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Review Article

REVIEW ON ROLE OF BIOFILM IN ORAL CAVITY INFECTION AND THEIR CONTROL AND PREVENTION STRATEGIES: A REVIEW

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A B S T R A C T

The formation of a biofilm is regulated by various physical, chemical, and biological processes. Bacterial biofilm infections are healthcare-related, including those associated with the use of dental implants and prostheses. Oral implants associated bacterial biofilm usually caused by *Staphylococcus epidermidis, Staphylococcus aureus, Escherichia coli and Pseudomonas aeruginosa*. Effectiveness of many antimicrobial drugs has been lost due to the evolution of pathogenic resistance. Biofilms have the unique ability to tolerate antibiotics and immune systems. Owing to this property, biofilms develop on oral implants and lead to various diseases such as cystic fibrosis, native valve endocarditis, otitis media, periodontitis, and chronic prostatitis. Biofilms also encourage gene transfers among bacteria, which can favor the incorporation of several virulent strains. Another possible component mediated by biofilm cells is differential gene expression. Therefore, an alternative way of reducing biofilm is very essential. The anti-adherence and anti-quorum sensing compounds can be used to eradicate the bacterial biofilm by enhancing susceptibility towards the bacteria.

INTRODUCTION

A bacterial biofilm is a complex community of bacteria attached or associated with a surface or interface encased in an extracellular polymeric substance (EPS). The composition of the EPS is complex and may contain polysaccharides, proteins, nucleic acid, lipids, and metals. The EPS provides the 'house' of the biofilm, giving the residing microorganisms a haven from the effects of host immunity or administered antimicrobials. Biofilms are well-structured, cooperating microbial communities that adhered to various types of surfaces. Microbes forming biofilms secrete slimy extracellular polymeric substances (EPSs), providing biofilms with their resistance against antibiotics. The formation of a biofilm is regulated by various physical, chemical, and biological processes (Fletcher 1980; Characklis and Marshal 1990). Bacterial biofilm infections are, in general, healthcare-related, including those associated with the use of dental implants and prostheses. Oral implants associated bacterial biofilm usually caused by *Staphylococcus epidermidis, Staphylococcus aureus, Escherichia coli and Pseudomonas aeruginosa*. Effectiveness of many antimicrobial drugs has been lost due to the evolution of pathogenic resistance. Biofilms have the unique ability to tolerate antibiotics and immune systems (Bryers, 2008). Owing to this property, biofilms develop on oral implants (Auler *et al*. 2010) and lead to various diseases such as cystic fibrosis, native valve endocarditis, otitis media, periodontitis, and chronic prostatitis. The potable water systems biofilms can harbor pathogens like *Legionella pneumophila*, non-tuberculous mycobacteria, and Helicobacter pylori (Donlan, 2002). Biofilms also encourage gene transfers among bacteria, which can favor the incorporation of several virulent strains. Another possible component mediated by biofilm cells is differential gene expression. Therefore, an alternative way of reducing biofilm is very essential. The anti-adherence and anti-quorum sensing compounds can be used to eradicate the bacterial biofilm by enhancing susceptibility towards the bacteria.

Structure of Biofilm

A biofilm is a multilayered community of the sessile cells that form a syntrophic association that remains embedded in hydrated extracellular polymeric substances (EPS). The EPS matrix of the biofilm layer provides the architectural integrity to the bacterial colonies present within the biofilm to ensure the stability of the biofilm in negative conditions and enhances cell division (Sehar and Naz, 2016). It also provides essential nutrients which enables genetic and intracellular transfer through quorum sensing of the biofilm-forming bacterial species (Ongenae, 2017). The major component of any EPS matrix is water which comprises about 95–97% of the total space. Apart from that, there are 2–5% of microbial cells of different species, extra cellular proteins and also the proteins which resulted from the lysis of the bacterial cells. This EPS

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helps the cells to colonize upon the living, inert or upon the boundary surface. The composition of the matrix contains various nutrients like carbohydrates, proteins, lipids, nucleicacids, and other minerals that provide nutrients to the dwelling cells. This influences the organisms that are living in the matrix of the biofilm to become virulent, as this encapsulation gives rise to the antimicrobial resistance, and is also associated with the phenotypic and genotypic changes within the organisms. This biofilm matrix is the preferred way for the bacteria to live in as it provides the cells with optimal conditions for the exchange of genetic materials involving the process of horizontal gene transfer, and hence biofilm becomes the natural state of its existence (Hall-Stoodley *et al*. 2004). The sessile micro-colonies dwelling within the biofilm develop intimate connection by cell-to-cell communications known as quorum sensing (QS). Quorum sensing is a density-dependent communication system existing between the sessile cells which help in establishing the biofilm. The QS involves various chemical inducers that vary from Gram-positive to Gram-negative bacterial cells. Auto-inducer (AI) molecules present within the EPS layer diffuse freely across the cell membrane and regulate the quorum sensing. At the initial stage of the biofilm formation, the AI concentration is very low, but with the increase of the cell population, the AI value reaches to the threshold level in order to activate or repress target genes. Biofilm can be formed by the microbes depending on various cellular and environmental factors including cellular recognition for specific or non-specific attachment sites, nutritional level or exposure of planktonic cells to sub-inhibitory concentration of antibiotics. The biofilm formation is regulated by environmental factors, nutrient supplied and the components present inside the biofilm layer.

Discovery of Biofilm

Bacterial assemblage in the form of biofilm on teeth enamel was first observed by Antonie van Leeuwenhoek with his simple microscope (Donlan, 2002) in the seventeenth century. The photomicrograph of slimy layer (Jones *et al*. 1969 a, b) revealed the cell morphology. Later by using a special stain, ruthenium red coupled with osmium tetroxide fixative, scientists could show the presence of polysaccharide in the biofilm matrix. It was found that those bacterial cells, associated with the consortium of microorganisms, can adhere to the surface and are able to develop biofilm. According to Costerton *et al*. (1978), microbes can stick to both biotic and abiotic surfaces to form biofilm. Later it was established that the biofilm formation is a complex process and generally is regulated by a combination of different variables present in nature, which is dependent on the growth medium, the substratum, and the cell surface (Jones *et al*. 1969 a, b). A well-formed biofilm is generally composed of microbial cells and EPS and possesses a surrounding which is used for the exchange of genes or genetic material between the cells (Characklis *et al*. 1990). The biofilm is protected from antibiotic, antiviral, antimalarial, antifungaland anthelmintic drugs (Corpe, 1980). Because of this, many of the medicines turnout to be not effective, and the infections dominate the body, increasing the risk of spreading of the infections (Rosenberg *et al*. 1982). Since then, study of bacterial biofilm got a significant role to play in the arena of health care, industrial process and environment.

Development process of Biofilm

Genetic studies show that the formation of biofilm is a multistep process. The process of biofilm formation requires a specific signaling mechanism, known as quorum sensing, occurring in between the bacterial cells. This process also involves the transcription of various genes with respect to the planktonic form of microbial cells of the same organism (Donlan, 2002). The existing channels within the biofilm help in separating the micro-colonies. The visco-elastic feature of the EPS matrix provides mechanical stability to the indwelling biofilm (Shaw *et al*. 2004). The process of the biofilm development involves events such as initial attachment or contact of the sessile communities with a surface, development of micro colonies, maturation and formation of the architecture of the biofilm and dispersion of the sessile communities resulting in the spread of the biofilm associated infections (Sutherland 2001a, b).

Integral components of bacterial biofilm

1. Extra cellular polymeric substances (EPS): Cationic groups present in amino Sugars and proteins (e.g. NH_3þ), Anionic groups of uronic acids, Proteins and nucleic acids (e.g.COO;HPO_4), A polar group from proteins, (present in aromatic amino acids), (phosphor lipidsand humic substances) (Grkovic *et al*. (2002).
2. Microbial cell outer membrane: Lipo-polysaccharides of gram- Negative bacterial cells, Cell wall consisting of *N*-Acetyl glucosamine and *N*-acetyl muramic acid, offers cationic and anionic sites and the lipo-teichoic acids in Gram-positive cells.(Grkovic *et al*. (2002).
3. Cytoplasmic membrane, offering a lipophilic region: Cytoplasm, as a water phase separated from the surrounding water minerals Precipitates (sulphides, carbonates, phosphates, hydroxides) Free and bound metals (Ca2+, Fe3 +, Mg2+)(Hellstrtom (1938).
4. Biogenic particulate materials (degradation products) environmentally relevant substances. Organic pollutants (e.g. biocides, detergents, xenobiotics) In organic pollutants (e.g. heavy metals) (Nickel *et al*. 1987).

Stage1. Initial contact and reversible attachment on the surface

The attachment of the sessile cells upon the biotic and abiotic surface occurs with the help of flagella and pili that provides them with physical forces like that of the electrostatic, vander Waals forces. Other factors which greatly influence the process of attachment involves the type of surface on which the attachment would take place and the cohesive forces existing between the sessile communities and the surface (Garrett *et al*. 2008). The two factors which also influence the attachment of the bacterial cells are the adhesion, which leads the attachment of cells to a solid biotic and abiotic surface, and cohesion leading to the interaction and attachment of cells that occur at the time of the biofilm formation (Garrett *et al*.2008). The interface between solid and the liquid can also be the potent cause for the biofilm formation and microbial growth (Costerton *et al*. 1999). The initial attachment of the motile cells to the surface includes the formation of the conditioning layer that mainly comprises organic (proteins, electrolytes, surface-active compounds and cholesterol) as well as inorganic (salts and ionic materials) compounds. After this initial step, biofilm formation occurs rapidly. The primary colony interacts to the surface in two different ways, either due to different

forces like Brownian motion, gravity or diffusion or the flow of the liquid or air or due to positioning mechanisms like flagella motility or surface appendages. The bacterial adherence to the surface may be reversible due to the interactive forces (hydrophobicity, electrostatic forces, charges interactions) applied in the single pole of the bacteria. Irreversible attachment is much more stable compared to the previous one as adherence proteins and extracellular proteins are expressed to cement the bacteria to the surface as the long axis of the bacterial cell is positioned parallel to the surface.

Stage 2. Cell accumulation and micro colony formation

The accumulation of cells involves the mechanism of cell-to-cell adhesion and provides them stability for the multiplication and division of them microbial cells, which are initiated by the cell signaling mechanism originating with the EPS. This leads to the development of micro-colonies within the cells (Costerton *et al*. 1999; Mckenney *et al*. 1998). The micro-colonies existing within the biofilm play an important role in exchanging substrate, distributing the metabolizing and excreting products. A multilayered bacterial micro-colony is formed as mid late colonizers adhere to primary colonizers. This occurs over a period of a few hours by the help of signaling molecules and quorum sensing pathways. After the attachment to the biotic and abiotic surface, cell divisions and multiplications of the microbial cells start. The microbial cells coordinate among themselves by several aspects, including exchange of the substrates, distribution of important metabolic products and excretions of metabolic end products.

Stage 3. Extracellular polymeric substance production

After cell accumulation and adherence to the surface, the bacterial cells develop extracellular and multilayered micro-colonies which cover themselves with a layer of extracellular polymeric matrix (EPS) (Sutherland 2001 a, b). This extra cellular polymeric matrix consists of polysaccharides, proteins, lipids, nucleic acid, multivalent compounds and inorganic substances. EPS is one of the major components of biofilm formation and can produce 50–90% of total biofilm mass Donlan (2002). It helps the bacterial colonies to communicate with each other and attach on any biomaterial surfaces. In Gram-negative bacteria, the outside of EPS is anionic in nature due to the presence of negatively charged compounds such as uronic acids and pyruvate, whereas, in the inner side of EPS, the compounds are positive in nature like calcium and magnesium ions. The major component present in EPS is extracellular DNA which provides the structure of biofilm.

Stage 4. Biofilm maturation

It is the fourth stage where the biofilm gets matured. Biofilm is a complex architecture and has pores of different sizes through which bacteria can freely move within the EPS. As the biofilm mature, more void spaces are produced through which nutrients, oxygen and other inorganic salts can freely move into the biofilm and the waste by products are removed through the void space (Costerton *et al*. 1994).

Stage 5. Detachment

It is the separation of the bacterial cells from the biofilm layer by the physical and chemical mechanisms. Physical mechanisms like shear force can cause erosion of biofilm. Chemical factors may stimulate detachment, for example, substrate changes, nutrient changes and changes in the EPS.

Establishment of Oral Biofilm

The mouth being the gateway of the digestive tract harbors diverse microorganisms. Indeed, the oral cavity is unique in the level of microbial diversity and complexity, supporting upto1000 different species of microorganisms. They have been estimated to be the second most complicated part of the body, after the colon (Mosaddad *et al*. 2019). Human oral microbiome comprises a large number of microbiota that are specific to particular niches like the cheek, teeth, surface of the tongue, palate, gums, lingual tonsils and gingival pocket (Krzyściak *et al*. 2016). Biofilm formation in the oral cavity is most widespread on the teeth because the tooth provides a non-shredding, stagnant surface with possible food compaction. So far, various investigations suggested that the oral cavity comprises approximately 700 different bacterial species, and about 10–20 species constitute about 90–95% of the bacteria present in an individual. These microbial cells can exist upon the oral mucosa comprising the cheeks, palate, lips and dorsal side of the tongue. Bacterial cells also exist on the tooth, sub-gingival areas, surface of the root, pits and fissures and upon the surfaces of the smooth muscles.

A broad spectrum of varied bacterial species is found within the buccal cavity that is formed by complex interactions existing between the microbial populations that determine the normal pathological and physiological conditions of both systemic and local levels (Kriebel *et al*. 2018). Other major inhabitants of gingival sulcus area and gingival cavities are *Bacilli*, *Moraxella*, *Neisseria* and *Spirochaetes* like *Treponema* (*T. denticola*, *T. orale*, *T vincentii*). Peridontal pockets are infested by *Mycoplasma orale*, *M. pneumoniae* and *M. hominis*. A large number of fungal flora are found in the oral cavity, gingival areas, periodontal abscess and infected root canal. Among them *Candida albicans*, *Penicillium*, *Hemispora* and *Aspergillus* are noteworthy. Protozoa like *Entamoeba* can be found from patient swith periodontitis, and some virus like mumps virus, EBV, influenza and measles virus can be found during the advanced stage of the disease.

The papilla on the upper surface of tongue provides an important shelter to oralmicroorganisms. *Micrococcus mucilaginosus* and *Streptococcus salivarius* are the predominant members which are generally not found on the teeth. Saliva also abodes a number of bacteria like *Streptococcus orali s*and *S. salivarius*. Tooth surface, pits, fissures and root canal all are very lucrative sites for the bacteria. The uninfected dental surface is especially infested by *Streptococcus sanguinis* and *S. mutans*. The gum or gingival area consists of the mucosal tissue lying over the mandible and maxilla regions of mouth remains protected from mastication, movements of tongue or flushing of saliva. It is occupied predominantly by *Actinomyces* and *Streptococci.* But there is a variation in the nature of inhabitants according to the location, as supra-gingival plaque is dominated by cocci, while subgingival plaque is infested by filamentous bacteria and spirochetes. *Bacteroides melaninogenicus* is a type of pathogenic organism that possesses the ability to exploit this habitat and bring about destruction to the gingival epithelium. Comprehensive microbiome analysis of tonsillar crypts indicates that the predominant bacteria are *Fusobacterium* spp., *Prevotella* spp., *Treponema* spp., *Sphingomonas* spp., *Porphyromonas* spp. and *Haemophilus* spp. (Watanabe *et al*. 2017). *Haemophilus influenzae*, *Streptococcus pneumoniae* and *Moraxella catarrhalis* are the groups of potential

pathogens that are found exclusively in the adenoids of patients with pharyngo tonsillitis; this is an indication that adenoids and platine tonsils are the store house of various microbial cells that are potentially pathogenic in nature.

Several systemic diseases have been shown to be influenced by dental plaque associated oral diseases, especially periodontitis. Periodontal inflammation may alter both the course and pathogenesis of these diseases. "Focal infection theory" explains the role of localized infection, often asymptomatic, in disseminating microorganisms or their products to distant sites causing disease. Microbial pathogens of the plaque biofilm have been linked to atherosclerosis and coronary heart disease. They may cause deregulation of the immune system, with progressive inflammation, and hence, disruption of endothelial cell function, an early indicator of cardiovascular disease (Slocum *et al*. 2016). Poor oral hygiene and the presence of dental calculus have also been linked with arthrosclerosis, which may lead to myocardial infarction, stroke, or death (Soder *et al*. 2014; Dai *et al*. 2015). The risk of infective endocarditis from oral bacteria is well documented (Parahitiyawa *et al*. 2009). Poor oral hygiene and plaque increase the risk of bacteremia when dental procedures like tooth extraction, or even tooth brushing, are carried out. Thus, antibiotic prophylaxis in susceptible individuals has become mandated and an improved oral hygiene can decrease the risk of infective endocarditis (Lockhart *et al*. 2009). The microbiomes of dental plaque, non-directed bronchial lavages (NBLs), and endotracheal tubes show high similarity suggesting the role oral cavity may play as a source of microorganisms involved in aspiration to the endotracheal tube and the lower airway (Marino *et al*. 2017). Diabetes mellitus has chronic periodontitis as one of its long-term complications; however, a "two-way relationship" between blood glucose control and periodontal disease is now being considered. Pro-inflammatory mediators, such as interleukin-6 (Dubey *et al*. 2003) and tumor necrosis factor-α, which are produced as a result of microbial insult in periodontitis sites, may reach the systemic circulation and can interfere with the functioning of insulin receptors. This would lead to developing insulin resistance and thus impaired glucose homeostasis (Gurav 2012). Maternal periodontitis is considered to be a risk factor for the baby's health. Preterm birth and low birth weight have been linked to periodontal disease in mothers (Ide and Papapanou 2013). The role of inflammatory cytokines or direct dissemination of bacteria and its products to the feto-placental unit are thought to be the mechanism by which plaque biofilm may influence outcome of pregnancy (Pitiphat *et al*. 2008). Approaches for Control of Dental Biofilm as per "National Centre for Health Statistics" in USA, approximately 37% children in the age-group of 2–4 years and 2.4 billion people in the world have dental caries (Dye *et al*. 2015; Kassebaum *et al*. 2015), while 15–20% of populace in the age-group of 35–44 years has severe periodontitis (WHO 2012a). Severity of the situation is self-evident. The primary step in management of biofilm-related dental diseases is physical treatment, which aims to reduce the bacterial load in biofilms. It also helps in preventing maturation of the biofilm. Systemic conditions, or co-existence of multiple disorders like diabetes mellitus, acquired immune deficiency syndrome (AIDS), and other immune suppressing conditions and genetic mutations like human Beta-defencin B1 make treatment much more complex and difficult (WHO 2012 b). Biofilm pathogens, if allowed to proliferate, may directly or via their products enter the systemic environment (Cullinan *et al*. 2009; Cullinan and Seymour, 2000) and cause further complications including diabetes mellitus (Holmstrup and Flyvbjerg 2016), cardiac diseases (Lockhart *et al*. 2012), osteoporosis (Wang and McCauley 2016), pneumonia (Laurence *et al*. 2015), stroke (Palm *et al*. 2016), etc. The main modality for control of supra-gingival plaque is mechanical debridement. Additionally, chemical agents in the form of mouth washes and antimicrobial agents may be used for supplemental therapy. Novel treatment methodologies are also being explored. The treatment approach for disruption of dental plaque is designed based on the status of periodontitis. If reversible, that is gingivitis, then conservative techniques. Biofilm-Mediated Dental Diseases for plaque removal are preferred. These may also be carried out by the patient. If the disease has progressed to periodontitis, then the severity of the disease is used to define the scope of the treatment. The most common technique for judging the severity of periodontitis is the "probe test" wherein a periodontal probe, an instrument with grading, is used to measure the depth of the "periodontal pocket," a pocket formed between the tooth surface and the gingiva due to apical migration of the junctional epithelium from the cement enamel junction (Slots *et al*. 1985). A 5 mm or less depth of the pocket indicates that non-invasive techniques may be sufficient. Professional plaque removal from the sub-gingival region by scaling is carried out together with root planning and smoothening of cementum surface of the tooth. Surgical intervention is indicated when the pocket depth increases beyond 5 mm. These procedures commonly include flap surgery, which can be supported by soft tissue grafting and/or bone grafting (Fernandesa *et al*. 2018). Flap surgery refers to elevation of a "flap" of gingival tissue, which allows cleaning of tooth surface, as well as the tissue part. This is then sutured back, either in the same place or apically or coronally depending on the treatment plan. Soft tissue grafting involves the placement of a "graft" tissue harvested from another site (commonly the hard palate) in order to restore the lost or damaged soft tissue of the gingiva. Bone grafting, similarly, involves the replacement of destructed bone by an autologous harvested bone or by alloplastic materials (Fernandesa *et al*. 2018). Mechanical plaque control daily disruption of dental plaque, at and above the gingival margin. Dental Implants Biofilms located on the surface of teeth are called dental plaque. Microscopic organisms multiplying in the dental plaque are associated with various diseases, for example caries, gum disease, periodontitis, and peri-implantitis. Such microbial assaults represent a significant reason for dental implant failure. Periodontal diseases and peri-embedded infections are explicit contaminations initiated by microbial species when the balance between host and microbial pathogenicity becomes unbalance.

Ecological factors responsible for oral biofilm

Various factors like nutrient availability, pH, oxygen, presence of other organism, mechanical activities, amount of gingival crevicular fluid and presence of antagonistic factors determine the nature of the microbiome present in a particular niche of oral ecosystem (Krzyściak *et al*. 2016; Marsh and Zaura, 2017). Microorganisms require hemin (Bacteroides *melaninogenicus*, *B. gingivalis* and *Capnocytophaga*), menaquinones, oestrogen and progesterone (certain oral bacteroids), while *Treponema denticola* needs permin as nutrients (Wyss1992). Serum contains large amount of

nutrients that are absent in saliva and are found within the gums or gingival crevice where they come in contact with enriched crevicular fluid (Asikainen *et al*.2010). Saliva comprises lysozymes, lactoferrin, lactoperoxidase and specific antibodies possessing an inhibiting effect upon the growth of bacteria. Production of H_2O_2, reduction of pH by acid secretion, synthesis of oxidizing enzymes and bacteriocin can inhibit the growth of certain species while promote the growth of others. Thus, the niche of a particular organism will be determined by the interplay of these ecological determinants.

Formation of dental biofilm and gastric biofilm formed due to dysbiosis may lead to a number of diseases. Microbial cells are omni present and live within any types of environments that provides suitable conditions for their higher mode of living. Microorganisms are highly sensitive to the change in pressure, temperature, pH and salinity, but sometimes it has been observed that certain groups of microbes are able to thrive in these extremes of physical conditions (Horikoshi and Grant 1998). The ability of the microbial cells to live within various conditions is due to the phenotypic plasticity and metabolic versatility (Davey and O'Toole 2000). The microorganisms at different situations exhibit complex differentiation and collective behavior. Researchers have shown that the microbial cells possess the ability to perform various types of intercellular interactions and communications which help them to exist in altered environmental conditions (Kaiser and Losick 1993). The knowledge about structure, functions and dynamics of the persistent human microbiome is provided by various metagenomics and high throughout studies (Qin *et al*. 2010; Huttenhower *et al*. 2012). The microbial communities do not exist in the planktonic forms but they remain encompassed by a self-producing polymeric matrix that help in the adherence of the cells to the inner surfaces of the body (Costerton *et al*. 1995; Hall-Stoodley *et al*. 2004). It is necessary to understand the biofilm formed by multiple species as they exhibit different types of physiology in comparison to the planktonic cells that result in the development of resistances and virulence (Burmølle *et al*. 2014). Various recent studies have been performed on oral microbiome that has been characterized by its involvement in periodontitis, dental caries and oral cancer (Zarco *et al*. 2012).

Strategies to Control Biofilm Formation

Formation of biofilm leads to increase in bacterial pathogenesis as well as antibiotic resistance. Long-term antibiotics are prescribed to prevent further growth of biofilm in patients where removal is impossible. It has been observed that premature biofilmis treated well with antibiotics as compared to the matured ones. However, inefficiency to detect premature biofilm makes it very difficult to start the diagnosis leading to clinical complications arising from mature biofilms. Antibiotics are selected on the basis of sensitivity and ability to penetrate the biofilm matrix owing to the fact that bacterial biofilms are likely to be highly antibiotic resistant than their planktonic counterparts. It is preferably good to opt for the combinatorial therapy rather than the mono therapy as far as the selection of antibiotics is concerned. This is due to the difference in the mode of action, proper dispensation with regard to dosages, and duration of these antibiotics. Some antibiotics are effective against growing bacterial cells, and others are against the dormant cells. Some antibiotics are coated with hydrophilic coatings such as PEG that build antifouling surfaces minimizing the microbial adhesion required for biofilm formation, whereas some are coated with nano-particles to prevent formation of biofilm. In addition, photodynamic therapy (PDT) is also widely used to dispense the bacterial cells in biofilm by carefully selecting and staining the bacterial cells by a photosensitizer dye (Percival *et al*. 2014). Lastly, there exists a long list of molecules that interact with signaling pathways of the bacterial cells, in both types of bacterial cells. Polyphenol molecules, enzymes, or peptides may act as anti-biofilm molecules.

Targeting the AHL-Mediated QS

AHLs or *N*-acyl homoserine lactones are the group of small signaling molecules used by Gram-negative bacterial cells to regulate the cell population density and swarming motility inherent during biofilm formation. Binding of these signaling molecules to Lux-R-type transcriptional regulator proteins helps in the target gene expression (Gambello and Iglewski1991; Passador *et al*.1993). Thus, on eplausible strategy to down regulate the biofilm-forming gene regulatory pathway is to search for the compounds that can compete with the AHL molecules during binding with the receptor proteins.

Preventing the Stringent Response in Bacteria

During nutritional stress conditions, bacteria produce signaling molecules known as alarm ones, guanosine penta-phosphate and guanosine-tetra phosphate, together r called as (p)pp Gpp. Change in (p)ppGpp pool affects the biofilm development in bacteria during starvation. There are various molecules that affect the functioning of (p)pp Gpp by inhibiting their accumulation within the protoplasm. Amphipathic cationic peptide 1018 surpasses the bacterial cell membrane and directly binds to (p)ppGpp, thus disrupting the biofilm in three ways. First, when added before biofilm initiation step, it prevents formation of biofilm. Second, it eradicates the bacterial cells present within biofilm without having any effect on the planktonic cells. Third, it can collapse the established biofilm which can be even as old as 2 days (Fuente-Nunez *et al*. 2014). Peptide 1037 was found to reduce biofilms formed by various Gram- positive and Gram-negative bacteria (de la Fuente-Nunez *et al*. 2012). Peptide 1038 is known to induce twitching motility and prevent initial attachment and quorum sensing of *Pseudomonas* during biofilm creation, thus destroying the biofilm. Derivatives of the peptide 1018 such as HE4 and HE10 are known to be active against *B. cenocepacia* and *P. aeruginosa.* Moreover, in some cases, synergistic actions of these peptides along with antibiotics have led to interesting results. Some secondary metabolite polyphenols like eugenol are found to prevent the stringent response in bacteria such as *S. mutans* by down regulation of gene, *relA*, involved in the control of stringent response.

Enzymatic Dispersion of EPS

EPS serves as a protective matrix providing nutrition and shelter to the bacterial cellswithin the biofilm. Thus, molecules that disperse the EPS layer will tend to exposethe microorganisms to the antimicrobial agents. DNases and polysaccharide lyases enzymes are capable of disintegrating the EPS (Stewart 2015). DNase I possesses the ability of denaturing the extracellular DNA (eDNA) present within the biofilm structure (Kaplan 2009; Izano *et al*.2008).

Disrupting the Peptidoglycan Layer

Peptidoglycan layer in the cell wall acts as a firewall

preventing and helping the bacteria against antimicrobial agents. Thus, cleaving this layer will inhibit the biofilm generation. Polyphenolic compounds like tannic acid and epigallocatechin gallate reduces biofilm formation by directly or indirectly affecting the peptidoglycan layer.

Molecules Causing Biofilm Dispersal

Biofilm disassembly involves disruption of the EPS matrix by production of extra-cellular enzymes causing degradation and dissolving of the adhesive component s being present with the matrix found within the biofilm. This leads to detachment of bacterial cells from the colony and its release into the environment.

Disassembly of Lipopolysaccharides /Membrane permeabilization

One effective way to stop biofilm formation is the use of antimicrobial peptides (AMP) as an alternative to conventional antibiotics. AMPs are low weight proteins that are evolutionary conserved possessing antimicrobial activity and can act effectively against bacteria, fungi and viruses. They possess hydrophobic and hydrophilicsides that help in inserting into the lipid bilayer or lipopolysaccharides, there by solubilizing in aquatic environment (Izadpanah and Gallo 2005). This mechanism results in destabilization of lipid head groups by the formation of multiple pores, causing the disruption of cellular membrane integrity. PTP-7 is an example of lytic peptide that can enter deep in the biofilm and kill bacteria within the biofilm (Kharidia and Liang 2011). Polymyxin E or B and colistin can bind to LPS in Gram-negative bacteria, making the outer membrane permeabilized. Gramicidin Scan distort the membrane integrity of the Gram-positive and Gram-negative bacteria. Alteration of membrane potential by pore formation also helps in biofilm disruption.

Pore formation

A toroidal pore formation (Mihajlovic and Lazaridis 2010; Gottler and Ramamoorthy 2009), barrel-stave through carpet-like mechanism (Shai and Oren 2001), causing efflux of intra cellular materials. Lantibiotics are another class of ribosomally synthesized peptide antibiotics that are modified post-translationally in Gram-negative bacteria and serve as anti-biofilm agents. Their mode of action involves damaging the bacterial membrane and preventing the production of enzymes. Common lantibiotics such as nisin and subtilisin induce leakage to the cytoplasmic membrane by forming pores that causes the cytoplasmic solutes to leak out of *B. subtilis* and *Staphylococcus simulans* (Bierbaum and Sahl 2009). In another study, bio-surfactants such as sophorolipids show its efficacy against biofilm byenhancing the membrane permeability. The sophorolipids of *B. subtilis* help indisrupting the cytoplasmic membrane causing the leakage of various intracellular enzymes like malate dehydrogenase which in turn results in the efflux of their cytoplasmic contents (Rienzo *et al*.2015).

Prevention of Cell Division

There are a wide range of molecules starting from metal ions, antibiotics, chelating agents, natural polymers, and antimicrobial peptides that are known to disturb the membrane potential of the plasma membrane, thereby preventing cell division. For example, accumulation of silver within the intracellular vacuoles leads to pore formation in plasma membrane (Tiwari *et al*. 2015; Percival *et al*. 2014 a, b). Antimicrobial peptides (AMPs). There has been lot of research work and studies in the field of biofilm formation by Gram-positive as well as Gram-negative bacteria. The greatest challenge in the medical world is to combat the antibiotic resistance of the bacterial biofilms. Therefore, various effective and newer techniques have to be developed with main focus on different anti-biofilm molecules and modifying different signaling pathways related with quorum sensing. Poly-microbial model systems have been studied, and it is found out that quorum sensing is important for cooperation and also for competition among various bacterial species. These models also help us to understand social behavior and evolution of quorum sensing. Cyclic-di-GMP signaling pathway is absent in higher eukaryotes, and therefore this knowledge can be used to design anti-biofilm molecules. Another way to reduce the process of biofilm formation is by targeting the amyloids; this in turn leads to weakening of the adherence of the bacterial cells to the surface (Wu *et al*. 2015). The presence of virulence factor in pathogenic bacteria helps in spreading of infections within the host. An idea about the genetic and virulence factors may help us design drugs that can fight against the infections and also help in inhibiting the infection through QS mechanism. There may be different mode so faction of every anti-biofilm molecule, but more than one mechanism can be followed by a single molecule, for example, the anti-biofilm molecule ECGC can perform their action either by disrupting the membrane and degrading the peptidoglycan layer or by hindering the AHL-mediated quorum sensing pathway. The antimicrobials which are derived from natural sources have more diversity regarding their structure and biochemical properties when compared with synthetic drugs. Therefore, as a result, it has better binding capability to the target molecules and can be used for various in silico approaches in the field of pharmacy and also for creating alternative therapies. There are some disadvantages of using naturally derived anti-biofilm agents, that is, they are time-consuming, are expensive, can show various results when extricated from their sources, and are less sustainable. On the other hand, manmade drugs may be of nominal price and are relatively faster in action but can have adverse side effects. A few methodologies involve preventing microbial cells attaching to surfaces, hence preventing the development of biofilms (Francolini and Donelli 2010; Sousa *et al*. 2011). Similarly, there are a few strategies that control the development of biofilms on the surfaces of medicinal gadgets.

Cell Repellent and Non-Adhesive Coatings

A few materials like silicon are utilized in the development of urinary catheters and contact lenses. However, cells can promptly cling to surfaces of hydrophobic materials, for example, polydimethylsiloxane (PDMS) elastomers, because of the impact of van der Waals interactions and hydrophobicity. The functionalization of gadget surfaces with self-assembled monolayers (SAMs), polymer brushes, and polymer coatings is a profitable and successful methodology for forestalling cell bonding on these surfaces (Hou *et al*. 2007; Raad *et al*. 2008). The Active Release of Antimicrobial Compounds and Biofilm Inhibitors Coatings that effectively discharge antimicrobial mixes or biofilm-inhibitory mixes can be utilized to avert biofilm development and gadget-related diseases in patients (Wenderska *et al*. 2011; Worthington *et al*. 2012). Such coatings comprise PDMS elastomers and

ceragenin acholic corrosive inferred antimicrobial operator that has a quick, expansive range, and a nonspecific strategy for assault on bacterial cell films (Epand *et al*. 2010). Antimicrobial Coatings with Tethered Biocides, the coatings comprising certain cationic mixes, in a similar manner to polymers, anticipate biofilm arrangement by killing or hindering microorganisms after their adherence to a surface. Their mode of operation is for the most part connected to changes in film porosity or layer disturbances in cells (Gottenbos *et al*. 2002). Competitive Adherence by Benign Organisms Coatings that consolidate antimicrobial peptides (AMPs) can prevent biofilm development on the surfaces of various restorative gadgets (Bahar and Ren 2013). Biofilms and Healthcare-Associated Infections Tainting of restorative gadgets for the most part happens as a consequence of a few microorganisms that move to a gadget from the skin of patients or medical staff, polluted water, or numerous other external ecological sources (von Eiff *et al*. 2005). The Role of Biofilms in Medical Devices and Implants a wide range of microorganisms have been ensnared within therapeutic gadget-related contaminations of which *S. epidermidis* and *S. aureus* are most regularly connected with biofilms and are generally referenced as causes of HCAIs (Gotz 2002; von Eiff *et al*. 2005; Vuong *et al*. 2004). According to past investigations, roughly 80% of the microorganisms engaged in material-related contaminations are S. epidermidis. Most of them are multidrug resistant isolates, which is one of the greatest challenges in clinical practice. Multidrug resistance is amongst the top three threats to global public health and is usually caused by excessive drug usage or prescription, inappropriate use of antimicrobials, and substandard pharmaceuticals. These species are regularly identified as the cause of biofilm-based HCAIs, including catheter-associated urinary tract infection (CAUTI). In addition, several biofilm-forming bacteria can be found in different medical devices. Central Venous Catheters Focal venous catheters are used to convey liquids, medicines, blood components, or drugs, and are further used in dialysis treatments (Donlan 2008; Percival and Kite 2007). Both the external parts of the catheter and catheter lumen can become sullied and thereby offer opportunities for biofilm arrangements—the length of catheter in situ affecting areal extent and level of colonization (Donlan 2008). It has been documented that within the initial 7-day period after catheterization, extra-luminal biofilm is considered a significant reason for catheter-related circulation system contaminations. In actual fact, vascular catheters that had been in situ for more than 30 days showed proof of heavy luminal colonization and biofilm development (Raad *et al*. 1993). Consequently, patients who require the utilization of such gadgets for intravenous access over long periods of time, for example, bone marrow transplant patients, may indeed face the very real danger of circulatory system contamination (Donlan 2001). It has also been noticed that catheter colonization and biofilm development in focal venous catheters happens rapidly. Urinary Catheters are cylindrical latex or silicone gadgets that are utilized to quantify urine yield and furthermore to gather urine during medical procedures, counteracting urine maintenance and controlling urinary incontinence. For patients, associated dangers increase by roughly 10% each day after catheterization. Biofilms can promptly occur on both the internal and external surfaces of urinary catheters (Donlan 2001), and rising colonization cannot be prevented by cleanliness measures alone. In anticipation of such issues, it is important that clinicians only use catheters when absolutely essential and for limited periods of time (Talsma 2007). Research has centered upon various complex techniques for sanitization and the alteration of therapeutic gadgets to avoid microbial development and biofilm arrangement. The development of antimicrobials attached to the outside of medicinal gadgets like catheters incorporates connection of a flimsy film on the outside of catheters, that is, bound to their surface, or attached to their surfaces within a polymer lattice. Various elements impact the viability of catheters. Their method of treatment with antimicrobial agents, including solvency, hydrophilicity, and fondness to penetrate tissue are for the most part factors that influence their ability to fight against infection. The utilization of bioactive atoms and catalysts is a novel methodology used as an anticipatory action against biofilm development on embedded materials. In one investigation, Ren and colleagues utilized a counterfeit biofilm model to evaluate different cleansers for their capacity to evacuate E. coli from adaptable endoscopes. This examination underscored that increasingly bacterial biofilms are discovered utilizing enzymic cleanser treatments rather than non-enzymic cleanser treatments (Ren *et al*. 2013). In an ongoing examination by Gawande and colleagues the adequacy of a normally occurring protein, combined with a gel, is being assessed with respect to constant injury-related microorganisms (Gawande *et al*. 2014). The diverse methodologies for preventing biofilm development on therapeutic gadgets are provided in Past Present Future. Material Selection Antibiotic Incorporation Novel Strategies Bulk composition Surface topography Implant Dimensions Protein-based materials Bone Graft-based materials Polymer-based materials Dispersal agents. Bacteriophage Releasing materials Surface Modifications and Coatings Bacterial interference. The Role of Biofilms in Medical Devices and Implants Future research should expand our understanding of microbial biofilms and their cooperation with biotic and abiotic surfaces and furthermore build up conceivable control systems including the utilization of antimicrobial-treated therapeutic gadgets and locks for biofilm avoidance and control. A perfect inhabiting therapeutic gadget should have surfaces that are similar to those found in the human body, providing no more hospitable surfaces and thereby anticipating and preventing contamination. To accomplish biocompatibility, the outside of restorative gadgets ought to be smooth and uniform to permit the development of solid tissue and the avoidance of pathogens. The utilization of infection causing agents, taking the surface physico-substance properties of the therapeutic gadgets is the key factors which lead to medicinal gadgets pre-treated with antimicrobials. In the future, to better comprehend and control biofilms inhabiting medicinal gadgets, science must pursue advancements in several areas. A few solid procedures for gathering and estimating biofilms need to be created.

CONCLUSION AND FUTURE PROSPECTS

Treatment of biofilm infections is presently a problematic and intricate challenge for clinicians. Antibiotic treatment alone is often insufficient to overcome biofilm infections. However, the developments of research provide us with more thorough inside knowledge to better understand the nature of microbial biofilms, which has benefited and will continue to support our efforts of combating biofilm infections. Ideally, an effective remedy for biofilm associated conditions should contain

antibiotics, anti-inflammatories, and anti-biofilm activities (3A remedies). The road from molecular mechanisms of biofilm formation to anti-biofilm products is promising, but long. Non-invasive and/or minimally invasive detection methods and standard biofilm assays that mimic clinical conditions are opening the door for new, biofilm oriented solutions. Biofilm treatment at present should include removal of infected indwelling devices, selection of well penetrating and sensitive antibiotics, early administration of high dosage antibiotics in combination and supplemented with anti-QS treatment and/or biofilm dispersal agents. Additionally, nanomaterial impregnations of antibiofilm devices are believed to provide extended antimicrobial effects and to be minimally toxic as compared with small molecule antimicrobials, which exhibit short term activities and are environmentally toxic.

However, Future research must strive to better understand the biologic forces governing Biofilm formation in order to develop more effective strategies to suppress it with new antiseptics that exhibit much higher and more prolonged levels of surface activity. Further studies are warranted to fully explore the molecular mechanism of microbial adherence to prosthetic surfaces in order to develop new materials intrinsically resistant to colonization. Attempt should be made to design devices that fundamentally deny microbial assess and to identify new technology to allow quick detection of contamination of device colonization. In fact, even in last two decades, although boundless advances have been made from both the scientific and the industrial points of view, most of the targets discussed remain unreached, even though a huge number of research papers have been published on these life threatening issues. Manufacturing medical devices that are refractory to microbial colonization and biofilm formation remains an uphill task and it is obligatory to establish closer partnerships between scientists working in universities or research institutes and industrial investigators to accelerate accomplishment the objectives and find more advanced solutions to prevent biofilm related nosocomial infections.

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