DOI: https://doi.org/10.54393/fbt.v5i3.188

FUTURISTIC BIOTECHNOLOGY
https://fbtjournal.com/index.php/fbt
ISSN (E): 2959-0981, (P): 2959-0973
Vol 05 Issue 03, (July-Sep, 2025)

Review Article

OPEN ACCESS

Biofilm-Associated Infections on Biomedical Implants and Control Measures

Iram Liaqat[1*], Meer Karam Shah[1], and Noor Muhammad[1]

[1]Department of Zoology, Government College University Lahore, Pakistan

ARTICLE INFO

Keywords:
Biofilms, Biomaterials, Device-Related Infections, Implants, Nosocomial Infections

How to Cite:
Liaqat, I., Shah, M. K., & Muhammad, N. (2025). Biofilm-Associated Infections on Biomedical Implants and Control Measures: Biofilm-Associated Infections on Biomedical Implants. Futuristic Biotechnology, 5(3), 19-27. https://doi.org/10.54393/fbt.v5i3.188

Corresponding Author:
Iram Liaqat
Department of Zoology, Government College University Lahore, Pakistan
dr.iramliaqat@gcu.edu.pk

Received Date: 1st August, 2025
Revised Date: 21st September, 2025
Acceptance Date: 24th September, 2025
Published Date: 30th September, 2025

ABSTRACT

Biofilms are bacterial colonies that adhere to surfaces, forming protective barriers against immune responses and antibiotics, which contribute to the development of chronic infections, particularly in medical implants. This study aims to investigate the factors that influence biofilm formation on medical implants and evaluate current strategies for preventing biofilm-related infections. A review of the literature on biofilm formation mechanisms, including quorum sensing and recalcitrance, was conducted, focusing on intrinsic (e.g., quorum-sensing molecules, c-di-GMP) and extrinsic factors (e.g., temperature, surface properties). Biofilm-related infections are common in medical devices, complicating treatment and contributing to increased mortality. New strategies, including antimicrobial peptides, quorum-sensing inhibitors, and nanotechnology-based approaches, show promise in preventing biofilm formation. Surface modifications, such as antibiotic-loaded and nano-silver coatings, significantly reduce bacterial adhesion. Despite progress in biofilm prevention, further research is necessary to refine strategies for controlling implant-related infections and improving patient outcomes.

INTRODUCTION

Biofilms are heterogeneous bacterial colonies that adhere to surfaces and can act as a shield against the host immune system and antibiotic treatment. The colonies are embedded in a self-secreted matrix called extracellular polymeric substance (EPS), which is primarily composed of biological macromolecules and provides structural support to nearby cells, enabling the exchange of genetic material and facilitating quorum sensing [1, 2]. Approximately 80% of all human microbial infections are caused by biofilms, thereby posing a significant risk of chronic illnesses. Biofilms on medical implants are associated with severe morbidity and mortality [3]. Artificial medical implant devices, which are inserted either partially or entirely, are used to replace damaged structures and restore body functions in patients, whose conditions would otherwise be impaired. These devices provide structural support and therapeutic benefits [4, 5]. With advancements in device technology, their demand has increased significantly; for example, in 2018, the annual growth rate of the US medical device market reached approximately $90 billion. Approximately 0.4 to 5 million devices of various types are implanted in the US each year [6]. While these devices have improved the treatment of numerous diseases and enhanced patient well-being, they remain a global health concern due to their medical and economic implications [7]. Unfortunately, implanted devices are often associated with infection problems. Nosocomial infections (NIs), defined as infections acquired after two days of hospitalization, are frequently linked to medical devices and biofilms, accounting for

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approximately 60–70% of cases. These are commonly referred to as medical device-associated infections (MDAIs). The risk of such infections is significantly higher in patients in intensive care units (ICUs), organ transplant recipients, and neonates. Various bacterial species, including both Gram-positive and Gram-negative organisms, contribute to these infections. Their capacity to form biofilms renders conventional treatment methods, such as antibiotic therapy, less effective [8, 9]. Medical device-associated infections include catheter-associated urinary tract infections (CA-UTIs), which are the most common type, accounting for 40% of nosocomial infections globally, 70% of urinary tract infections, and 20% of urinary catheter use. Venous catheters (VCs) and urinary catheters (UCs) are widely used in hospitals. The insertion of a VC can allow skin flora or environmental contaminants to reach underlying tissues, causing severe complications such as central venous catheter-related bloodstream infections (CRBSIs) in ICUs, with mortality rates ranging from 12–25% [10, 11]. After contamination of an implanted device with bacteria, biofilm formation is influenced by several factors, including the type and number of bacterial cells, which affect the rate of attachment. Additionally, fluid flow through the device, surface properties such as hydrophobicity and charge, and the duration of surface exposure before permanent attachment play important roles [12]. Once bacteria are attached and mature, factors such as flow rate, nutrient composition, temperature, and antibiotic exposure can further influence biofilm development and stability [8]. New practical approaches are being implemented to prevent biofilm infections, including the use of antimicrobial peptides and quorum-sensing inhibitors that inhibit biofilm formation [13, 14]. Additionally, surface modification of medical devices has been explored to control biofilm formation and contamination. Various modification strategies, such as antifouling, anti-adhesive coatings, and lamination, have shown promise [15]. This review aims to discuss the intrinsic and extrinsic factors affecting biofilm formation, infections caused by bacterial biofilms on medical implants, and their clinical impacts. It also examines recent control measures and strategies designed to minimize the adverse outcomes associated with these infections.

Biofilm Formation

Biofilm development is a complex, gradual process involving sequential stages of adhesion, aggregation, microcolony formation, maturation, and dispersal [12, 16]. During adhesion, bacteria initially attach reversibly to surfaces through electrostatic and hydrophobic interactions, followed by irreversible binding mediated by adhesins such as pili, fimbriae, and flagella, whose expression marks this stage [17]. Free-floating bacteria then aggregate via cell-to-cell adhesins and proliferate to form microcolonies, with quorum sensing activated at a threshold density to coordinate EPS production and collective behavior [18, 19]. In the maturation stage, EPS secretion, extracellular DNA release, and formation of water-filled channels support nutrient exchange and waste removal, stabilized by active gene regulation and intercellular signaling [20]. Finally, bacteria disperse from mature biofilms through proteolytic activity, alterations in intracellular signaling (e.g., c-di-GMP), or mechanical forces, enabling colonization of new surfaces [21] (Figure 1).

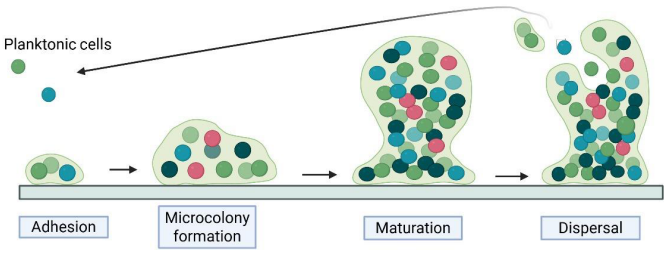

Figure 1: Various Stages of Biofilm Formation on the Surface of the Biomedical Devices

Factors Affecting the Formation of Biofilm

Various factors, both intrinsic and extrinsic, significantly affect biofilm formation, as illustrated in Figure 2. Environmental factors and the mechanism of gene expression in bacterial cells largely influence the development of biofilm. Intrinsic Quorum-sensing (QS) molecules, C-di-GMP, and efflux pumps are intrinsic factors that regulate the formation of biofilms. Quorum Sensing (QS): It is a means of communication mediated by pheromones and extracellular molecules, which make possible the structural and developmental stability of the biofilm [22]. Quorum-sensing molecules like acyl-homoserine lactones (AHLs) induce adhesion expression by binding with receptor proteins that promote attachment and stable aggregation of bacteria [23]. They regulate the production of EPS and also coordinate activities that develop microenvironments within biofilms, where functions such as nutrient acquisition, defense mechanisms, and active growth are carried out [24]. C-di-GMP: It is a signaling molecule having a direct relation with biofilm formation and has an inverse relation with the motility of bacteria [25]. C-di-GMP functions as a regulator. It regulates the transition from a free-floating state to a sessile lifestyle, characterized by a biofilm. Like QS molecules, it also promotes attachment and aggregation by increasing the expression of adhesion genes and other EPS matrix proteins and polysaccharide genes. A high level of c-di-GMP leads to the synthesis and secretion of EPSs, as well as the upregulation of genes involved in biofilm development and the formation of a strong matrix [26]. Efflux Pumps: As the name implies, "pump out." These

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pumps play a role in enhancing antibiotic resistance by effluxing antibiotics and toxic compounds [27]. Their involvement in biofilm formation lacks specific pathways; however, the long-term persistence of bacteria with reduced vulnerability to antibiotics is a potential effect of the activity and presence of efflux pumps [28]. Extrinsic Factors: Temperature, oxygen level, osmotic pressure, and hydrodynamic effects are extrinsic factors (Figure 2) that influence the physiological states of biofilm cells. Temperature: Temperature can affect both physical and physiological properties of biofilms and substrata. An optimum temperature is required for bacterial growth; any increase or decrease below this temperature has a consequential effect on the growth rate. The surface attributes of cells, such as hydrophobicity and charge, may also be influenced by incubation temperature [29]. For example, in Listeria monocytogenes, the hydrophobicity level of the cell surface increases with an increase in incubation temperature, which leads to biofilm formation. The rate of biofilm formation is independent of the temperature effect. The EPS matrix responds to stress, such as temperature, by forming a thick film and realigning polymers to avoid biofilm dissolution. Rise in temperature affects the viscosity of polysaccharides, resulting in a gel-like substance. Biofilms are favored at low temperatures where the polysaccharides are more uniform and stable [30]. Oxygen Concentration: Within a biofilm, a low level of oxygen mitigates metabolic activities and the growth of bacteria. Low oxygen cannot supply enough energy to sustain attachment, this triggers dispersal e.g., *Staphylococcus aureus* in the presence of oxygen minimizes biofilm formation through the sigB gene activity, whose lower expression promotes detachment while in *Staphylococcus epidermidis*, the high expression of the sigB gene activates operon icaADBC, which produce enzyme that results in the synthesis of adhesion polysaccharide leading to biofilm formation [26]. Osmotic Pressure: It is a pressure exerted on a membrane due to a concentration difference between the cell and its environment. A high level of osmotic pressure alters the composition of the extracellular matrix and the general structure of the biofilm. Specific genes regulate the osmotic level response and can affect biofilm formation. High osmotic pressure alters adhesion gene expression in the *Aeromonas hydrophila* cell, affecting attachment and the initiation of biofilm formation [31]. Surface/Charge: A rough surface favors the initiation of biofilm. Opposite charges on surfaces favor attachment due to electrostatic interactions. Hydrodynamic Effects: High shear rates lead to an increase in the detachment of attached bacteria, while making the biofilm thinner and denser [32] (Figure 2).

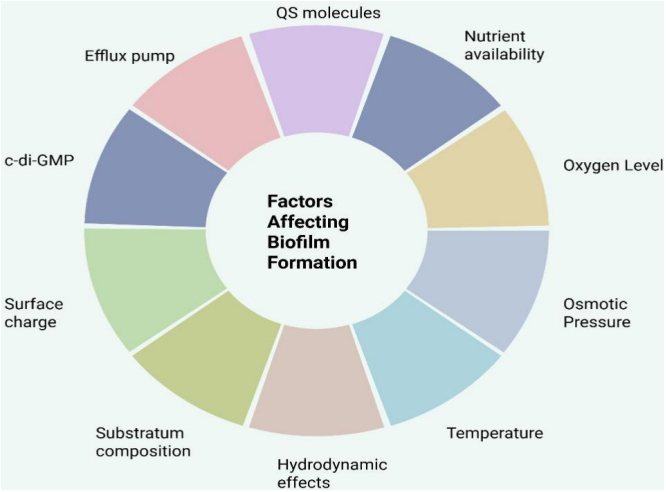

Figure 2: Intrinsic and Extrinsic Factors Affecting Biofilm Formation

Device-Related Biofilm Infections

Factors involved in device-associated infections are primarily related to the biomaterial, host, and microbial origins. Host factors include tissue damage and improper integration of tissue at the junction of biomaterial, which lead to immunity loss and inflammation, respectively. These conditions initiate an infection associated with the device [33]. Biomaterials regulate biological processes, such as cell attachment and body defense, at their surfaces. Tissues are more hydrophobic, so they do not attach to polymer surfaces. Hydrophobic cells adhere well to the hydrophobic surfaces of biomaterials [34]. Microbial factors, such as the outer surface of bacterial cells, create pathogenicity, and many cells produce a glycocalyx that facilitates attachment and colonization [35]. Intravascular Catheters: Intravascular catheters are commonly used to monitor blood circulation and the administration of nutrition, medicine, and various fluids, as shown in Table 1. As the device passes through the skin, contamination with germs can result in colonization of the inner (lumen) side of the catheter, which is the second most common cause of infections associated with these devices [36]. Reports demonstrate that 82% of 2073 hospital-acquired bacteremias are linked with intravascular catheters. In the USA, at least 120,000 cases per year of septicemia are CVC-related. Prevalent pathogens associated with catheter-related infections include *S. aureus,* which is often isolated from skin contamination at the insertion site on the catheter hub. *Candida* species attach to the catheter surface. *S. epidermidis* enhances colonization [37]. *Pseudomonas* and *Xanthomonas maltophilia* are also other agents. *E. coli* and enterococci strains rarely cause catheter-associated infections [38] (Table 1).

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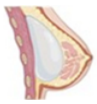
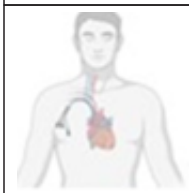
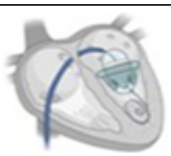
Table 1: Biofilm and Device-Related Infections

Infection Type	Common Bacterial Species	References
 Breast implants	Staphylococci > Anaerobes	[39,40]
 Contact lenses	*Pseudomonas aeruginosa* and staphylococci	[41]
 Endotracheal tubes	*P. aeruginosa* > *S. aureus* > *Escherichia coli*	[42]
 Intravascular catheters	Coagulase-negative staphylococci > Enterococci > Gram-negative bacilli > yeasts	[43]
 Orthopedic devices	Staphylococci > Gram-negative bacilli > Anaerobes	[44]
 Valves, pacemakers, grafts	Staphylococci, Streptococci	[45,46]

Vascular Prosthesis

A prosthesis is used to replace damaged blood vessels. Vascular grafts (tubes) are used in atherosclerosis (a type of cardiovascular disease). Various agents cause infections of these grafts, such as coagulase-negative staphylococci, which are responsible for late prosthetic graft infections (Table 2) and the pseudoneurysm condition in occult graft infections [47] (Table 2).

Table 2: Infections and Pathogens Associated with Vascular Prosthesis

Infections / Conditions	Associated Pathogen (s)	References
Bacterial biofilm infections	*S. aureus*, coagulase-negative staphylococci, and Gram-negative bacteria	[48]
Late prosthetic graft infections	Coagulase-negative staphylococci (especially CoNS forming biofilms)	[49,50]
Occult graft infection	Coagulase-negative staphylococci	[51,52]
Anastomotic femoral pseudoaneurysm	Coagulase-negative staphylococci (e.g., S. epidermidis)	[53]

Orthopedic Prosthesis

Patients who receive orthopedic devices are at risk of infections, such as septic arthritis and bacteremia [54]. These infections are a significant cause of failure of such devices. The risk of infections is increased by polymethylmethacrylate cement, which is used to fix prostheses to nearby bone, as well as by the heat released during the polymerization process, which damages tissue and ultimately increases the likelihood of infections [55].

Endotracheal Tubes (ETTs)

Polyvinylchloride endotracheal tubes enable bacterial colonization more easily than those made of Teflon and polyurethane. These tubes are placed in the mucosal environment of the respiratory tract in patients who require mechanical ventilation. The colonization of the tube can cause pneumonia infection. According to a study by de Mendonça Bisneto *et al.* [56], 84% of endotracheal tubes are covered with biofilm.

Contact Lenses

Eye infections involve multiple factors, including low tear production, a compromised cornea due to inadequate oxygen exposure, and contaminated solutions used for cleaning purposes [57]. Contact lenses serve as a substrate for colonization and also as a source of infection sites, where bacteria detach and spread to other areas. *P. aeruginosa* and *S. epidermidis* are pathogens associated with these devices [58].

Intracardiac Prosthesis

Prosthetic valve endocarditis is a heart-related infection that can occur during the preoperative period or during surgery (Figure 3). Microorganisms gain entry during implantation. At early and late onset, the organisms found in prosthetic valve endocarditis are Coagulase-negative staphylococci and *S. aureus*, respectively [59]. *Streptococcus viridans* and enterococci are also found in late-onset cases. Treatment often needs the removal of the prosthetic device (Figure 3).

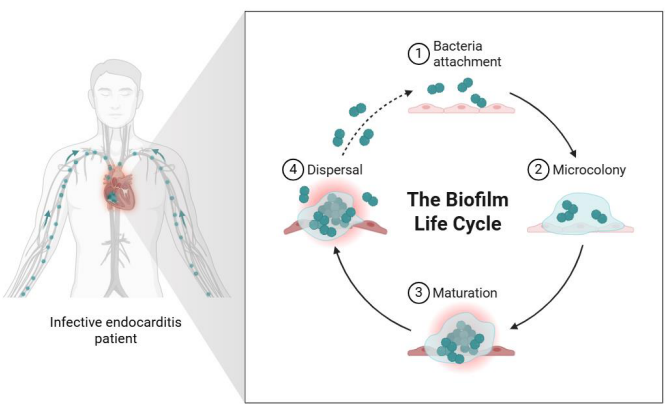


Figure 3: The Biofilm Life Cycle While Causing Infections

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Breast Implant Infections

The most common problem reported in 5% to 30% of patients with breast implants is the association of biofilm with the advancement of capsular contracture [60]. *S. epidermidis* and *S. aureus*, as well as anaerobes, are frequently found in cultures of breast implants. Studies show that povidone-iodine used for irrigation of the implant was the best antiseptic for removing biofilm [61].

Control Measures

Prevention of biofilm-related infections relies on interventions that target microbial mechanisms such as adhesion, aggregation, and EPS formation. Surface modifications, including antimicrobial peptide coatings, quorum-sensing inhibitors, enzyme-based treatments, antibiotic-loaded hydroxyapatite, and nanomaterial or nano-silver coatings act by disrupting bacterial communication, attachment, and EPS synthesis, while locally delivering antibiotics to inhibit growth and reduce adhesion, thereby minimizing resistance and directly counteracting microbial colonization [62].

Antibiotic hydroxyapatite-based coatings are effective in long-term therapy because they deliver antibiotics directly to the local site, thereby controlling infections [63]. In this method, the quantity of drugs is kept low, which possibly reduces antibiotic resistance. Amoxicillin, vancomycin, cephalothin, gentamycin, and tobramycin are used in controlled-release medications. The common carrier of antibiotics is polymethylmethacrylate [64]. The controlled release of antibiotics in biodegradable carriers, such as polyglycolic acid (PGA), poly (lactic-co-glycolic acid) (PLGA), and polyethylene glycol (PEG), is highly effective in preventing infections in the long term. A biodegradable gentamycin-hydroxyapatite coating for infection prophylaxis in cementless hip prostheses, and coating PLGA with gentamycin reduces bacterial adhesion by 99%. The immersion technique is used on the surface to facilitate the absorption of antibiotics [65]. Antiseptic coatings reduce the potential for antibiotic resistance in implants [66]. Hydroxyapatite (HA), which consists of antiseptic coatings, has been proven effective in preventing infections during implant fixation development in goats [67]. Nano-silver coating effectively controls infections by killing bacteria [68]. These particles are directly applied to the surface of implants or polymer coatings, where they eliminate bacteria through their gradual release. Silver is integrated in various devices, where nearby bacteria may be significantly influenced [69]. Silver ions disrupt cell membrane functions, protein functions, and interrupt DNA [70]. Nanomaterials are very useful in the development of modern biomedical implants and their coatings. Nanofilms, nanostructured surfaces, and nanocoatings are more beneficial than usual coatings due to their controlled drug release process [71]. Inorganic Nanocoating for Drug Delivery in Implantable Sensors and Stents. Ceramic nanoparticles promote bioactivity, adhesion, and fracture toughness to the substrate without requiring high temperatures. Diamond nanoparticles (NDs) have captured widespread attention in local drug release due to their superior physical properties and biocompatibility [72] (Figure 4).

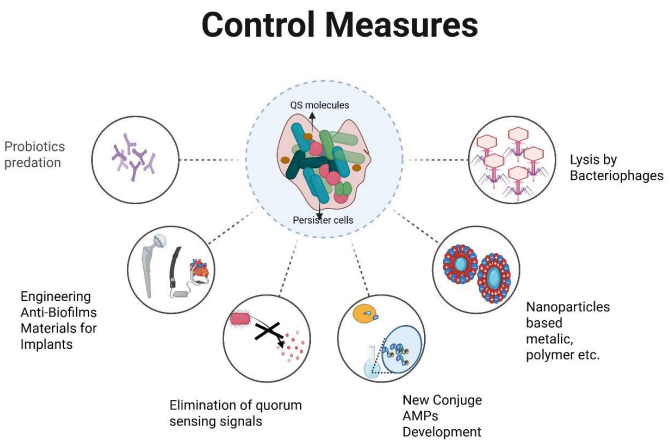

Figure 4: Some of the Control Measures for Biofilm-Associated Infections

CONCLUSION

The biofilm can be associated with the diagnosis and severity of medical infections related to the device. Infections related to biofilm increase the risk of disease and mortality because the free-floating cells can migrate from the initial infection site to the bloodstream, potentially leading to systemic complications. However, significant advancements have been made in the prevention and treatment of biofilm-related infections, which are based on effective technologies and novel compounds. Advances in antiadhesive coatings on the surface of medical implants, which consist of nanoparticles and lipids, are used to decrease the infections related to implants. Both types of coatings play a crucial role in enhancing the performance of biomedical implant devices. The molecular apparatus is becoming increasingly advanced and accessible, enabling the physiological analysis of these small and complex biofilms. The progression in omics technologies also allows us to understand the development of biofilms. Overall, this review highlights the importance of integrated strategies for preventing and managing biofilm-related implant infections. Despite the emergence of these technologies, further efforts are needed to advance knowledge of the various microbiota compositions associated with a particular device. A successful plan of action to counter biofilm-related implant infections must be preemptive, merging advanced material design, strict aseptic procedures, and timely intervention. Sustained interdisciplinary research is crucial for advancing to more

DOI: https://doi.org/10.54393/fbt.v5i3.188

effective, safe, and clinically applicable solutions that promote implant durability and improve patient outcomes.

Acknowledgment

All the figures were designed using BioRender software.

Authors Contribution

Conceptualization: IL
Methodology: IL, MKS, NM
Formal analysis: IL, NM
Writing review and editing: IL, MKS, NM

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The authors received no financial support for the research, authorship and/or publication of this article.

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