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Review Article

Bacterial biofilm formation on implantable devices and approaches to its treatment and prevention

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Abstract

In living organisms, biofilms are defined as complex communities of bacteria residing within an exopolysaccharide matrix that adheres to a surface. In the clinic, they are typically the cause of chronic, nosocomial, and medical device-related infections. Due to the antibiotic-resistant nature of biofilms, the use of antibiotics alone is ineffective for treating biofilm-related infections. In this review, we present a brief overview of concepts of bacterial biofilm formation, and current state-of-the-art therapeutic approaches for preventing and treating biofilms. Also, we have reviewed the prevalence of such infections on medical devices and discussed the future challenges that need to be overcome in order to successfully treat biofilms using the novel technologies being developed.

Keywords: Microbiology, Biomedical engineering, Infectious disease

1. Introduction

Typically, unicellular and multicellular organisms co-exist through a symbiotic relationship in which the unicellular organisms rely on nutrients and biochemical cues from their multicellular counterparts to survive. A representative example of such symbiosis is the *Escherichia coli* found within the small and large intestines of most mammals, which helps to digest sugars [1, 2]. The human microbiome which consists of bacteria, protozoa, fungi, and even viruses outnumbers human cells by a factor of 10 [2]. In a 70 kg male, the number of bacteria alone, found mostly in the colon, almost match that of the human cells with a ratio of 1:1.3 [3]. Most of the microbial flora resides in the saliva, gastrointestinal tract, oral cavity, ear canal, and mucosa or on the skin where they help mammals in numerous metabolic activities, including ATP production, vitamin synthesis, and in the innate defense mechanisms against pathogens [2]. In some instances, however, the growth of these mutually beneficial microorganisms can become uncontrolled, leading to infection [1, 2]. The human body can be infected by various pathogenic agents such as viruses, fungi, and bacteria. Bacterial infections are the most common type of acute and chronic infections causing worldwide morbidity. The prevalence of untreatable bacterial infections is predicted to rise at an alarming rate due to an increase in the number of antibiotic-resistant bacteria strains.

Bacteria exist in two different forms, *i.e.* planktonic state (free floating) and sessile state (adhered to a surface), both of which have existed on earth since the first bacteria evolved [4]. Interestingly, bacteria display very distinct characteristics between these two states, as attachment of the bacteria to a surface results in the rapid alteration in the expression of a number of genes responsible for exopolysaccharide (EPS) or “slime” production and maturation. This transformation begins almost immediately after bacterial colonization of both biotic and abiotic surfaces and results in the production of a protective barrier that protects the bacteria against the organism’s endogenous defense system or from external agents such as antibiotics [1, 5, 6]. This barrier is in some cases referred to as “slime” or the exopolysaccharide matrix. Although the first observation of surface-associated bacteria was made by Anthony van Leeuwenhoek in 1684, the term ‘biofilm’ was not used and defined until a report by Costerton et al. in 1978 [4]. Almost 15 years later, in 1993, the American Society for Microbiology recognized the significance of biofilms [4]. In 1999, biofilms were defined by Costerton et al. as “a structured community of bacterial cells enclosed in a self-produced polymeric matrix, adherent to a surface.” [4].

Both gram-positive and gram-negative bacteria can form biofilms on medical devices, but the most common forms are *Enterococcus faecalis*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus viridans*, *E. coli*, *Klebsiella pneumoniae*, *Proteus mirabilis* and *Pseudomonas aeruginosa* [7]. Amongst them, *S. aureus* and *S. epidermidis* are estimated to cause about 40–50% of prosthetic

heart valve infections, 50–70% of catheter biofilm infections and 87% of bloodstream infections [7]. The staphylococcal species are a diverse group of gram-positive bacteria that mainly inhabit the skin and mucous membranes of humans and other mammals. *S. aureus* and *S. epidermidis* are the leading cause of hospital-acquired, surgical site, and bloodstream infections [8, 9, 10, 11, 12, 13, 14, 15, 16]. Two-thirds of implantable device associated infections are caused by the staphylococcal species, with the majority being associated with *S. aureus* and coagulase-negative staphylococci [17, 18]. *P. aeruginosa*, another common gram-negative bacterium known to adapt to harsh environments and antibiotics rapidly, has been widely used as an *in vitro* model for studying biofilm formation [12, 19].

In humans, biofilms account for up to 80% of the total number of microbial infections according to National Institute of Health [20, 21, 22, 23], including endocarditis, cystic fibrosis, periodontitis, rhinosinusitis, osteomyelitis, non-healing chronic wounds, meningitis, kidney infections, and prosthesis and implantable device-related infections [1, 2, 5, 6, 8, 23, 24, 25, 26, 27]. Despite efforts to maintain sterility, implantable and prosthetic medical devices can easily become contaminated with bacteria. Major challenges in treating biofilms are their difficult diagnosis and lack of suitable biomarkers [8], and in the clinic, biofilms can also be difficult to eradicate due to a high tolerance to antibiotics [8].

In patients, biofilms that form are resistant to the host's endogenous defences [28, 29], and as such are treated with a combination of antibacterial therapies and tissue debridement. Paradoxically, the large doses of antibiotics used to treat biofilms clinically have also contributed to the development of antibiotic-resistant bacteria strains [1, 21, 30, 31]. Additionally, it has been seen that some bacteria within biofilms, called “persister cells,” are dormant variants that exhibit antibiotic tolerance and can become active when the therapy is withdrawn [1, 8, 32, 33, 34, 35].

Bacterial resistance and tolerance are differently defined by authors; however, according to most, bacteria are said to be tolerant when they are unable to proliferate (yet continue to persist) under antimicrobial therapy, whereas proliferation under the same conditions is considered as resistance [36]. It is reported that sessile bacteria are 500–5000 times more tolerant towards antibiotics in comparison to their planktonic state [6, 37, 38]. Tolerance, an active and adaptive process [39], typically occurs when bacteria aggregate at high density, while resistance is a result of intrinsic and external factors such as mutation [1, 6, 24, 39].

Various mechanisms are known to contribute to bacterial tolerance and resistance, some of which, are mentioned below:

1. When a high density of bacteria is accumulated in a specific region, starvation is induced, and this tends to promote the development of nutrient and oxygen

gradients that slow the penetration of antibiotics to the core of the biofilm, mediating tolerance [1, 36, 39].

2. It is also hypothesized that due to the environmental stresses such as decreased nutrition, pH, temperature etc., biofilm bacteria express stress response genes including σ -factors that protect them from antibiotics, host immune factors and environmental toxins [40].
3. Differences in the physiological properties of established biofilms and actively growing planktonic cells can also explain the decreased sensitivity of biofilms towards antibiotics, which are known to target active cell processes [23].
4. Sometimes due to the lack of oxygen, bacteria within biofilms undergo anaerobic metabolism, thus limiting the potency of antibiotics [6, 37].
5. Extracellular DNA (eDNA) released by autolysis in the EPS has also been reported to neutralize the activity of antimicrobial drugs such as tobramycin via its cation chelating properties, as seen in *P. aeruginosa* biofilms [41, 42]. This property of the EPS also makes the biofilm cells tolerant to metals like zinc, copper, and lead [1].
6. Enzymes produced by bacteria, such as β -lactamases, have also been found to degrade antimicrobials, preventing them from reaching the biofilm [36].
7. Bacteriophages including filamentous phage particles help in releasing eDNA and the development of antibiotic tolerant colonies within biofilms [36].
8. Several biofilms are also able to inhibit or block leukocytic predation through various mechanisms. One such mechanism is the quorum sensing (QS) induced production of rhamnolipids by *P. aeruginosa* in response to phagocytic leukocytes [1].

Mechanisms of biofilm resistance to antibiotics are still under debate; however, some mechanisms have been proposed including:

1. Delayed or failed penetration of antibiotics and altered bacterial growth within the biofilm, inducing resistance [23, 36, 39, 43].
2. Some bacteria like *P. aeruginosa* can acquire resistance via horizontal gene transfer [1, 6].
3. In some cases, bacteria can use multidrug efflux pumps to pump antibiotic agents out of the maturing biofilms and into the extracellular matrix, contributing to resistance [1, 36, 44].
4. Interactions between bacteria and fungi have also been found to be relevant in polymicrobial biofilms. For example, Adam et al. showed that a dual species biofilm of *S. epidermidis* and *C. albicans* had increased resistance to vancomycin due to a fungal matrix component that acted as a barrier to the antibiotic [45].

Hence, bacterial biofilm tolerance and resistance has contributed in the difficulties with applying the current antibiotic therapies to treat biofilm causing infections

including implant associated infections. The rapid advancement of implantable biomedical devices has brought the issue of implant associated infections to the forefront [30, 32, 46, 47, 48]. Prosthetic and implantable devices can get contaminated either immediately during surgery or anytime thereafter [2, 25, 49, 50, 51, 52]. Factors such as differences in implant surface hydrophilicity, surface charge, surface energy, and biomaterial composition play a role in increasing the rate of infection in implants [13, 18, 25, 52, 53, 54, 55]. In addition to surgical risks associated with replacing an infected implant, there is no guarantee that the bacteria will not re-colonize upon the new device [15]. One of the reasons why implantable devices get contaminated is that a considerably lower bacterial load ($\approx 10,000$ times less) is needed to colonize a given biomedical device in comparison to native tissue [38, 56, 57]. One explanation for this is the lack of vascularization, making implants more susceptible to colonization than other tissues and organs in the human body. Thus, understanding the underlying mechanism of biofilm formation can help in the design of novel strategies to prevent or treat implant-associated infections, thus providing an alternative to antibiotics and device replacement surgeries. The present mini-review presents a revision of the most recent advances in technological approaches for preventing and eradicating biofilms from the surfaces of biomedical devices. To facilitate the non-expert or novice reader on this topic, we have added introductory sections on the nature and *in vivo* formation of biofilms as well as their impact in the clinic.

2. Main text

2.1. Biofilm formation

Biofilm formation is a complex multi-step process (usually cyclic) involving multiple bacterial species [49]. Bacterial biofilms secrete a mixture of polysaccharides, proteins (composed primarily of D-amino acids), fatty acids, and a variety of nucleic acids which is referred to as extracellular polymeric substance or EPS [1, 6, 37, 39]. It is said that biofilms consist of about 80% EPS which plays an important role in biofilm formation; however, the EPS is still considered to be poorly characterized in most biofilms [39]. The EPS is a sticky matrix comprised mostly of water channels that serve as a medium for the distribution of nutrients and oxygen. In addition to protecting the bacteria from the host's defenses (antibodies, white blood cells, monocytes) and antibiotics [1, 6, 24, 37, 58], the EPS serves as a basic platform for surface attachment [19]. It has also been shown to facilitate the functioning of intercellular signaling molecules such as cyclic dimeric guanosine monophosphate (c-di-GMP) that is found in most bacterial species. This signaling mechanism stimulates the growth and adherence of bacterial species [5, 6, 24, 34, 59].

C-di-GMP helps in the synthesis of matrix components including polysaccharides and proteins that are part of a feed-forward loop as seen in *P. aeruginosa*, where

c-di-GMP stimulates the production of different polysaccharides including pentasaccharide (PSL), glucose-rich polysaccharide (PEL), and alginate [23]. PSL and PEL act as signal molecules to further stimulate c-di-GMP production [1, 5, 6, 37], leading to increased levels of c-di-GMP and resulting in thicker and stronger biofilms [5, 6]. The proteins that promote EPS production are specific to the various species of bacteria. For example, proteases, nucleases, teichoic acids and phenol soluble modulins promote EPS production and biofilm formation in staphylococcal bacteria. Whereas glucan binding proteins like GbpC are responsible for EPS growth in streptococcal bacteria [8, 23, 26, 27]. Furthermore, extracellular DNA is reported to be responsible for cellular communication in *P. aeruginosa*, staphylococcus and streptococcus biofilms, especially in the early stages of biofilm development [6, 8, 22, 26, 27, 60]. Interestingly, the extracellular nucleases of *S. aureus* have also been shown to degrade neutrophil extracellular traps (NET), thus protecting the biofilm from NET-mediated killing [61, 62].

Biofilms are typically formed due to a default defense mechanism to achieve a favorable habitat, retain nutrients, and to ensure survival [1]. While the overall mechanism is similar amongst the species of bacteria, there can be slight differences between them [1, 6, 8, 24, 37, 63]. Bacterial biofilm growth is typically a result of physical, chemical, and biological events [6]. The formation is typically classified into three stages; (i) initial attachment (reversible and irreversible), (ii) maturation of microcolonies, and (iii) dispersion/detachment [1, 8, 21, 23, 27, 64, 65, 66, 67, 68]. Fig. 1 summarizes the main stages of biofilm formation on an implantable device. Attachment is characterized by the production of bacterial adhesins that stick to the surface, while cell-cell adhesion mechanisms mediate maturation, and enzymes that degrade the biofilm matrix mediate dispersal [69, 70, 71].

2.1.1. Initial attachment

Pathogenic bacterial cells are opportunistic; thus, when planktonic cells come in contact with a conditioning film, they adhere to it via physical forces or by bacterial

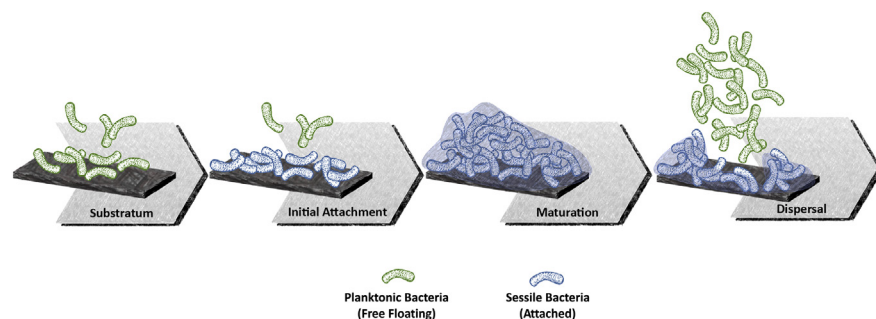


Fig. 1. Schematic representation for the main stages of biofilm formation on solid surfaces, see text for further details.

appendages such as pili or flagella [1, 6, 23, 24, 34, 50]. A conditioning film, as shown in Fig. 1, is a thin layer that forms on indwelling medical device or living tissues consisting of proteins such as fibronectin, fibrinogen, vitronectin, thrombospondin, laminin, collagen, von Willebrand factor, and polysaccharides [24, 50]. This stage is termed reversible attachment as the initial interaction can be transient and reversible due to weak interactions between the bacteria and surface [24, 27, 34]. The ability, rate, and extent of adherence of the bacteria on an implant surface depends on the composition of the material, temperature, pressure, and the surface properties of the bacterial cell [6, 50]. When bacterial cells attach to a surface, it is termed as adhesion, while attachment amongst the cells is referred to as cohesion [6]. The adherence of biofilms to materials is mainly governed by hydrophobic interactions, steric interactions, protein adhesion, electrostatic interactions, and Van der Waal forces all of which help the bacteria remain adhered to the surface [2, 6, 24, 27, 50, 72, 73].

When the attractive forces are greater than the repulsion, some of the reversibly attached cells remain immobilized and become irreversibly attached, which is succeeded by specific and strong adhesion and monolayer formation [6]. Staphylococcal biofilms are known to possess more than 20 surface-associated adhesins, which mediate initial attachment of the biofilm, and intercellular adhesion during maturation [74]. These adhesins include covalently anchored cell wall proteins (like SasX) [75], and non-covalently associated proteins and non-protein factors [8]. Initial attachment of *S. epidermidis* to a polymer surface is found to be mediated by surface associated autolysin (At1E), and the biofilm formation is mediated by biofilm-associated protein [24]. *S. aureus* expresses two fibronectin binding proteins, FnBPA and FnBPB, which induce bacterial invasion into epithelial cells, endothelial cells, and keratinocytes [76, 77, 78]. Cell wall-anchored adhesins, such as SasX, can be responsible for adhesion but at the same time play an important role in virulence as it has been linked to the spread of methicillin-resistant *S. aureus* (MRSA) in China [54, 79]. Some proteins change the adherent behavior of the bacteria by altering the physiochemical characteristics of the bacterial surface. For example, fibronectin, fibrinogen, and laminin are observed to promote bacterial adhesion to biomaterials and tissues, while albumin and whole serum are found to inhibit bacterial adhesion to polymer, metal and ceramic surfaces [18].

2.1.2. Maturation

In this phase, the adhered cells grow and mature by interacting amongst themselves by the production of autoinducer signals which results in the expression of biofilm-specific genes [6]. The increased production of autoinducer molecules corresponds to signaling cues that help in virulence and gene regulation [65]. In this stage the bacterial cells start secretion of the EPS that encloses the cells, thus stabilizing the

biofilm network and protecting themselves from antibacterial agents [6, 24]. It is reported that during maturation, *P. aeruginosa* releases three polysaccharides (alginate, Pel and Psl) which provide stability to the biofilm [6]. In addition to EPS, e-DNA is also found to be responsible for cellular communication and the stabilization of the biofilm [6]. The *S. epidermidis* polysaccharide intercellular adhesion (PIA) antigen plays a role in initial attachment and also protects the proliferating bacteria from polymorphonuclear leukocytes [80]. During their accumulation and aggregation, different layers of cell clusters are formed on the surface. These resulting microcolonies then mature into macrocolonies which also get encased within the EPS where inter-cellular signaling and quorum sensing (see quorum sensing section for details) takes place [6, 24]. Overall, there are two stages of maturation: Stage I involves inter-cell communication and the production of autoinducer signal molecules such as N-acylated homoserine lactone (AHL), while stage II corresponds to an increase of the microcolony size and thickness to a value around 100 μm , forming a macrocolony [6, 8, 58].

It has been shown that the connections formed between the bacterial cells of the biofilm are mediated by dynamic interactions and that linkage between clusters will depend on the distance between them [65]. Bacteria can sense the size and distance of adjacent clusters during their maturation stage, this helps them to form clusters that can bind with neighboring cells in a much more efficient fashion [65]. The entire bacterial biofilm colony controls both gene and protein expression, rather than being controlled by individual cells [65]. In summary, the maturation stage involves EPS production, aggregation of cells, chemical interactions, quorum sensing and formation of micro and macrocolonies [6, 73].

2.1.3. Dispersal

Dispersion is a crucial stage in the progression of biofilm formation as it is the mechanism by which the bacteria expand from one region of the body to another, thereby spreading infection. Typically, a biofilm is composed of two distinct layers. There is the base film layer where the microbial cells exist, and the surface film where they get dispersed into their surroundings for expansion and continued existence, as shown in Fig. 1 [24]. This stage causes chronic infection and other severities like embolic complications, which require immediate treatment [24]. As such, this process is often referred to as metastatic seeding [1, 6, 26, 73].

As the biofilm matures, resources become limited and toxic products can accumulate. Thus, in order to expand, get nutrition, and eliminate stress-inducing conditions and waste, the cells disperse to other regions of the host's body or other regions of the medical implant [6, 24, 37]. The dispersion of cells occurs either as single cells or as clumps of cells which are sloughed off the biofilm [6]. This is said to be a programmed process that is initiated by oxygen level (in case of aerobic biofilms) or

nutrient starvation. This starvation stimulates small molecules like fatty acid DSF (cis-11-methyl-2-dodecenoic acid), which triggers autophosphorylation and leads to activation of c-di-GMP phosphodiesterase that degrades c-di-GMP. Degradation of c-di-GMP leads to the tearing of clusters by shear forces or the release of planktonic cells that dissolve a portion of the EPS [1, 24, 37]. While this is one mechanism, there are others apart from gene regulation pathways involved in the dissolution of EPS [24, 37, 60]. For instance, the bacterial cells inside the biofilm produce saccharolytic enzymes, which break the biofilm stabilizing polysaccharide, thereby releasing the surface bacteria [6]. Once released, the bacterial cells either establish more biofilms at other regions of the body or freely float on the surface by upregulating the expression of flagella proteins to help them in motility [6, 24]. Dissolution of the EPS is a major area of interest as it could hold the key to treat the biofilms and prevent expansion [37, 60].

2.2. Quorum sensing

The bacterial cell envelope plays a crucial role in intercellular signaling as well as communication between neighboring cells in small microcolonies that help in decision-making processes [6, 8, 24, 37, 58]. Part of this communication occurs through quorum sensing (QS), a phenomenon which involves cell density-dependent control of gene expression. For QS to be possible, a minimum number of bacteria must be aggregated within a specific volume. The bacterial cells can determine the local density of cells by sensing when signaling molecules (*e.g.* auto-inducers) that are generated by neighboring cells reach a critical threshold [1, 22, 34, 58, 63, 65, 81, 82]. It should, however, be mentioned that some authors believe auto-inducer molecules to be merely a metabolic side product in some bacterial species and not a signaling molecule [83]. Either way, a variety of cell growth models and mathematical equations describing the dynamics of QS systems have been proposed to understand QS better [58].

As disruption in the QS system can inhibit the growth of bacteria within the EPS, it has become an important research area [84]. It has been proposed that by manipulating the underlying pathways of QS, one can trigger the disassembly of pre-established biofilms through a phenomenon termed quorum quenching, thus serving as a pathway for the development of potential treatments [37]. Additionally, quorum quenching has been shown to increase biofilm susceptibility to antibiotics, as seen by administration of the quorum sensing inhibitors cinnamaldehyde and baicalin hydrate, which decreased biofilm resistance of *P. aeruginosa* and *B. cepacia* towards tobramycin [85].

2.3. Biofilm modelling systems

Understanding biofilm morphology and physiology can be quite challenging. Several biofilm model systems have been designed and studied to understand biofilm

formation, signaling mechanisms, structure-function relationships, and biofilm resistance. These biofilm models have also contributed to the development of therapeutic strategies to prevent and control biofilm formation. Some of them are described below.

In vitro biofilm models such as microtiter flow-based biofilm systems have shown that after initial attachment and accumulation, biofilms of *S. aureus* disperse cells in a process referred to as “*Exodus*,” and that these cells mature into a separate biofilm through a different regulatory system [86]. Some cellular dynamic models and intercellular network models have shown a mathematical relationship between the network dynamics of the biofilm population and biofilm metrics, providing clarity in intercellular communication within the biofilm [58]. The modified Robbins method uses a device that can immediately produce and form a biofilm in a fluid, whose application has shown the potential of antibiotic lock therapy for biofilm removal from colonized surfaces [24]. A Centers for Disease Control and Prevention (CDC) biofilm reactor consists of several plastic rods holding discs of different materials where a biofilm can be formed. This device is accepted as a perfect tool to grow *P. aeruginosa* biofilms with high shear and continuous flow, and has been used to investigate the multiple high dose antibiotic activity against *S. aureus* biofilms, along with other biomaterial applications [24]. A well plate microfluidic device that consists of microchannel combined into a microtiter plate has been used to allow high throughput evaluation of biofilms [24], along with biofilm sensing using electrical impedance spectroscopy [87], and biosensors [88]. Numerous techniques have been used to quantify biofilms on abiotic surfaces *in vitro* including LIVE/DEAD fluorescence staining, confocal laser-scanning microscopy, standard plate counting method and resazurin viability assay that measure the extent of biofilm formation on surfaces [89].

In vivo models are highly important to study as they give a better insight into the interactions of bacterial biofilms within a living organism, which is a challenge to mimic entirely *in vitro* [24, 57, 87, 90, 91]. Furthermore, *in vivo* models can be quite advantageous as they can reduce the randomness of biofilm growth [92]. These models can be used for investigating and comparing various biofilm treatments as well as in designing new prosthetic and implantable devices [24, 26, 93]. Commonly used general purpose models include the subcutaneous foreign body infection model (where a foreign body is inserted into subcutaneous pockets of mice, rabbit, guinea pigs or rats and biofilm is grown on the implant), and the tissue cage infection model (perforated cylinders are implanted in the subcutaneous tissue filled with interstitial fluid and biofilm is grown on it). Other studies require more specialized models; for example, a catheter-associated urinary tract infection model (in rabbits) was designed to study the effect of various antibiotics on *E. coli* biofilm developed on the catheters and adjacent tissues, along with the effect of peptide-coated catheters in avoiding the biofilm formation [24]. Similarly, Ear-Nose-Throat (ENT) infection

models (allows direct visualization of the biofilm on the middle ear mucosa) were used to determine the efficacy of *S. pneumoniae* to form nasopharyngeal and middle ear mucosal biofilms with transbullar inoculation [24]. Designing an appropriate model is very important to better understand biofilm mechanisms *in vivo* for various reasons, one being that pseudomonas species are frequently used in *in vitro* studies when they are the primary cause of acute infections rather than biofilm causing infections [23].

2.4. Implant-associated infections and prevalence

A medical device is an instrument, apparatus, appliance, tool or equipment used in the prevention, diagnosis, treatment, mitigation, rehabilitation and/or generation of information of a disease or medical condition [94]. The Medical Devices Bureau of Health Canada has recognized 4 classes of medical devices based on the level of control necessary to assure the safety and effectiveness of the device that are [95, 96]:

1. Class I: Presents low risk to patients and do not require a license or requires lowest regulatory normative (such as surgical instruments, dental material, etc.)
2. Class II: Require the manufacturer's declaration of device safety and effectiveness (such as contact lenses, ultrasound machines, medical catheters, etc.)
3. Class III: Presents greater potential risk to the patient (such as orthopedic implants like bone cement and hip implants, hemodialysis machine, surgical meshes, etc.)
4. Class IV: Presents greatest potential risk and is subject to in-depth scrutiny and premarket regulatory approval (such as cardiovascular implants, pacemakers, ventricular assist devices, etc.)

The Therapeutic Products Directorate (TPD) is the governing body in Canada in charge of monitoring and evaluating the safety and effectiveness of medical devices through assurance of pre-market review, post-market approval surveillance and quality systems [94]. Prosthetic and indwelling medical devices are medical devices that are used to support, replace or repair tissue, organ or any bodily functions that are lost or damaged in trauma or disease. These devices may or may not be meant to be used throughout the lifetime of the patient. Most prostheses and indwelling medical devices are made of biomaterials which are broadly classified into metals, polymers, ceramics, composites and natural [97]. Orthopedic implants such as bone plates, wires, hip implants, screws; cardiovascular implants such as coronary stents, pacemakers and implantable cardioverter defibrillators are usually made of metals and its alloys. Urinary catheters, heart valves, corneal implants, etc., are usually made of polymers. Various other dental and orthopedic implants are made of ceramics and composites. The global implantable biomaterial market was valued at

\$79.1 billion in 2014, and is estimated to grow at a compound annual growth rate reaching \$133 billion in 2022 [97]. The increase in use of biomaterial-based medical devices is associated with the aging population, the growing prevalence of diseases and deteriorating lifestyle (consumption of unhealthy food, increased number of traumatic accidents, increased demand in donor grafts and organs, etc.) [97]. Numerous books and articles in the past decade have been published on the subject of biofilm-causing infections, implant- and biomaterial-associated infections and some common strategies under research for its treatment, some of which is given by Barnes et al., Moriarty et al., Campoccia et al., and G. Donelli [98, 99, 100, 101].

Bacterial contamination on implants and prosthetic medical devices causing infections can be life-threatening [102], leading to device failure, chronic infections and high mortality and morbidity rates. Treatment of implant-associated infections includes delivery of high dose antibiotics and/or replacement of the implant involving costly and risky surgeries, both of which are ineffective due to antibiotic-resistant strains and high chances of re-infection on the new implant, as mentioned earlier. The first report of healthcare-associated infection rates was published by the CDC in the 1970s and has been updated constantly since to include current standards methods and definitions [103]. In the early 2000s, nosocomial infections (hospital-acquired infections that appear within 2–30 days of hospital stay) accounted for 2 million cases of infections and 90,000 deaths in the US alone [17, 104]. Out of those, implant-associated infections comprise 50–70% of all nosocomial infections [17, 105, 106, 107]. In 2007, nosocomial infections were reported to be the most common type of adverse events in healthcare in Canada [108]. There is an estimated 220,000 cases of nosocomial infections resulting in more than 8,000 deaths every year in Canada [108]. The most common post-operative complication is surgical site infections (SSIs) that arise at the exposed site of the body where the surgery took place, constituting between one fourth and one-third of all nosocomial infections, which accounted for 6–23% in most studies [109, 110, 111, 112]. In the US, it is estimated that more than 500,000 SSIs occur each year, at a rate of 2.8 per 100 operations [112]. Data from the National Cardiovascular Data Registry (NCDR) ICD registry show that 47% of patients with an ICD implant underwent repeat surgeries due to device upgrade, end of battery life and systemic infections, within a year [113]. Although prosthetic joint infection is less problematic, it has been shown that the mortality rate due to infected prosthesis removal is still around 2.7–18% in the US [114]. In a recent Dutch multicenter surveillance study, infection rates in total hip prosthesis was found to be 3% and in total knee prosthesis it was 4.1% [111]. Table S1 (see supplementary information) summarizes the infection rate of some indwelling medical devices mentioning the species that colonize the corresponding biomaterials and the routes through which it is commonly colonized. From the table, it can be observed that ventricular assist devices (VADs), dental implants and orthopedic devices are most commonly colonized by bacterial biofilms.

Treatment of infected prosthesis removal and antibiotic therapy is estimated to cost more than \$50,000 [114]. Hence, there is an urgent need for an alternative to antibiotics for infection treatment to control the morbidity and mortality rates arising from acute and chronic infections worldwide.

2.5. Current treatments and new therapeutic approaches

Biofilms causing infections are progressive, and in some cases can become a chronic problem. As mentioned earlier, current treatment of implant-associated infections includes the delivery of high dose antibiotics according to the severity of infection [30, 39], and if symptoms persist, then surgical replacement must take place. The increase in resistance towards antibiotics poses an issue for treating patients with contaminated medical devices [6, 23]. Thus, much research has been conducted looking for alternative strategies to prevent and treat biofilm-based infections. It has been said that the best possible treatment for biofilm-based infections is to inhibit the initial attachment stage thus preventing the infection from starting. Fig. 2 provides a summary of the technologies being developed to prevent and/or treat biofilm causing implant-associated infections.

2.5.1. Electrical and electromagnetic methods

It is known that cells are sensitive to electric fields because the induced stress causes both reversible and irreversible membrane breakdown, through a process termed as electroporation, which is dependent on the magnitude and duration of the electric field [115]. For this reason, electric and electromagnetic fields are being currently investigated for the treatment of bacterial colonization. The application of electrical

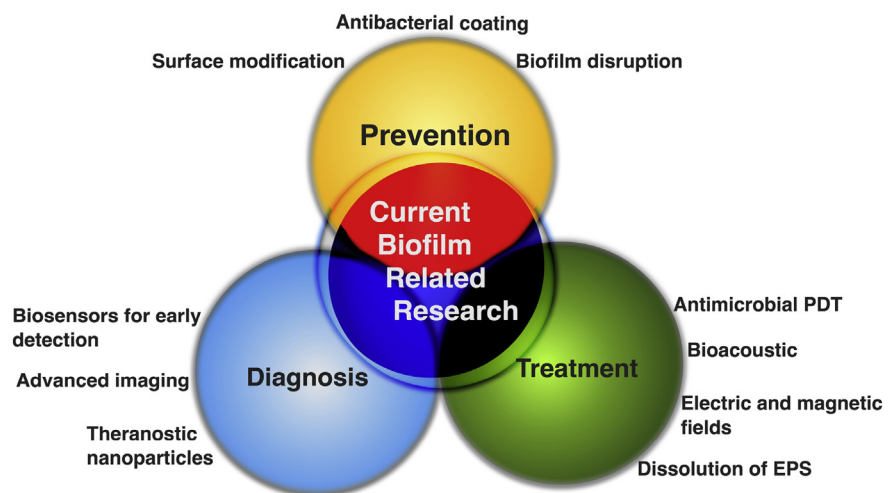


Fig. 2. Schematic representation of some relevant strategies currently being investigated to overcome the bacterial colonization on implantable devices. The main strategies aimed to address bacterial infection include prevention, diagnosis, and treatment.

methods to treat biofilms such as DC voltage [116], low AC currents, pulsed electric fields, capacitive coupling treatment, and extremely low-frequency electromagnetic waves (ELF-EMF) are said to be electricidal [117]. When these methods are used in combination with antibiotics or with host immune responses to create synergistic effect, it is termed a bioelectric effect [116, 117]. Giladi et al. showed the efficacy of non-homogenous electric fields (3–4 V/cm) to effectively control the *P. aeruginosa* and *S. aureus* growth rate and showed a synergistic effect when applied alongside chloramphenicol treatment [118]. Some studies have also demonstrated the effectiveness of a pulsed electromagnetic field (2000 μ A, 1210–7500 V/cm) with increased number of pulses and pulsed electric field that leads to bacterial cell wall disintegration and internal alteration of the core in an *in vitro* and rabbit spine infection model, which also showed a synergistic effect with the antibiotic ceftriaxone [115, 119, 120, 121]. Studies have also shown the eradication of *S. epidermidis*, *S. aureus* and *P. aeruginosa* biofilms with the use of DC currents (1800 μ A) [122, 123]. Fadel et al. showed *S. typhi* inhibition by using the frequency of ELF-EM waves (0.8 Hz) that resonated with the bioelectric signal generated by the *S. typhi*, creating 2 V/cm of electric field. [124] Electric fields (1.25 V/cm) combined with autoinducer 2 analogs (small molecule inhibitors of bacterial QS) was shown to be effective in preventing *E. coli* growth, which showed a synergistic effect with gentamicin [125]. These methods have shown effectiveness at preventing and treating planktonic bacteria and biofilms, and represent alternative options to the removal of infected devices through a minimally invasive technique and its associated trauma. Although promising, these therapies have been minimally tested in animal studies, and further investigation is required [46, 117, 126].

2.5.2. Antibacterial coatings

Coating implants with antibacterial and antibiofilm agents is a promising approach that can inhibit the initial attachment of planktonic cells on the implant surface [24]. Antibiotic coatings were once studied widely, although concerns over antibiotic resistance have led to research involving other types of preventative coatings [100]. Various strategies have been designed to produce antibiofilm coatings using natural and synthetic materials [24]. Hydroxyapatite coatings are widely applied in the medical field, and they can be altered by surface adsorbed antibiotics by immersion in antibiotic solutions, thus producing antibiotic hydroxyapatite based coatings [24]. Photoactive based coatings [24] and antiseptic based coatings have been applied as a coating for catheters applied for intramedullary implants in a rabbit model, and they were shown to have antimicrobial function [105, 127]. Other strategies to reduce the adhesion of bacteria on catheters *in vitro* and *in vivo* include hydrophilic polymers such as hyaluronic acid, hydrogel coatings and heparin coatings [7, 128]. While there are a variety of silane coatings, nanoplasma trimethyl silane coatings specifically have been shown to be most effective on hydrophilic surfaces

and stainless steel to prevent *S. epidermidis* biofilms [6]. In some studies, antimicrobial peptides produced by various animals, plants, bacteria, fungi and viruses have been shown to be effective in killing bacterial cells, such as LL37 peptide when grafted on titanium surfaces [99]. There are also covalently coupled quaternary ammonium silane coatings used in the coating of silicone devices and plasma treatments which are commercially available and useful, however, they tend to be time-consuming and overly specific [129]. For long-term anti-fouling, some biomaterials have also been treated with ceramics such as calcium phosphate and other biodegradable polymers which can serve as an effective coating [130]. Surfaces have also been functionalized with anti-adhesive high-density polymers that present steric repulsion in order to make bacterial attachment more difficult which can be served as another potential coating [131].

Nanomaterials, nanofilms, nanocoatings and nanostructured surfaces are being widely studied for biomedical applications [24]. Silver's antibacterial properties have long been known [132], and nanosilver coatings have been widely studied and applied to several medical devices such as catheters, heart valves and wound dressings [24, 99]. Silver nanoparticles have a unique mechanism for eradicating bacterial cells, which involves binding to cell wall causing membrane disruption [24] and the accumulation of peroxides that oxidise the cell walls [133], attacking the respiratory chain of the bacterial cell, and cell disruption via hydroxyl radicals and other reactive oxygen species [134]. Silver nanoparticles have been shown to be biocompatible, as mammalian cells can phagocytose the nanoparticles and subsequently degrade them by lysosomal fusion, thus reducing/eliminating toxicity and free radical damage [24]. Silver nanoparticles also have antibacterial and antibiofilm properties that can produce synergistic effects with some antibiotics [132, 135]. However, it is reported that nanosilver applications are useful for short-term purposes only as the extent of their biocompatibility is unknown, making them most suitable for surgical site infections [136, 137, 138]. Gold, diamond and titanium coating treatments have also been demonstrated to be highly effective in reducing microbial adhesion, proliferation and biofilm growth, as have nanomaterials containing zinc oxide, titanium oxide, polymers and carbon nanotubes [24].

2.5.3. Disruption of biofilm formation and antibiotic enhancers

A strategy to prevent QS is to inhibit the signaling molecules involved from binding to their receptors on the bacterial cell surface. This can be accomplished by using analogues of the signal molecules that compete for the binding sites. Hence the use of molecules that interfere with QS is a promising method to prevent biofilm formations [128]. It is reported that if the formation of aggregates is prevented or if the EPS is dissolved, the exposed bacterial cells can be susceptible to therapies once again [1, 37]. Qin et al. demonstrated that *S. epidermidis* biofilm formation could

be inhibited on polystyrene, glass and mica surfaces if treated with two benzoate derivatives. They also showed that two carboxamide derivatives could inhibit initial adhesion and cell division by reacting with the bacterial cells. However, it was found that these compounds did not affect pre-established biofilms [139]. Recently, it was reported that sulphathiazole could inhibit *E. coli* biofilms by disrupting its c-di-GMP biosynthesis [6]. Various compounds including polymers (such as silicone elastomers with triclosan, silicon rubber, RGD [140] and mangainin I peptides [141]), nisin peptides in combination with lipid II [141], rosmarinic acid, allyl sulphide, ginger extracts [142], Chinese medicinal plants, and proteases like trypsin and proteinase K [143], are known to disrupt QS pathways and inhibit biofilms in multiple species including *E. coli*, *S. epidermidis*, *S. aureus*, *S. mutans* and *P. aeruginosa* [6]. It was reported that since eDNA is used to form biofilms, DNase I can degrade the DNA released by *S. aureus*, preventing biofilm formation [144]. Albumin adsorbed on material surfaces has also been found to inhibit bacterial adhesion to polymers, ceramics, and a variety of metal surfaces [145, 146]. Intraoperative vancomycin powder application at the time of implantation has also shown efficacy in decreasing biofilm formation in a rabbit model [109]. A technique, named as the antimicrobial lock technique, can also be employed to inhibit biofilm formation in catheters [38, 72, 126]. This approach uses solutions such as anticoagulants and antimicrobial agents to disrupt bacterial growth [147]. D-amino acids secreted by certain bacteria are also found to inhibit *P. aeruginosa* biofilm formation when combined with antibiotics [148, 149]. Vaccination against specific biofilms is also an area under research for biofilm treatment [6, 16]. Antibiotics enhancers have also been studied widely to treat biofilms, as shown by Jia et al. They showed that an antimicrobial enhancer D-tyrosine could successfully enhance ciprofloxacin for prevention and treatment of *P. aeruginosa* biofilm grown on C1018 carbon steel, while reducing the ciprofloxacin dosage [149]. Similarly Xu et al summarized about various components such as D-amino acids, ethylenediaminetetraacetic acid, ethylenediaminedisuccinate, norspermidine, bacteriophages etc. that can enhance antibiotics and biocides to prevent and treat industrial biofilms, which can be studied and applied in medical biofilms as well [150].

2.5.4. Bioacoustic effect

It has been reported that ultrasonication (500 KHz) in combination with antibiotics increases the transport of antibiotics across biofilms, in a process known as the bioacoustic effect [38, 43, 117]. It also effectively bypasses the conditioning film hence preventing the surface adhesion of most bacteria including *E. coli* and *P. aeruginosa* [117]. A study showed that ultrasound waves in combination with gentamycin entrapped in bone cements were able to prevent 70% of biofilm formation in a rabbit model [151]. A device transmitting low-frequency surface acoustic waves was studied on the indwelling catheter, and it was able to eradicate more than 85% of *E. coli*,

S. epidermidis and *P. aeruginosa* biofilms when applied with gentamicin [152]. Various studies have been performed on ultrasonication (28–70 KHz) and ultrasound mediated microbubbles (300 KHz) methods combined with vancomycin, aminoglycoside or gentamicin, which have demonstrated antibiofilm effects in *S. epidermidis*, *E. coli*, and *P. aeruginosa* [145, 153, 154, 155, 156, 157]. Another study reported on the use of low-frequency vibration therapy in successfully assisting tobramycin in killing *P. aeruginosa* biofilms at subminimal inhibitory concentrations [158]. These technologies may be used as efficient noninvasive alternatives for treating implant associated infections that have shown antibiofilm effects when combined with antibiotics.

2.5.5. Surface modification of biomaterials

Another approach of interest is the surface modification of biomaterials used in implantable devices [84]. It is believed that prevention will be easier, safer and more cost-effective than treating a biofilm that has already formed. Although it is meant to serve the same purpose, surface modification differs from forming a coating on a biomaterial, in that it performs its function without the use of any coatings (*i.e.* the non-adhesive properties are a part of the material itself). Using various techniques, including matrix-assisted pulsed laser evaporation, researchers are trying to modify biomaterial surfaces to prevent initial attachment of bacteria. Biomaterial properties such as surface area, surface roughness, surface energy, and hydrophilicity can enhance or lessen protein adsorption and microbial attachment [100]. For example, increase in material's stiffness has shown an increase in bacterial adhesion observed in *S. epidermidis* and *E. coli* [159]. Such correlations can help modify and optimize the surface of a material in order to prevent bacterial adhesion. Thus, such factors are investigated for modifying the biomaterial surfaces in order to prevent infection [130, 131, 160, 161].

2.5.6. Antimicrobial photodynamic therapies

Photodynamic therapy is based on the production of reactive oxygen species when light absorbing compounds (photosensitizers) react with light and oxygen. When this technique is used to eradicate bacterial cells, it is termed antimicrobial photodynamic therapy [98]. Various light sources have been used in *in vitro* and *in vivo* studies, such as yttrium aluminum garnet (YAG) lasers [162, 163], potassium yttrium tungstate (KYW) lasers [164], and femtosecond [165] and near-infrared lasers [166], showing the potential of photodynamic therapy to treat and control biofilm-based infections. Multiple bacterial biofilms have been shown to be eradicated using diode lasers (405–940 nm) and different photosensitizers on acrylic resin, glass, titanium, and zirconia, which in some cases was shown to be synergistic with antibiotic treatment [163, 167, 168, 169, 170, 171, 172, 173, 174]. LEDs (385–660

nm) have also been used to inhibit and eradicate bacterial formation on silicone coupons, dental implant surface, acrylic resin and titanium [162, 168, 175, 176, 177, 178, 179, 180]. A wide range of light in the electromagnetic spectrum has been shown to be useful in destroying bacteria, including the higher energy UVC and blue light, when combined with antibiotics [170]. Although these non-invasive technologies seem to be effective, there needs to be further investigation, especially regarding their cytotoxicity.

2.5.7. Early diagnosis of biofilm formation using biosensors

Early diagnosis of infections using biosensors and hyperspectral imaging methods are also active fields of research for the diagnosis, prevention, and control of biofilm growth on material surfaces such as stainless steel, titanium, and titanium alloys [181]. While the treatment of bacterial biofilms is difficult, proper and efficient diagnosis has also proven to be a challenge. Current diagnostic tools include blood tests for increased leukocytes, scanning electron microscopy (SEM), C-T scans, MRIs, atomic force microscopy (AFM), and colony forming unit (CFU) counting [18]. However, even with these available methods, biofilm-based infections are not efficiently diagnosed [39, 56]. As such, there is an interest in improving and developing new diagnosis/quantification techniques. Some of these techniques include improved CFU counting, light microscopy, SEM, confocal scanning laser microscopy, AFM, Fourier transform infrared spectroscopy, radiolabeling, contact angle measurements, and qPCR [18]. Impedance microbiology, which can detect the presence of microorganisms in samples, has been used to develop an interdigitated microelectrode sensor system that showed low frequencies (10–100 Hz) to be more sensitive for *S. epidermidis* detection [182]. Surface-enhanced Raman spectroscopy (SERS) is another label-free technique widely studied today for molecular sensing. Raman spectra usually contain many sharp peaks that correspond to specific molecular vibrational frequencies that provide detection of the presence of specific molecules in a sample [183]. The high sensitivity of SERS has allowed for the effective detection of Salmonella, Listeria, *E. coli*, *S. epidermidis* and Bacillus using silver nanoparticle synthesis on the bacterial cell walls [183]. As mentioned earlier, bacterial biofilm prevention is better approach than eradicating pre-formed biofilms, hence bacterial sensing/detection technologies will be critical in the clinical setting for preventing biofilm-causing infections.

3. Conclusions

It is now clear that bacterial biofilms are pervasive and resilient and it is a challenge to eradicate them [6]. This review outlined the stages of bacterial formation on implants and various technologies that have the potential to prevent and/or treat biofilms causing infections. Bacteria tend to behave differently *in vitro* and *in vivo*.

Hence the behavior of bacterial biofilms *in vivo* must be thoroughly studied. Currently, their resistance towards antibiotics and phagocytes is a pressing concern, and recurrence of infections after treatment is another major problem. An alternative to antibiotics and repeated surgeries is required to control the morbidity and mortality rates associated with their use. The technologies mentioned in the review are currently studied in *in vitro* and *in vivo* models. Further mechanistic research is required and the limitations that have been identified need to be overcome in order for these potential therapies to move ahead into clinical trials. With growing success in the development of effective therapies one can expect their introduction to the market in the near future.

Declarations

Author contribution statement

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Competing interest statement

The authors declare no conflict of interest.

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