)

Concerning the possible link between antibiotic resistance and BF development, the data is still not conclusive. A planktonic strain of Klebsiella pneumoniae needed an ampicillin minimum inhibitory dose of 2 µg/ml, according to research by Anderl et al. yet the same strain in BF was only mildly impacted by a concentration of 5000 µg/ml.(31) In contrast to non-BF producers, 93.3% of BF positive isolates were resistant to nalidixic acid, 83.3% to ampicillin, 73.3% to cefotaxime, and 80% to cotrimoxazole, according to another study. (32)

Though Cepas et al. looked into the link between antibiotic resistance and BF manufacturing potential, they discovered no correlation between multi drug resistance and BF formation potential. (33)(34)

The majority of bacteria seen in nature live in communities called biofilms. When cells within a biofilm are compared to their planktonic counterparts, they show significant physiological changes.(35)

Many various kinds of illnesses are linked to biofilms, and these infections can have devastating effects on patients.(36)

Some physical characteristics of biofilm infections make them resistant to antibiotics, including the ability to synthesise extracellular matrix, sluggish growth rates, altered production of drug targets, and successful exchange of resistance genes.(37)

This research delves into the biofilm lifecycle, phenotypic traits, and the significance of matrix and persister cells in the intrinsic resistance to antimicrobials of biofilms. Additionally, we detail the process by which biofilms can acquire resistance to antibiotics and spread resistance genes to other parts of the biofilm.(38)(39)

This work aimed to explore multiple virulence indicators to better understand the relationship between the antibiotic resistance profile and biofilm-forming capacities of K. pneumoniae isolates.(40)

Research Gaps & Challenges in Biofilm Formation and Antibiotic Resistance in *Klebsiella pneumoniae*

Even though we now know a lot more about how Klebsiella pneumoniae forms biofilms and how it resists antibiotics, several critical research gaps and challenges persist. Addressing these limitations is crucial for developing effective treatment strategies and combating antimicrobial resistance (AMR).

- The molecular pathways regulating biofilm initiation, maturation, and dispersal in *K. pneumoniae* remain incompletely understood. Further studies are needed to elucidate the genetic and environmental triggers influencing biofilm dynamics.
- The role of quorum sensing and its interplay with other regulatory networks in *K. pneumoniae* biofilm formation requires deeper investigation.
- The influence of host factors, such as immune responses and microbiota interactions, on biofilm development is not well characterized.

Discussion

Antibiotics were widely used, infection-related deaths plummeted. Along with these initiatives, vaccinations and improved personal hygiene greatly reduced the number of people affected by infectious diseases.

The rise of antibiotic resistance was, however, caused by bacterial evolution and the paucity of new

antibiotic discoveries. Furthermore, clinicians faced yet another hurdle to treatment due to the abundance of surface-associated bacterial biofilms.

As a result of its involvement in implanted medical devices and persistently infected cystic fibrosis, biofilms have become more important in the past forty years. A novel phenomenon that contributes to many infections is biofilm-related disorders. The purpose of this research was to try to paint a broad picture of the impact biofilms have on antibiotic-based clinical therapy.

The discovery of antibiotics marked a turning point in the history of modern medicine. There was a dramatic drop in deaths caused by infections after antibiotics were widely used. Hygienic practices and immunisations supplemented these efforts, greatly reducing suffering caused by infections. However, antibiotic resistance developed due to evolution in bacteria and insufficient funding for antibiotic research and development. Clinicians also had the additional challenge of surface-associated bacterial biofilms, which made therapy more difficult. Biofilms have gained significant attention in the last forty years, mainly because of their role in implanted medical devices and chronically infected cystic fibrosis. Infections that are associated with biofilms are a relatively new phenomenon. The overarching goal of this research was to provide light on how biofilms affect antibiotic-based clinical treatment.

This result supports previous research that found a favorable correlation between the antibiotic resistance profile and the biofilm-forming capabilities of XDR K. pneumoniae strains. Infections caused by Klebsiella pneumoniae, which is resistant to carbapenems and other "last line of defence" antibiotics, may be better treated with the use of this new data.

Bacterial communities known as biofilms are extremely resistant to antimicrobial treatments because they are organised and enclosed in an extracellular matrix that the bacteria generate themselves. By efficiently combating bacterial infections, antibiotics have sparked a medical revolution. But bacterial biofilms, which cause illnesses to last longer and antibiotic resistance to rise, pose a serious threat to their effectiveness. Biofilms, which consist of bacterial populations contained in an extracellular matrix that the bacteria produce, are extremely resistant to antimicrobial treatments.

- **Use of antibiotics in treating infections**

The mechanism of action of antibiotics is to disrupt vital bacterial functions, including β-lactam cell wall formation, tetracycline and aminoglycoside protein synthesis, and fluoroquinolone DNA replication.

Diseases caused by planktonic bacteria, which float freely in the water, are effectively treated with antibiotics. However, the effectiveness of bacteria is greatly reduced when they congregate into biofilms.

- **Problem caused by biofilms**

Chronic infections: Endocarditis, chronic wounds, and infections caused by medical devices are all examples of persistent infections that might be linked to biofilms.

Reduced antibiotic penetration: Antibiotic efficacy is diminished due to the extracellular polymeric substance (EPS) matrix's inhibition of antibiotic diffusion.

Increase resistance: Because the bacteria in biofilms are able to withstand medications, treating illnesses has become more challenging.

Immune evasion: Bacteria form biofilms to evade the host immune system, which results in chronic infections.

- **Mechanisms of antibiotic resistance in biofilms**

Biofilms increase the likelihood of antibiotic resistance in a number of ways

Physical barrier effect: Inadequate antibiotic concentrations in the biofilm's deeper layers are a result of the EPS matrix's restriction of antibiotic penetration.

Altered microenvironment: Metabolically inactive bacterial subpopulations are produced by nutrient and oxygen gradients within the biofilm; these subpopulations are less vulnerable to drugs that target active bacterial development.

Efflux pump activation: To prevent antibiotics from building up inside their cells, bacteria that form biofilms increase the activity of efflux pumps.

3. Conclusion

Klebsiella pneumoniae infections, which are drug-resistant and biofilm-forming, have been on the rise, which might worsen patient prognosis. Biofilm development is linked to 60–80% of hospital-acquired bacterial illnesses. Infections with comparable symptoms are more challenging to cure since the pathogen can evade detection by the host immune system and antibacterial drugs because of this protective layer. If we want to know how to create new drugs and treat them in the clinic, we need to know the molecular principles of biofilm growth and how it relates to antibiotic resistance. Klebsiella pneumoniae biofilm growth is controlled by both genetic and environmental factors. The production of biofilms in Klebsiella pneumoniae is mainly controlled by four genes: fibrae, polysaccharides, the efflux pump, and the quorum sensing system.

Consistent with the pervasiveness of BF across species, this review found that BF-forming isolates were common among clinical K. pneumoniae samples. Other bacterial species have also shown a similar frequency. This highlights the need for studies that change perspectives in order to concentrate on BF alternatives of planktonic bacteria in order to create efficient therapeutic substitutes. In order to motivate additional study, concrete proof of antibiotic resistance's mechanism is needed. The results of this study add to the growing amount of evidence suggesting that BFs play a role in antibiotic resistance. However, the authors also note that the capacity of bacteria to produce BFs is not necessarily an acquired trait. Disseminated germs from a BF may also develop antibiotic resistance, according to the available research.

4. Future directions

Targeting biofilm-specific pathways: (e.g., quorum sensing, EPS production, and persister cells) can enhance the efficacy of antimicrobial therapies.

Novel combination therapies including antibiotics with biofilm disruptors (such as quorum sensing inhibitors, phage therapy, and nanoparticles), will improve treatment outcomes in biofilm-associated *K. pneumoniae* infections.

Advancements in diagnostic techniques, particularly real-time imaging and molecular-based detection methods, will enable early identification and targeted intervention against *K. pneumoniae* biofilms.

Environmental and nosocomial control measures, such as surface coatings with anti-biofilm properties and stringent infection control strategies, will help in mitigating hospital-acquired *K. pneumoniae* infections.

Antibiotic resistance and biofilm formation are molecular processes that need to be better understood in future investigations of Klebsiella pneumoniae. This may be achieved by conducting transcriptomic, proteomic, and epigenetic studies. To address treatment failures, novel anti-biofilm medicines that target bacteriophages, antimicrobial peptides, nanoparticles, and quorum sensing inhibitors must be developed..

Early detection and focused treatments will also be made easier with better monitoring and diagnostic technologies, such as real-time imaging, AI-driven prediction models, and fast molecular testing methods. Healthcare facility-acquired Klebsiella pneumoniae biofilm infections should be managed by enhancing

surveillance procedures, developing medical device coatings that prevent biofilm formation, and conducting genomic investigations to identify genes related with resistance to biofilms. Possible new vaccine candidates and immunotherapies might emerge from research on host-pathogen interactions, including measures used by pathogens to evade the immune system and the effects of the microbiota. Transforming scientific findings into successful public and clinical health policies requires bolstering antimicrobial stewardship programs, encouraging multidisciplinary partnerships, and expanding funding for biofilm research. If we want to slow the spread of antibiotic-resistant K. pneumoniae biofilms, we must focus on these potential future possibilities.

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