

Deciphering the Contribution of Bacterial Biofilms to Persistent Chronic Infections and Multidrug Antibiotic Resistance Mechanisms

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Abstract

Bacterial biofilms are organized microbial communities that attach to living or nonliving surfaces and become embedded in a self-produced extracellular matrix composed of polysaccharides, proteins, and extracellular DNA. This growth pattern promotes survival under adverse environmental conditions and contributes to the persistence of infections. This overview examines biofilm development, mechanisms underlying reduced antibiotic susceptibility, and approaches to preventing and controlling biofilm-associated infections. Biofilm formation generally proceeds through initial surface attachment, irreversible adhesion, microcolony formation, maturation into a three-dimensional structure, and dispersal of cells capable of colonizing additional surfaces. Adhesion molecules, extracellular matrix production, and quorum-sensing systems contribute to the establishment and organization of biofilms in many pathogenic bacteria. Biofilms are clinically important because of their association with chronic infections and infections involving implanted medical devices. Their persistence reflects several interacting mechanisms, including limited penetration of some antibiotics, altered bacterial metabolic activity, and the presence of dormant persister cells. Biofilm communities can also facilitate the transfer of genes that confer antibiotic resistance. Biofilm-associated antibiotic tolerance and genetically mediated resistance represent distinct mechanisms, both of which can complicate bacterial eradication. Preventive and therapeutic approaches include antimicrobial surface coatings, combination antibiotic therapy, enzymatic disruption of the extracellular

matrix, and removal of contaminated medical devices when clinically indicated. Emerging approaches, including nanotechnology-based interventions and bacteriophage therapy, offer additional possibilities but require further evaluation of their effectiveness and applicability. The discussion highlights the importance of addressing bacterial cells, the protective matrix, and colonized surfaces when developing biofilm-control strategies. Further research should clarify how these approaches can be integrated to improve the prevention and management of persistent biofilm-associated infections.

Keywords: Bacterial Biofilms; Antibiotic Tolerance; Antibiotic Resistance; Chronic Infections; Quorum Sensing

Introduction

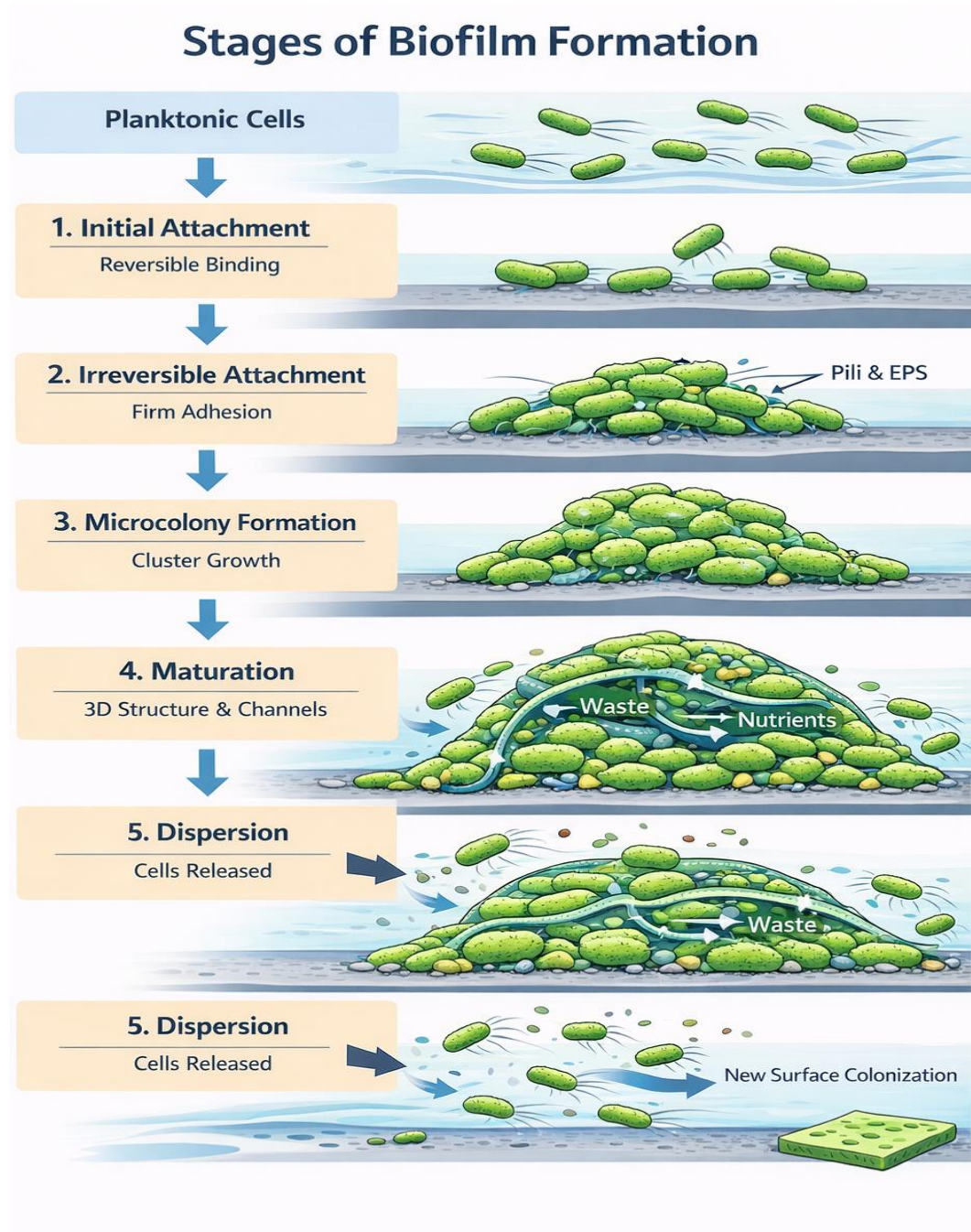
Biofilms are complicated and highly structured microbial communities that originate from microorganisms. This mode of development is now supposed to be the primary type of microbial life in the environment and clinically, as opposed to the previous belief that bacteria exist primarily in a free floating planktonic state (1,2). Microorganisms within biofilms exhibit unique physiological and genetic changes that make them more resistant to stressful and hostile environments.

Research has greatly increased the knowledge of biofilms. Previous studies found that microorganisms naturally favor the attachment and formation of communities on surfaces over being free-living cells (1). Biofilms can develop on many biotic and abiotic substrates (3,4). They are widely distributed and thus have a significant role in healthcare, industrial processes, and environmental biology. Biofilms have a number of key traits, including the extracellular polymeric matrix. (3,10). In addition, the matrix facilitates communication among the bacteria by quorum sensing, a cell-density-dependent signaling system that controls the expression of bacterial genes and coordinated microbial behavior (5,6). In the later b of the biofilm, some of the microorganisms break off and travel to other sites where the cycle repeats with the formation of new biofilms. Medical perspectives: Biofilms are considered as health problems because of their close association to chronic and recurring infections and the transfer and maintenance of the microbial population between environment. *P. aeruginosa*, *S. aureus* and *E. coli* are a few pathogenic microorganisms that have the amazing capability of forming biofilms, particularly on implanted medical devices and in immunocompromised patients (6, 9). One of the major possessions of biofilms is

biofilm resistance it is often difficult to treat these infections and can necessitate repeated or continuous treatment. The increased resistance of the biofilm can be accredited to a mixture of influences such as the poor penetration of the antibiotics in the biofilm, physical changes that occur within the biofilm (e.g. oxygen limitation and pH changes), and the attendance of dormant persevered cells that are less susceptible to the antibiotics (7,8). (8) Aside from their medical importance, biofilms are also important in environmental and industrial applications. They are involved in beneficial environmental processes such as wastewater treatment, degradation of contaminants and nutrient recycling (10). On the other hand, biofouling is a problem with industrial machinery and water supply systems due to the formation of biofilm, causing significant economic losses and lowering the efficiencies of the systems. In summary, biofilms play a pivotal role in microbial ecology and have diverse implications in medicine, industry, and the environment.

The Development of Biofilm

Formation is a multistep process and it is well regulated in which planktonic bacteria are converted to an organized community on surfaces. The first stage is reversible attachment, in which bacterial cells physically attach to the surface with weak forces, for example, electrostatic and van der Waals attractions (11,12). Adhesion is still temporary and can be easily broken. The bacteria then develop into irreversible adhesion, in which they start to produce surface appendages such as pili and extracellular polysaccharides that enhance the ability to attach to the surface. During this stage there are profound changes in the patterns of gene expression among the bacteria that help to establish a biofilm (12,13). Once the microorganisms have established stable attachment they multiply and form small cell aggregates called microcolonies. In this stage, the bacterial cells are actively producing extracellular polymeric substances (EPS), the building blocks of the structure of the biofilm matrix. Concurrently, intercellular mechanisms of communication like quorum sensing allow coordinated communication between bacterial cells (13,14). As the biofilm matures, the biofilm moves into the maturation phase, in which an organized, 3-dimensional structure with interconnected water channels develops. These channels carry nutrients and remove metabolic waste products. Mature biofilms also have enhanced resistance to antimicrobial agents and adverse environmental conditions (14,15). The last step is called dispersion, where some bacteria in the established biofilm are released and reappear to the planktonic state. Released cells can move and settle on new surfaces, and start new cycles of biofilm formation and spread (11,15).



Biofilm development stages (Adapted from Stoodley et al., 2002)

Pathogenic Bacteria in Biofilm Formation (with in-text citations)

Biofilms are an important contributor to chronic and recurrent infections and pathogenic bacteria are essential players in developing, initiating and maintaining a biofilm. These microorganisms have adaptive mechanisms that allow them to adhere, persist in a hostile environment, evade the immune system and resist antimicrobial drugs. Thus, the

aptitude to procedure biofilm is considered as one of the virulence factors of many medically important bacteria (18,19). The initial stage in the formation of a biofilm is the adhesion of bacteria to living or inert surfaces. Pathogens like *Staphylococcus aureus* and *Pseudomonas aeruginosa* have special surface structures such as pili, fimbriae, and adhesion proteins, which are used to facilitate adherence and colonization (19,20). This attachment process is of special significance with medical devices like catheters, prosthetic devices and other body-inhabiting materials, and in infections linked to such devices. After attachment, pathogenic bacteria actively excrete extracellular polymeric substances (EPS), which form the structural structure of the biofilm. The EPS matrix protects the microbial community from antibiotics and the host immune response and helps to stabilize the community (20,21). In this "protected environment," bacteria cells can survive under circumstances that would otherwise kill free swimming bacteria. Quorum sensing, an inter-bacterial communication system that is based on the density of the bacteria, is another major factor in pathogenic biofilm development. This way, bacterial communities regulate functions like biofilm maturation, secretion of virulence factors and activation of resistance pathways (21,22). This concerted activity increases the chances of bacterial survival and pathogenicity.

The bacteria within the biofilms are also more resistant to antimicrobial treatment and have a greater capacity to evade host defenses. The EPS matrix creates a physical barrier to antibiotic penetration and a subpopulation of bacteria enters a physiologically dormant state called persists that are less susceptible to antimicrobial agents (22,23). Furthermore, biofilms prevent the phagocytosis and other immune defense mechanisms, enabling microorganisms to cause infection for a long time (23,24). These infections are often chronic and may require extended and/or combination therapy. Finally, pathogenic bacteria play a pivotal role in the biofilm formation process because of their capacity to adhere to a surface, produce of protecting extracellular matrix, regulate collective behavior by quorum sensing, and increase antimicrobial resistance. The ability of these bacteria to form a biofilm is still a huge challenge in the management of infection and in the clinical treatment.

Medical Significance of Biofilms

Biofilms is huge because of their high association with chronic, persisting and device-related infections. They can shield pathogenic bacteria against the host immune system and antimicrobial drugs, so they are a significant problem in today's medical care (25,26). Biofilms

are often associated with chronic wound (slow healing) infections, diabetic foot ulcers, and otitis media (ear infections) and may production a role in late wound healing and recurrent infections. In such instances, bacteria inside the biofilms are very resistant to the conventional treatments, and eradication is difficult (26,27). Medical expedient linked contagions are also a major source of infections caused by biofilms. Microbial addition and biofilm creation are facilitated by devices like urinary, central venous and prosthetic joints, heart valves, and contact lenses. Once infection occurs, this can persist and the infection may require removal or replacement of the device (25,28). One is in the area of respiratory infections, especially in patients with CF. These patients develop chronic infections in the lungs with *P. aeruginosa*, which form biofilms and cause inflammation and damage to the lungs. The biofilm structure offers protection and these infections are especially challenging to treat (27,29). Biofilm is also a factor in urinary tract infections (UTIs), particularly in continuous catheterisation. The bacterial species *Escherichia coli* and *Proteus mirabilis* form a layer of encrustation on the catheter which has been linked to continued infection and complications (28,30). One of the principal reasons that biofilms are clinically significant is that they are significantly more resistant to antibiotic therapy and the immune system. Limits antibiotic penetration: extracellular matrix; Slow growing or dormant cells (persister cells): reduces antibiotic effectiveness. Furthermore, biofilms prevent phagocytosis and other immune processes and persistent infections (29,31). Biofilm infections are costly when it comes to health care. Such infections may result in prolonged hospital stays, recurrent therapy, and an increase in healthcare costs, especially straining health care systems worldwide (25,31). In conclusion, biofilms are a key factor in many clinically important infections. They have been an important focus of medical research and infection control due to their ability to increase the survival of the bacteria, their resistance, and the difficulty of treatment.

Antibiotic Tolerance and Resistance in Biofilms

Bacteria in the biofilms are more resistant to antibiotics than planktonic cells, and can withstand up to 1000 times as much antibiotic as planktonic bacteria, causing infections to be hard to eradicate (38,39). It is not a single mechanism, but rather a combination of physical, physiological and genetic factors that give this enhanced resistance. This matrix limits the ability of antibiotics to penetrate the biofilm, and can also bind antimicrobial agents

making them less available and effective (39,40). This causes a bacteria in deeper layers to be exposed to sub-lethal doses of antibiotics. Another factor is the presence of metabolically inactive or slow-growing bacterial cells within the biofilm, called "persister cells". These dormant cells also survive antibiotic treatment and re-colonize the biofilm, causing a recurrent infection (40,41), as many antibiotics affect active cellular processes. Biofilms are also metabolically heterogeneous; that is, different parts of the biofilm contain different oxygen, nutrient and pH levels. These gradients result in subpopulations of bacteria in varying metabolic states, some of which are less sensitive to antibiotic treatment (41,42). For instance, anaerobic cells might be less susceptible to some antibiotics. Moreover, bacterial horizontal gene transfer occurs in biofilms, enabling bacteria to share genes, such as those for antibiotic resistance. These cells can transfer resistance traits as a result of the strong physical contact among them, enabling mechanisms like conjugation, transformation and transduction, which speed up the dissemination of resistance traits (42,43). Another mechanism is the over-expression of efflux pumps, which actively pump antibiotics out of the bacteria, thus decreasing the drug levels in the bacteria and consequently resistance (38,43). In addition, biofilms offer resistance to the immune system of the host. The EPS matrix and the biofilm structure can impede phagocytosis, and can also compromise the effectiveness of immune responses, enabling the bacteria to remain despite the therapy (39,42). In conclusion, antibiotic resistance in biofilms is a complex phenomenon and cannot be explained solely by structural factors, physiological changes of the bacteria and genetic modifications. Elucidating these mechanisms is important to formulate new and effective approaches to tackle biofilm associated infections.

Prevention and Treatment Strategies of Biofilms

The use of anti-adhesive and antimicrobial-coated surfaces is one of the most important preventive strategies, particularly on various medical devices like catheters, prosthetic joints and implants. The coatings can be silver, antibiotics, or hydrophilic materials that help to prevent bacterial attachment and the initial stages of biofilm formation (45,47). Early detection and prompt intervention are other important strategies. Early detection of biofilm infections makes them more amenable to treatment before the biofilm has matured and is extremely resistant. Molecular tools and imaging tools are being increasingly used for this purpose (46,48). As far as treatment, combination antibiotic therapy is sometimes used

to enhance effectiveness. Combining several antibiotics that have different modes of action may increase the killing of bacteria and decrease the chance of bacteria becoming resistant to the drugs (47,49). But some care must be taken to prevent toxicity and the further development of resistance. Another promising strategy is the use of agents that disrupt the "biofilm". Enzymes like DNase, proteases and dispersin B may degrade EPS matrix (extracellular polymeric substance) components and enhance antibiotic penetration and efficacy (48,50). Furthermore, quorum sensing inhibitors can disrupt the communication system of bacteria, and stop the maturation of the biofilm. Sometimes, physical removal or replacement of a medical device infected with bacteria might be required. This method is sometimes the best way to treat chronic biofilm infections with implants (45,49). New treatments such as those using nanotechnology and bacteriophage (phage) are promising. Bacteriophages specifically kill the bacteria in the biofilms and nanoparticles can improve drug delivery and penetration into biofilms (50,51). Finally, proper hygiene and sterility measures are important to avoid the development of biofilm, particularly in the healthcare environment. Proper cleaning, disinfection and infection control procedures can greatly mitigate the risk of biofilm associated infections (46,51). To sum up, the prevention and treatment of biofilms must be multifaceted approach with use of advanced materials, antimicrobial strategies and strict implementation of infection control measures. Further studies are needed to find new and better ways to tackle the problem of infections caused by biofilm.

Conclusion

Biofilms are complex and dynamic microbial communities, which have important implications in healthiness. This can render them very difficult to treat and of clinical concern when the infection is in the form of a biofilm. As in this study, it is very evident that the formation of the biofilm is a complex multi-staged process with initial attachment, maturation and dispersion stages. In addition, pathogenic bacteria can facilitate the structure and functions of biofilms through various mechanisms such as by quorum sensing, secreting extracellular polymeric substances and exchanging genes. These properties play a key role in the emergence of antibiotic resistance and in the development of chronic infections. Moreover, the clinical importance of biofilms is huge and they are linked to different kind of infections especially medical device-related infections and chronic infections.

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