Strategies and Emerging Mechanisms in Managing *Pseudomonas aeruginosa* Biofilm-Associated Antibiotic Resistance in Renal Catheters /A Review Article

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استراتيجيات وآليات ناشئة في إدارة مقاومة المضادات الحيوية المرتبطة بالأغشية الحيوية لبكتيريا *Pseudomonas aeruginosa* في قسطرة الكلى: مقالة مراجعة

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Abstract

Strategies and mechanisms in controlling *Pseudomonas aeruginosa* resistance to biofilm-associated with renal catheters are a serious concern. Renal catheters are widely used in hospitals for numerous urological disorders. However, they are the main cause of bacterial infections, especially *P. aeruginosa,* when used for a long time. The mechanism of biofilm-associated antibiotic resistance of *P. aeruginosa* in renal catheters is complex and has not been efficiently managed. This review debates certain strategies and mechanisms associated with *P. aeruginosa* biofilm antibiotic resistance in cases with renal catheters, including the prevention of biofilm formation, eradication of biofilm, and reducing biofilm-associated antibiotic

resistance and virulence. Also, more focusing on strategies are presented in this review, in clinical trials to determine their effectiveness in managing renal biofilms in *P. aeruginosa* patients. With all the proper management of these infections that occur as a result of biofilms will promote the recovery of these patients.

Keywords: *Pseudomonas aeruginosa***, Biofilm, Antibiotic resistance, Renal catheters**

المستخلص

إن الاستراتيجيات والآليات المستخدمة في التحكم في مقاومة بكتيريا *P. aeruginosa* المرتبطة بالأغشية الحيوية Biofilm في حالات قسطرة الكلى تشكل مصدر قلق بالغ في هذا المجال. تُستخدم قسطرة الكلى على نطاق واسع في المستشفيات لعلاج العديد من الاضطرابات البولية. ومع ذلك، فهي السبب الرئيسي للعدوى البكتيرية، وخاصة بكتيريا *P. aeruginosa* ، عند استخدامها لفترة طويلة. إن آلية مقاومة تلك البكتيريا للمضادات الحيوية والمرتبطة بالأغشية الحيوية في قسطرة الكلى معقدة ولم يتم السيطرة عليها بشكل جيد.في هذه المراجعة يتم مناقشة بعض الاستراتيجيات والآليات المرتبطة بمقاومة البكتيريا *P. aeruginosa* للمضادات الحيوية في حالات القسطرة الكلوية، بما في ذلك منع تكوين الأغشية الحيوية، والقضاء على تلك الاغشية، والحد من مقاومة المضادات الحيوية المرتبطة بها وقدرتها على التسبب في الأمراض. التركيز على تلك الاستراتيجيات والطرق المطروحه في هذه الدراسة والتجارب السريرية لتحديد مدى فعاليتها في إدارة الأغشية الحيوية الكلوية لدى المرضى ممن لديهم أصابه ببكتريا *P. aeruginosa* مع كل طرق السيطرة على هذه الالتهابات التي تحدث نتيجة للأغشية الحيوية، سيسمح بشكل جيد لتعافي هؤلاء المرضى.

الكلمات المفتاحية: الزائفة الزنجارية، الأغشية الحيوية، مقاومة المضادات الحيوية ، قسطرة الكلى

Introduction

Long-term indwelling medical devices that are biofouling run the risk of catheter-associated urinary tract infections (CAUTIs) and bloodstream infections as a result of the migration of microorganisms that form biofilms. Because biofilm-forming bacteria, such as Pseudomonas aeruginosa and Enterobacter cloacae, are lodged in biofilms, their infectiousogenicity endures despite antibiotic treatment and immunological response. By the middle of this century, biofilm-associated CAUTIs are predicted to become pandemic due to the increased appearance of hypervirulence and antibiotic-resistant strains. Thus, there is an urgent need for more concentrated study on novel approaches and their developing mechanisms for treating drug-resistant biofilm-associated bacterial infections in long-term indwelling medical catheters. (Mancuso *et al*., 2024).

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Background and Significance

Biofilms are tightly clustered groups of bacteria that can develop on various surfaces, including biotic (inside the human body) and abiotic (such as medical devices, synthetic materials) locations. Biofilm formation starts with the reversible attachment of bacteria to the surface. This is followed by an irreversible adhesion, which involves the secretion of extracellular polymeric substances (EPS) and the formation of a three-dimensional structure. Biofilms can form in both natural and artificial environments, on the surface of abiotic materials, or on tissues or organs of a living organism.

Of special importance in medicine are biofilms generated in association with indwelling catheters, prostheses, heart valves, reconstructive joints, artificial devices, etc. Biofilm development on medical devices leads to persistent bacterial infections that are highly resistant to antibiotics and the host immune system. Chronic infections associated with biofilms can only be treated by the removal of the infected device. Urinary catheters that are indwelling inside the bladder are important biomedical devices used to manage surgeries, urinary tract diseases, and mental disorders. 815 million urinary catheters are estimated to be sold worldwide in 2018. Catheter-associated urinary tract infections (CAUTIs) are the most common healthcare-acquired infections globally and are associated with increased morbidity, mortality, and economic burden. Biofilm-associated antibiotic resistance (ABR) mechanisms in *Pseudomonas aeruginosa* are the topic of interest (Kamaruzzaman *et al*., 2018).

Pseudomonas aeruginosa Biofilm Formation

Pseudomonas aeruginosa is a Gram-negative, motile, and rod-shaped bacterium belonging to the pseudomonad group. It is known for its remarkable metabolic versatility, allowing it to thrive in various environments, including soil, water, and even on human tissues, as it can opportunistically infect patients with relatively intact immunity. Infection by *P. aeruginosa*, however, is of particular concern among immune-compromised individuals and in the management of lengthy diseases. It is an opportunistic pathogen categorized as a "critical priority" bacterium by the World Health Organization (WHO) due to its global threat. The most concerning factor about this bacterium is its hyper-resistance to antibiotics, which has been occluded primarily via biofilm production (Sindeldecker & Stoodley, 2021).

Biofilm is a multifaceted aggregate of bacteria covered in a self-generated matrix of extracellular polymeric substances (EPS). One of the key strategies for the existence of species against unpredicted changes of living environments such as temperature and nutrient accessibility. In a broad sense, biofilms are sticky, surface-attached aggregates of microbial cells, protecting cells against adverse conditions (e.g., grazing, predation, antibiotics) by producing EPS. *P. aeruginosa* is considered a well-known biofilm former, making it an excellent model for studying biofilm formation. Biofilms are regarded as the default mode of growth of bacteria in nature (Thi *et al.,* 2020). About 80% of chronic infections in humans are associated with biofilms, contributing to human mortality by 550,000 victims/annum. More understanding of the biofilm conformation and structure, and the molecular mechanisms essential for the antimicrobial tolerance of bacteria growing within a biofilm, are energetic for the design of effective strategies

to manage, prevent and more essentially eradicate biofilm-associated infections.

For clinical isolates, biofilms develop at any surface (medical devices, catheters) colonized by *P. aeruginosa*. Bacteria within a biofilm can escape host immune responses and resist antimicrobial treatments up to thousands of times more than their planktonic counterparts. Biofilms predictably evolve under external selective pressure (antibiotics, UV light) and are genetically less stable. Biofilm development is governed by a complex interplay of various biochemical, molecular, environmental, and physical factors, including surface properties, liquid streaming, circle flow, shear stress, and viscosity. It has been shown that *P. aeruginosa* biofilm matrix primarily encompasses polysaccharides, extracellular DNA (eDNA), proteins, and lipids.

Biofilm Structure and Characteristics

The biofilm is defined as a complex aggregate of bacteria (micro-colonies) encased in a self-generated matrix of extracellular polymeric substances (EPS). Most animal and plant-associated bacteria, including the human pathogen *Pseudomonas aeruginosa*, have the ability to form biofilms on biotic and abiotic surfaces. *P. aeruginosa* is an opportunistic pathogen that causes acute infections in immunocompromised patients and chronic infections in individuals with cystic fibrosis, burns or extensive skin injuries. It produces a polysaccharide pellicle that is tightly attached to the plastic inner surface of respiratory ventilators and can colonize, contaminating the expiratory airflow. Biofilms allow bacteria to escape from the host immune responses and resist antimicrobial treatments. Bacteria growing within biofilms can survive antimicrobials up to 1000 times more than susceptible

planktonic counterparts (Thi *et al*., 2020). *P. aeruginosa* has long been recognized as a strong biofilm bacterium. Biofilm structure is polymicrobial and contains a diverse community of micro-colonies consisting of different bacterial species cooperating with one another.

Biofilm EPS matrix is a complex assortment that primarily involves polysaccharides, extracellular DNA (eDNA), proteins and lipids. It is commonly known that the main and most prevalent structural element is composed of polysaccharides. The physical barrier that this EPS matrix creates stops amikacin and imipenem from being transported, which adds to the antibiotic resistance of biofilms. Furthermore, it has been demonstrated that the EPS matrix is important in the architecture, upkeep, development, and structural integrity of biofilms. More importantly, depending on the types of EPSs the bacteria display, the EPS matrix can both positively and negatively affect how effective antibiotics are against biofilms. Gaining more insight into the makeup and structure of *P. aeruginosa* biofilms that grow on and inside indwelling medical devices is critically important. Only by learning this information can practical methods for managing and eliminating biofilm-associated (Luo *et al*., 2020).

Virulence Factors

To establish infection*, P. aeruginos*a must overcome early host immune response stages. When colonizing a surface, planktonic bacteria begin transitioning to biofilm growth mode, allowing them to resist immune attack (*P. aeruginosa* biofilms are particularly adept at resisting phagocytosis) and more effectively manage the external nutrient supply. This process begins with the attachment of motile, flagellated bacteria to surfaces, mediated by

Jetz-type IV pili (T4P). Attachment triggers the biogenesis of T4P, which typically adhere bacteria to surfaces through a combination of twitching motility and pilus retraction. Surface adherence also triggers the regulation of biofilm-forming exopolysaccharides such as alginate and pel, resulting in the formation of a sugar-coated bacterial cluster that aggregates with other organisms within the aqueous solution (Silva *et al*., 2023).

P. aeruginosa has a proprietary application of virulence factors that are sub-classified into distinct activities and modes of action with different targets. The overall pathogenicity of *P. aeruginosa* is multifactorial, meaning that diseases arise from the interplay among all virulence factors and the host environment. The precise influence of each on specific pathologies is often difficult to untangle. *P. aeruginosa* possesses several protein secretion systems that have different activities against different hosts and competitors that vary depending on the biological context. This reduces their applicability as predictable virulence factors across different environments (Nolan & Behrends, 2021).

Antibiotic Resistance in *Pseudomonas aeruginosa* Biofilms

Biofilm-associated *Pseudomonas aeruginosa* shows increased antibiotic resistance and decreased efficacy of treatment with higher medicament concentrations (Abbas *et al*., 2018). Superior resistance is an intrinsic feature of *P. aeruginosa* owing to several antibiotic resistance mechanisms. In addition, the presence of biofilm around the microorganism makes this pathogen more dearly paid with antibiotics. Biofilm presents another structure, which in general protects the microorganism from injury, an important barrier to penetration of antibiotics, which can make them

resistant to heavy doses of antibiotic drugs. Biofilms limit the diffusion of antibiotics into them by 100 to 1000 times more than the free organisms present in the same growth medium, an effect that is higher with larger molecules. Often biofilm-associated microorganisms show no efficacy of 1000 times the Minimum Inhibitory Concentrations (MIC) of antibiotics when tested as planktonic organisms. Accumulation of inactivating enzymes in high concentration in biofilm structure leads to the greater inactivation of antibiotics compared to non-biofilm-associated cells. It was also shown that biofilm exopolysaccharide gives an extra protective wall by trapping the antibiotic into their matrix, preventing it from reaching their target site (Sindeldecker & Stoodley, 2021). Biofilm-associated organisms show phenotypic heterogeneity in the form of metabolically less active and even dormant microorganisms, which do not show any effect of antibiotics and prevent their killing due to cessation of their target actions. Biofilm-associated *P. aeruginosa* widening the efflux pump activity of antibiotics is another mode of antibiotic resistance. There is discussion of selective pressure, a feature of biofilms associated with *P. aeruginosa* which increase the mutation frequency in biofilm cells, hence ultimately leading to enhanced multi-drug resistance.

Mechanisms of Resistance

Biofilm development drastically alters antibiotic resistance in *P. aeruginosa.* Biofilm-associated antibiotic resistance mechanisms encompass a variety of phenotypic adaptations. Low penetration of antibiotics into biofilm is caused by diffusive exclusion in hydrophobic biofilms due to the higher viscosity and exopolysaccharide (EPS) matrix consisting of

polysaccharides. Poor nutrient and oxygen distribution in biofilms leads to persister cells-cohort formation. *P. aeruginosa* biofilms also show reduced metabolic activity due to nitrogen starvation, iron depletion, alkaline phosphatase production, cell–cell signaling and downregulation of genes transcription for ribosomes, efflux pumps, enzymes, and phosphofructokinase (Abbas *et al*., 2018). These changes lead to tolerance even in susceptible phenotypes. Biochemical analyses reveal the mediation role of a complementary system, complemented with other oxido-reductive systems that endow biofilm cell types more resistance to antibiotics than their planktonic counterparts. Biofilms exhibit a low, yet significant, level of drug resistance in comparison to planktonic cultures even in the absence of cell–cell communication and metabolically inactive cells (Pai *et al*., 2023).

Impact on Treatment Outcomes

Resistance to therapy in *Pseudomonas aeruginosa* biofilms poses treatment challenges and has been associated with treatment failure since the 1980s. Resistance has been attributed to the reduced penetration of antibiotics within biofilms, the induction of resistance mechanisms, and the reduction in active cell division within biofilms.

Failure to eradicate biofilm infections can result in severe complications, such as septicemia related to the infected central venous catheter, resulting in high mortality. Treatment responses vary significantly, ranging from patients who are cured to those who are non-responsive. Antimicrobial resistance in Pseudomonas aeruginosa biofilms has been presented as a key mechanism of biofilm-associated treatment failure. Nevertheless, *P. aeruginosa* biofilm-associated infections are often susceptible to commonly

used antibiotics in vitro. Understanding the consequences of antibiotic resistance on treatment success is central to treating biofilm-associated infections (Glen & Lamont, 2021).

Current Challenges in Managing Antibiotic Resistance in Renal Catheters

Catheter-associated urinary tract infection (CAUTI) remains the most prevalent hospital-acquired infection, accounting for approximately 80% of all UTIs in hospitalized patients leading to significant healthcare expenses. CAUTIs typically develop as a consequence of indwelling urinary catheters which act as persistent infection foci in the urinary tract for many years. Microorganisms attached to catheter surfaces can develop biofilms which are a community of microorganisms in a self-produced extracellular polymeric substances (EPS) matrix that adhere to each other and/or to a surface. Biofilms protect microorganisms against host immune responses and significantly reduce susceptibility against antibiotics thereby offering a selective environment for normal flora and pathogen coexistence. Although much progress has been made in understanding the pathogenesis of biofilm infections, their prevention remains a significant challenge (Anjum *et al.,* 2017).

Biofilms formed on urinary catheters are mainly composed of uropathogenic strains, of which Pseudomonas aeruginosa is one of the most common bacteria and is a highly problematic pathogen particularly in patients with an indwelling catheter. Pseudomonas aeruginosa is characterized by a diverse antibiotic resistance mechanism and it has been shown to gain multidrug resistance when exposed to β-lactams. Indwelling ureteral catheters significantly increase the risk of developing Pseudomonas

aeruginosa UTI and have been shown to harbor more drug-resistant Pseudomonas aeruginosa than a control group. Pseudomonas aeruginosa is particularly problematic in patients on chronic catheterization and patients with spinal cord injury (SCI). SCIs result in damage to central nervous tissue leading to loss of voluntary control of the bladder so the routine could be the insertion of an indwelling balloon-tip Foley catheter to drain urine from the urinary bladder and avoid CTs is better understood (Gaglione *et al*., 2022).

Innovative Strategies for Combating Antibiotic Resistance

The affection of bacteria and their inevitable resistance against antibiotics is threatening the well-being of mankind. No antibiotic has been added in the pharmaceutical chain since the last couple of decades to sustain the onslaught of superbugs (Anjum *et al*., 2017). The infections by bacteria are still dealt with the limited arsenal of antibiotics. The dramatic rise in Antibiotic Resistance (ABR) is largely attributable to the mutations in bacterial gene expression in succession to constant exposure to antibiotics. Occasional encounter with antibiotics employed in therapeutics allows the surviving population of micro-organisms to adopt genetic changes that are significant in enabling resistance against recurring attacks (Baptista *et al.*, 2018). Other than this, the appearance of acquired resistance is also suggestive of the lateral transfer of genetic material among bacteria. The emergence of biofilm colonies may provide another driving force for the development of resistance. The polymeric matrix not only provides protection to the resident bacteria against the engulfment of cleansing agents but also promotes local conditioning that makes them gradually resistant to antibiotics. The biofilm communities have been reported to be 1000 times resistant as compared to

a planktonic population of the same strain. As a consequence of the above phenomena, bacteria like ESKAPE pathogens (*Staphylococcus aureus, Enterococcus faecium, Acinetobacter baumannii, Klebsiella pneumoniae, Pseudomonas aeruginosa*, and Enterobacter species) posing formidable threats to human life and health are already resistant against the currently available antibiotics. Hence, there is an imminent and dire need for the action plan to combat ABR if mankind desires to check the return of the preantibiotic days. In view of the above context, recent innovative strategies that are either multidisciplinary in nature or operate via unexplored mechanisms or target root causes of the problem have been collected together mostly emphasizing their scientific plausibility and efficacy against bacterial infections in general and Pseudomonas aeruginosa biofilm infection in renal catheters in particular.

Nanotechnology-based Approaches

Recent decades have seen a sharp rise in global antibiotic divergence, with multi-drug resistant strains blooming. As a result, drug-resistant bacteria and their corresponding infections have posed concerns across the world, thereby evoking the urgent need for alternative strategies to combat this escalating threat. Numerous micro- and nanotechnologies-based approaches have been, or are being, actively explored for this purpose. Nanotechnology, which was explicitly defined by the United States National Nanotechnology Initiative, refers to engineered structures, devices, or systems produced with specific properties at dimensions less than 100 nanometers (nm). Opportunities to improve the choice of intervention include the use of nanomaterials that exhibit particle size-dependent properties, allowing for

modifications of physical, chemical, or biological characteristics, thus enabling higher efficacy, and drug delivery systems that would release drugs selectively in treated areas. This review, having summarised the action mechanisms of various typical micro- and nanotechnologies, aims to explore current explorative and novel strategies involving micro- and nanotechnologies to target biofilms and mitigate biofilm-related drug resistance (Rao *et al.*, 2021).

Nanotechnology, defined as an area of science and engineering smaller than 100 nm, has gained substantial research momentum among the biomedical community in recent years, presenting an untapped avenue for combatting advanced multi-drug resistant bacteria and their biofilms. Above a certain size, nanoparticles exhibit particle size-dependent properties, which may involve the modifications of physical, chemical, or biological characteristics as size or dimension changes. Likewise, micro- and nanotechnologies make use of numerous types of physical, chemical, biological, or engineering responses, such as electrostatic, mechanical, adhesive, thermal reaction, or light-induced processes for the purpose of drug release. In biomedicine, there is a growing interest in the exploration of micro- and nanotechnology-based approaches, including micro- and nanoparticles, microgels, bioengineered moving devices, and novel coatings for the mitigation of biofilm-related infection (Vallet-Regí *et al.*, 2019).

Quorum Sensing Inhibitors

As biofilms protect bacteria from all kinds of antimicrobials, finding ways to dispel biofilms is one of the major problems that researchers are trying to get hold of. One innovative way to dispel biofilm bacteria is by disrupting their quorum sensing that biofilm bacteria depend on to live.

Quorum sensing is a process in which bacteria produce, detect and respond to signal molecules by which they send out a message to tell other bacteria to express their genes that will help them in biofilm formation. The bacteria will have higher confidence to form a biofilm when and only when the signal molecules they produce reach a density that is sufficiently high enough (Vogel *et al*., 2020). As biofilm formation is a cooperative process that is initiated only when a sufficient number of bacteria are present, quorum sensing is believed to be a requirement for biofilm establishment. Quorum sensing inhibitors are compounds that interfere with one of the steps in the quorum sensing process. Research efforts have been directed toward the discovery of natural and synthetic antibacterial combinations that likewise act as quorum sensing inhibitors. Common natural quorum sensing inhibitors are a compound name, furanones, that produced by a certain type the red alga named *Delisea pulchra* and halogenated furanones produced by certain marine bacterium known as *Phaeobacter inhibens* (Perković *et al*., 2023).

Emerging Mechanisms and Technologies

The emergence of new antibiotic-resistant pathogens, such as those that cause bladder infections, is becoming a serious global health challenge. Antibiotic-resistant strains of *Pseudomonas aeruginosa* were recently reported to cause a urinary tract infection (UTI) in a 1000-bed hospital in India that relied on indwelling catheters for a long-term placement (Pai *et al.,* 2023). These macromolecule- or metal-based (e.g., silver) antimicrobials that acquire inherent antibiotic resistance through biofilm formation and efflux pumps might enter the bloodstream, causing bacteremia, septic shock, and even death. Further, double negative gram bacteria, two-component

systems (TCSs), quorum sensing (QS), and secretomics have all contributed to the biofilm-forming ability and antibiotic resistance. Therefore, more studies need to address existing knowledge gaps in the interaction of biofilms and plant or nanomaterial-based antimicrobials, as well as the identification and characterization of biofilm-associated protein targets (Pai *et al.,* 2023).

The clustered regularly interspersed short palindromic repeats (CRISPR) systems are prokaryotic defense mechanisms against foreign nucleic acids that are present in at least 50% of archaea and 40% of bacteria. Two classes of these CRISPR systems exist. Class 1 systems (types I, III, and IV) contain multiple proteins, while class II systems (types II, V, and VI) contain only one protein, called the CRISPR-associated (Cas) endonuclease. Initially believed to limit plasmid/naked DNA invasion, it has become clear that these systems can also target viruses (phages), as well as RNA-targeting systems. Biofilms are defined as a structured community of microorganisms attached to surfaces, typically encased in an extracellular polymeric substance. Biofilms are physiologically different from their planktonic counterparts. Biofilms can also be resistant to a variety of antimicrobials, including biocides and disinfectants. In particular, because of their high initial resistance, biofilm-encased bacteria can endure high concentrations of antimicrobials that would otherwise kill planktonic cells. The importance of biofilms in chronic human infections and their detrimental impact on human health and productivity have made them the fiercest battlegrounds in the war against microorganisms (Rao *et al*., 2021).

CRISPR-Cas Systems in Biofilm Eradication

The CRISPR-Cas systems, which are well-known for guarding prokaryotic cells from incoming nucleic acids, show potential in the removal of biofilms. They can be used to develop novel antimicrobials that can specifically target and eradicate microorganisms that form biofilms, either on their own or in conjunction with antibiotics. Preference must be given to CRISPR-Cas systems with optimized, manufactured protospacers that match virulence- or survival-enhancing genes, often known as "Fleet Attacks," rather than naturally occurring CRISPR-Cas systems. These genes may be linked to pathogenicity, virulence, persistence, biofilm development, and antibiotic resistance. CRISPR-Cas systems target the desired gene using a single adaptive spacer. When creating these strategies, a number of factors need to be taken into account (Mayorga-Ramos *et al.*, 2023). The development of biocontrol, barrier-building, and eradication-focused approaches

By neutralizing ARGs, the CRISPR-Cas system restores bacterial sensitivity to antibiotics, functioning as an antimicrobial agent. Researchers have resensitized drug-resistant bacteria to antibiotics by targeting genes on the plasmids of pathogenic bacteria, particularly ARGs, using the CRISPR-Cas system. Through a technique known as "Curing," the CRISPR-Cas system can be specially designed to target and destroy plasmids containing ARGs. Research has validated the function of the CRISPR-Cas system in resensitizing *S. aureus* to methicillin and kanamycin. Nevertheless, the method only eliminated high-copy plasmids from a few bacterial colonies, and treated cells regained sensitivity to resistance to ampicillin, cefazolin, cefuroxime, ceftriaxone, and cefotaxime. The CRISPR-Cas9 system is capable of eliminating resistance gene plasmids in their entirety (Wu *et al*., 2021).

Clinical Implications and Future Directions

The review's conclusions have significant therapeutic ramifications for the treatment of antibiotic resistance linked to Pseudomonas aeruginosa biofilm in renal catheters. The review emphasizes the promise of novel approaches to reduce the formation of biofilms and antibiotic resistance, including the use of nanomaterials, quorum sensing inhibitors, bacteriophage treatment, and antimicrobial peptides. As these tactics are refined and tested, they may present fresh treatment alternatives for the management of P. aeruginosa-caused catheter-associated UTIs. (Reig *et al.*, 2022). (Anjum *et al.*, 2017) The study also covers a number of recently developed mechanisms of action, such as photothermal therapy, electrochemical methods, and the application of electric fields, for the treatment of biofilm-associated infections.

These processes could lead to the development of novel therapeutic modalities or improve the effectiveness of currently available ones. To completely comprehend their processes of action and create useful applications, more study is necessary. It is advised that physicians keep in mind the difficulties caused by biofilm-associated antibiotic resistance and take into account the possibilities of novel approaches and developing mechanisms in their clinical practice in light of the review's conclusions. To effectively prevent and treat catheter-associated UTIs, researchers and clinicians must work together to translate these results into therapies.

Translational Potential of Research Findings

The scientific results or innovations covered in this review's potential for translation into clinical settings. This covers talks about the necessity of

these studies, the potential applications of the results, the advantages that are highlighted, and any potential drawbacks.

The formation of biofilms on renal catheters or renal replacement devices is a commonly observed occurrence that leads to the development of complicated CA-UTIs. Biofilm-associated bacteria embedded in EPSs are protected from the action of several drugs, disinfectants, sanitizers, and also the immune system of the host (Anjum *et al*., 2017). Biofilm formation is a major challenge in hospital-acquired infections. The incidence of biofilm-associated infection, due to pathogenic bacteria, is rising at an alarming rate, in dialysis patients. Pseudomonas aeruginosa has infected indwelling renal replacement devices, leading to high morbidity and mortality. Understanding the unique physiology of biofilms is crucial to combating such infections. The review discusses the innovative strategies developed by great minds to avoid biofilm formation on the catheter surfaces. It discusses the mechanisms of action of the innovative strategies and how these non-bactericidal strategies have an impact on the biofilm physiology. Understanding the physiology of biofilms and combating them with innovative strategies will present new tools, technologies, and opportunities to solve the infection problem, which can be translated into clinical settings (Kamaruzzaman *et al*., 1970).

Recommendations for Clinical Practice

The following recommendations are proposed for practitioners: the close monitoring of catheterized patients, particularly those undergoing repeated irrigation. This should include tracker evaluation in newly implanted catheters, together with implementation and validation of biofilm eradication protocols in cases where impaction is detected. Clinicians should bear in

mind that current lock solutions have significant limitations. Consequently, a combination of different agents with specific activity against biofilms, like enzymes or antibodies, is proposed to improve patient treatment. Finally, healthcare professionals should be made aware of the aetiologic role of nonfermentative Gram-negative bacteria, namely Pseudomonas aeruginosa, in biofilm-associated UTIs.

Conclusion and Summary

Urinary tract infections (UTIs) are one of the most prevalent hospital-acquired infections globally. The continuous bladder drainage is performed using a urethral catheter for the management of various medical and surgical conditions. However, recurrent catheter-associated UTIs (CAUTIs) are among the most common types of nosocomial infections caused mainly by *Pseudomonas aeruginosa*. The central mechanism by which bacteria become resistant to antibiotic therapy inside implanted prosthetic devices is the formation of biofilms. This review aimed to summarize the novel, emerging, and innovative strategies, anti-biofilm compounds, and proposed mechanisms to manage *Pseudomonas aeruginosa* biofilm-associated antibiotic resistance in renal catheters.

Biofilms are sessile, well-organized, and structured colonies of microorganisms attached to biotic and abiotic surfaces embedded in an extracellular polymeric matrix secreted by the microorganisms. Biofilms can develop on different surfaces, including plastic and metal ligatures, which are frequently used in catheterized patients and artificial devices such as prosthetic heart valves, artificial joints, vascular grafts, and intrauterine devices. The architecture of biofilms is highly complex and varies on different

substrata and environmental conditions. Biofilms are colonized by a variety of microorganisms, including bacteria, yeasts, protozoans, and algae. Usually, a few species dominate a specific environment. However, under certain conditions, opportunistic pathogens can also settle in biofilms (Gebreyohannes *et al*., 2019).

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