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Review on biofilm formation and its control options

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Abstract

The generalized idea that bacteria have a unicellular way of life is not entirely accurate, given that pure planktonic growth is uncommon. Biofilms are defined as an organized group of microorganisms living within a self-produced matrix of polymeric substances which gets attached to several surfaces. This review was done with the objective to give an overview on the mechanism of biofilm formation and highlight its veterinary and public health implications and control options. The formation of a biofilm occurs in five stages, stage of cell attachment, stage securely affixing of cells, stage of micro-colonies formation and beginning to mature, Stage of more maturation, and stage of dispersal of cells from the biofilm. Factors controlling cell attachment include nature of surface, properties of medium and properties of the microbial cell surface. Formation of a biofilm is dependent on the interaction between the environmental stimuli and the reciprocation of the corresponding signalling events by the microorganisms. Biofilms are composed primarily of microbial cells and EPS. The importance of biofilm in disease processes in humans and animals is now widely recognized. In animal species, the risk of infection is probably greater than the risk in humans. In human infections associated with biofilm formation were medical device-related infections including Pacemakers, electrical dialysers, joint prosthetics, intravenous catheters, urinary catheter. As food is identified to be a very efficient vehicle for bringing a large number of people into contact with a potential hazard, food processing equipments can be persistent source of spoilage and pathogenic bacteria if microorganisms form biofilm on them. Ideally, preventing biofilm formation would be a more logical option than treating it. The main strategy to prevent biofilm formation is to clean and disinfect regularly before bacteria attach firmly to surfaces. This process can remove 90% or more of microorganisms associated with the surface. Biofilm detectors, acid shock treatment and recently using bacteriophages have been tried. The prevention and control of biofilm formation is somewhat difficult but prevention is the ideal approach even if there are control methods too. The development of better control and prevention methods with better effect need to be given special emphasis.

Keywords: Biofim, Biofilm Formstion, Control, Public Health

Introduction

Throughout their evolution, bacteria have constantly modified their metabolism and physical characteristics, adapting to practically all environments of the planet. The generalized idea that bacteria have a unicellular way of life is not entirely accurate, given that pure planktonic growth is uncommon; bacteria frequently develop in complex communities (March, 1999).

One of the biggest paradigms in microbiology is the concept of the existence of bacteria as social organisms, whose only activity was to divide to generate a new bacterium, each one identical to the other. However, for more than 60 years it has been suggested that far from this isolated behavior, there may be a group behavior of bacteria (Colon-Gonzalez and Membrillo-Hernandez, 2008). Direct observations of an extensive variety of bacteria have allowed

establishing that most microorganisms remain bounded to the surfaces inside an structured ecosystem named biofilm, and not as isolated organisms (Costerton et al., 1987).

Various definitions of the term biofilm have been proposed over the years. According to the omniscient encyclopedia Wikipedia a biofilm is "a structured community of microorganisms encapsulated within a self-developed polymeric matrix and adherent to a living or inert surface. Costerton et al. (1987) indicates that in their natural environment, over 99% of microbes live in micro-ecosystems as biofilms.

Microorganisms have the ability to adhere to and grow on surfaces (e.g. stainless steel, polypropylene, rubber and wood) and develop ecosystems called biofilms. This may be a cause of contamination in different industries, as wet surfaces can provide a solid substrate for bacterial growth and persistence (Bridier et al., 2014).

Biofilm formation is a survival strategy microbes adopt to enable them survive unpredictable environmental stressors such as temperature changes, desiccation, ultraviolet radiation, cleansing agents such as biocides and disinfectant pressure as well as host immune systems. Biofilm-associated microbes have therefore been implicated in a host of difficult to treat human infections (Costerton et al., 1978) with public health consequences even though some useful applications of biofilms have been acknowledged in waste water /sewage/ treatment and in heat transfer units(Rao et al., 2005).

The ability to stick to surfaces and to engage in a multistep process leading to the formation of a biofilm is almost ubiquitous among bacteria. Therefore, biofilm formation has substantial implications in fields ranging from industrial processes like oil drilling, paper production and food processing, to health-related fields like medicine and dentistry. The cellular mechanisms underlying microbial biofilm formation and behavior are beginning to be understood and are targets for novel specific intervention strategies to control problems caused by biofilm formation in these different fields and in particular for the food-processing environments. Food spoilage and deterioration not only results in huge economic losses, food safety is a major priority in today's globalizing market with worldwide transportation and consumption of raw, fresh and minimally processed foods. Biofilm formation depends on an interaction between three main components: the bacterial cells, the attachment surface and the surrounding medium (Stoodley et al., 2002).

Bacteria in biofilm behave differently from planktonic bacteria, especially in terms of their response to antibiotic treatment (Donlan, 2001). Biofilm-associated bacteria are highly resistant to antibiotics. The complicated structure of biofilm with extracellular polymeric matrix could prevent antibiotics from reaching the bacteria. Bacteria in biofilm could also adopt a slow growing or starved state due to the altered microenvironment such as depletion of nutrition and accumulation of waste. The changed physiological state of bacteria could make them more resistant to antibiotics, which target more active cell processes (Otto, 2008). Therefore the objectives of this review paper are to give an overview on the mechanism of biofilm formation and adherence to surfaces and to highlight veterinary and public health implications of biofilm formation and its control option.

Literature review

Steps in Biofilm Formation

Biofilm formation takes place in a sequence of steps. At each step, the biofilm becomes more firmly attached and the microorganisms within it become more protected from the action of cleaners and sanitizers (Garrett et al., 2008).

The formation of a biofilm occurs in five stages. In the first stage, bacterial cells use van der Waals forces to attach to a surface (MSU, 2016). In stage 1, cell attachment is still reversible, but in stage 2 the cells affix themselves more securely by forming exopolymeric material, which is a stronger adhesive compound. In stage 3, micro-colonies begin to form, and the biofilm begins to mature. Stage 4 involves more maturation, and the biofilm becomes a three-dimensional structure containing cells packed in clusters with channels running between them. And lastly, in stage 5 the biofilm disperses cells (Once the structure has developed, some bacteria are released into the liquid medium, enabling the biofilm to spread over the surface) (Hall-Stoodley, 2005; Stoodley, 2002) so that they can move on to initiate the formation of new biofilms. It is important to note that cell division is uncommon in mature biofilms. In the mature state, biofilm cells use energy predominantly to produce exopolysaccharides, which the cells use as nutrients (Watnick and Kolter, 2000).

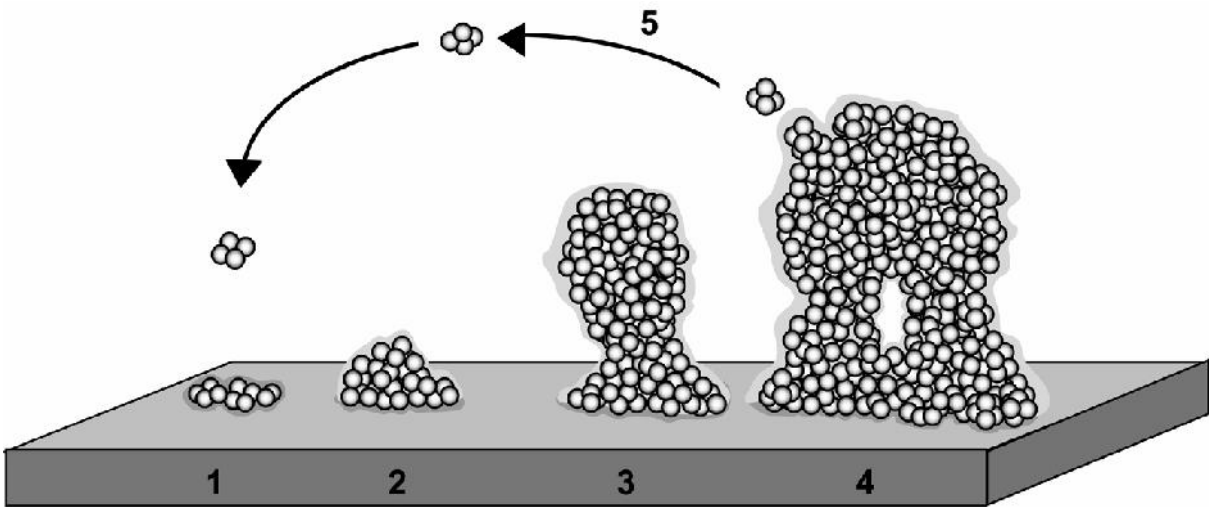

Figure. 1. The development of a biofilm, depicted as a five-stage process. Source: (Lasa, 2006)

Stage 1: initial attachment of cells to the surface; stage 2: production of the extracellular exopolysaccharide matrix; stage 3: early development of biofilm architecture; stage 4: maturation of biofilm architecture; stage 5: dispersion of bacterial cells from the biofilm (Lasa, 2006).

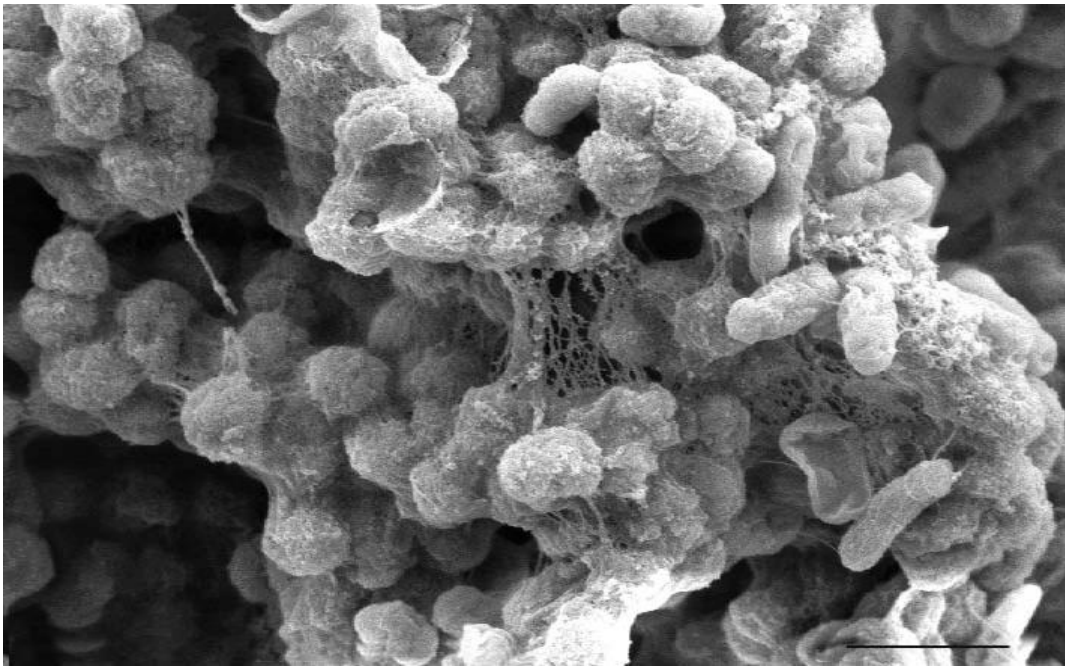

Figure 2. Scanning electron micrograph of the biofilm pellicle produced by Salmonella enteritidis in the air-liquid interphase of Luria-Bertani (LB) medium after 3 days of incubation at room temperature (bar = 2 µm). Source: (Lasa, 2006)

Factors Controlling Cell Attachment

Initiation of biofilm formation commences when bacteria encounter and get adsorbed to surfaces conditioned by small organic mol-ecules (Meier-Davis, 2006). The level of attachment of microbial cells is regulated by factors such as nature of the surface, conditioning films on the surface, characteristics and hydrodynamics of the aqueous medium, various properties of the microbial cell surface, gene regulation and quorum sensing (Mahami and Adu-Gyamfi, 2011).

Nature of surface

A variety of surfaces (dead, living tissue or inert) can serve for biofilm attachment. Although several characteristics are important in the attachment process, evidence suggests that microbial colonization appears to increase with surface roughness (Characklis, 1990) as a result of lower shear forces and greater surface area on rougher surfaces. Studies have confirmed that microorganisms attach more rapidly to hydrophobic, nonpolar surfaces such as Teflon and other plastics than to hydrophilic materials such as glass or metals (Bendinger et al., 1993).

Properties of medium

Conditioning films are important in the attachment process. These are organic polymers from the medium that coat submerged surfaces thus affecting the rate and extent of microbial attachment. Conditioning films are formed within minutes of exposure, and continue to grow for several hours (Loeb and Neihof, 1975). Mittelman (1996) noted that a number of host-produced conditioning films such as blood, tears, urine, saliva, intravascular fluid and respiratory secretions influence the attachment of bacteria to biomaterials. Characteristics of aqueous medium, such as pH, nutrient levels, ionic strength, and temperature, may also play a role in the rate of microbial attachment to a surface (Donlan, 2002). For example, an increase in the number of attached bacterial cells was observed as a result of an increase in nutrient concentration in medium (Cowan et al., 1991) and an increase in the concentration of several cations (Fletcher, 1988). Additionally, hydrodynamic properties of the aqueous medium such as velocity characteristics of the liquid influence the rate and extent of attachment (Characklis, 1990).

Properties of the microbial cell surface

The rate and extent of attachment of microbial cells is influenced by cell surface properties such as production of extracellular polymeric substances (EPS), cell surface hydrophobicity, presence of fimbriae and flagella. Hydrophobicity of the cell surface which is contributed by the presence of fimbriae (Rosenberg and Kjelleberg, 1986) is important in adhesion because hydrophobic interactions tend to increase with an increasing non-polar nature of surfaces involved. Evidence indicate that flagella play an important role in the early stages of bacterial attachment by overcoming the repulsive forces associated with the substratum (Korber et al., 1989) and that surface proteins also play a role in attachment. EPS and lipopolysaccharides are more important in attachment to hydrophilic materials. Motile cells therefore attach in greater numbers and against the flow more rapidly than do non-motile strains(Bendinger et al., 1993).

Signalling Events in Biofilm Formation

Formation of a biofilm is dependent on the interaction between the environmental stimuli and the reciprocation of the corresponding signalling events by the microorganisms. There are many sensing systems that can integrate the environmental stimuli into signalling pathways. These sensing systems can induce responses from two-component systems (TCS), extra cytoplasmic function (ECF) signaling pathway and quorum sensing (QS) events. Secondary messengers like c-di-GMP (cyclic guanosine monophosphate**)** are also involved in triggering biofilm formation (Jonas et al., 2009). For the development of biofilm, a coordinated network of gene expression is required in a stepwise manner. Thus, these signalling events play a very important role for microbial biofilm formation by developing adaptive responses against external and internal stimuli (Bordi and de Bentzmann, 2011).

Two-component signalling system consists of histidine kinase (HK) and response regulator (RR) protein. HK is a sensor protein usually has an N-terminal ligand-binding domain and a C-terminal kinase domain. Signal transduction occurs through thetransfer of phosphoryl groups from adenosine triphosphate (ATP) to a specific conserved histidine residue in HK. Subsequently, HK transfers the phosphoryl group from histidine residue to the aspartate residue of RR (Stock et al., 2000). This phosphate activates RR which acts as a transcriptional regulator. Two component systems of GacS (HK)/GacA (RR) are generally involved in the formation of *Pseudomonas aeruginosa* biofilm (Rasamiravaka et al., 2015). This system induces the expression of rsm genes which code for RsmY and RsmZ which control the transition between planktonic and sedentary forms (Brencic et al., 2009). The two additional histidine kinases have been reported to be associated with the Gac system, namely RetS and LadS (Rasamiravaka et al., 2015). RetS suppresses the genes needed for biofilm formation (Kong et al., 2013), whereas LadS activates the genes that help in biofilm formation Gac system confers resistance against aminoglycosides like amikacin and gentamycin (Brinkman et al., 2001).

Quorum sensing is a multicellular response in a biofilm population that works in a density-dependent way (Schauder and Bassler, 2001). It is a process of bacterial communication that makes use of autoinducers or pheromones. For gram-negative bacteria, the autoinducer is *N*-acyl homoserine lactones, whereas for gram-positive bacteria the autoinducer is oligopeptides. These molecules gather on the outside of the cell, and when the microbial population reaches a certain threshold level, these autoinducers can regulate the expression of genes related to virulence and biofilm formation (Bordi and de Bentzmann, 2011).

In addition to these pathways, a secondary messenger c-di-GMP in high concentration also acts as a stimulus for the formation of biofilms in bacteria (Bordi and de Bentzmann, 2011). The high amount of c-di-GMP is generally regarded as the stimuli for the formation of microbial biofilm by the synthesis of extracellular polymeric substance (EPS) or alginate polymer formation or adhesive surface organelles (pili) (Rasamiravaka et al., 2015).

Biofilm structure and composition

Biofilms are composed primarily of microbial cells and EPS which may account for 50 to 90% of the total organic carbon. The composition of the extracellular matrix is complex and variable among different bacterial species and even within the same species under different environmental conditions. Despite their heterogeneous composition, exopolysaccharides are an essential compound of the biofilm matrix, providing the framework into which microbial cells are inserted (Branda et al., 2005). Among the many different exopolysaccharides that have been described, cellulose and β-1,6-linked N-acetylglucosamine are the most common components of the biofilm matrix of many different bacteria. The synthesis of exopolysaccharides incorporated into the extracellular matrix is highly regulated, and recent evidence has revealed that different bacteria use the same secondary signal, c-di-GMP, for this purpose (Lasa and Penades, 2006).

The transcription of specific genes required for the synthesis of EPS takes place during and after micro colony formation. Microbial cells are embedded in the extracellular matrix which develops channels to convey water and substrate into the biofilm and waste product from the communities of cells in the micro-colonies. EPS may vary in chemical and physical properties, but it is mainly composed of polysaccharides. EPS of gram negative bacteria is polyanionic due to the presence of uronic acids such as D-glucuronic, D-galacturonic, and mannuronic acids (Sutherland, 2001), but that of some gram-positive bacteria, such as Staphylococci have been found to be mainly cationic consisting of teichoic acid mixed with small quantities of proteins (Hussain et al., 1993). EPS is also highly hydrated and most types of EPS are both hydrophilic. The composition, structure and uniformity of the polysaccharides have been observed to have a marked effect on the biofilm (Leriche et al., 2000). EPS prevents desiccation in some natural biofilms and may also enhance the antimicrobial resistance properties of biofilms by impeding the mass transport of antibiotics through the biofilm, probably by binding directly to these agents (Donlan, 2000).

Veterinary Importance of Biofilm Forming Bacteria

Bacterial adaptations to diverse environments, including human hosts, involve collaborative group behaviors, such as quorum sensing, swarming and biofilm formation (Solano et al., 2014). In general, quorum-sensing during host tissue colonization is associated with virulence gene expression and acute-phase infections, whereas biofilm formation facilitates the development of chronic infections, evasion of host immune response and increased tolerance to treatments (Furukawa et al., 2006)

The importance of biofilm in disease processes in humans and animals is now widely recognized. In animal species, the risk of infection is probably greater than the risk in humans. This is due to the difference in animal housing and living environments (Zambori et al., 2012).

In dogs and cats mouth normal bacterial microflora is structured in a variety of aerobic, facultative or strictly anaerobic bacteria. In the oral cavity, teeth provide constant humidity and adherent surfaces causing the attachment of extensive deposits of microorganisms (Pavlica, 2006).

Periodontal diseases are a collection of infections involving the degradation of the supporting tissues of the teeth, including the gum, periodontal ligament, alveolar bone and root cement of the tooth (Pavlica, 2006).

Periodontal diseases are the number one health problem in small animal patients. By just two years of age, 70% of cats and 80% of dogs have some form of

periodontal diseases. Periodontal disease is described in two stages, gingivitis and periodontitis. Gingivitis is the initial, reversible stage of the disease process in which the inflammation is confined to the gum. This inflammation is created by plaque bacteria and may be reversed with a thorough dental prophylaxis and consistent home care. Periodontitis is the later stage of the disease process and is defined as an inflammatory disease of the deeper supporting structures of the tooth (periodontal ligament and alveolar bone) caused by microorganisms (Brook, 2008). The development of periodontal disease is associated with deepening of the gingival crevice into a periodontal pocket that can be several millimeters in depth and bleeds after probing. Periodontitis is a chronic bacterial infection of the gingival crevice that is caused by mixed-species bacterial biofilm (Richard and Howard, 2010).

Biofilm Mediated Infections

Microorganisms attach to surfaces and develop biofilms which have been implicated in a variety of human diseases with great importance for public health .Unfortunately, biofilm-associated diseases are resistant to conventional biocides and host immune systems. As a result there is a rise in difficult to treat human infections with an increase in cost to the health sector (Mahami and Adu-Gyamfi, 2011).

The presence of biofilms in bacterial infections can increase the pathogenicity of the bacteria and protects the bacteria from being destroyed by external treatment. Biofilm formation is an ancient mode of survival for bacteria in hostile environments. Biofilms protect the cells from assaults like UV radiation, pH stress, chemical exposure, phagocytosis, dehydration and antibiotics (Gupta et al., 2015).

One of the first clinical infections associated with biofilm formation was medical device-related infections. Pacemakers, electrical dialysers, joint prosthetics, intravenous catheters, urinary catheter are indispensible for the patients as there has not been any other alternative against these devices. These devices also come up with a heightened risk of biofilm-associated infection. Mostly, Staphylococci and Pseudomonas species opportunistically infect a medically intervening device and get entry to the host. Such infections are nowadays referred to as chronic polymer-associated infection (Gotz, 2002). In this regard, it has been observed that Staphylococci can infect both open wounds and implants. *S. epidermis* has also been reported to colonize the medical devices efficiently (Otto, 2009).

Recent literature has documented the presence of biofilm associated bacteria in chronic wounds which leads to their persistence (Alhede and Alhede, 2014). It has been observed that *S. aureus* biofilms are related to chronic wounds like diabetic foot ulcer, pressure sores and venous ulcers. It has been reported that the dermal tissues of chronic wounds house many bacteria which can cause persisting infections in wounded tissues (Bjarnsholt, 2013).

Food Borne Biofilms and Food Safety

Generally, food has been identified to be a very efficient vehicle for bringing a large number of people into contact with a potential hazard (Jordan, 2007). Thus, from a population perspective, food-borne exposure may be the most critical pathway for transfer of biofilm-associated infections to humans. Fruits and vegetables are particularly noted (Saper, 2005) in this regard as high risk foods because most of them are eaten raw or minimally processed. Multispecies biofims including human pathogens attach to plant surfaces before harvest from the soil and environment. These biofilms form on plant tissue so firmly that they are not easily removed with simple washing techniques. Food borne illness associated with fresh fruits and vegetables occur as a consequence when fruits and vegetables are eaten raw or minimally processed (Sivaplalasinggam et al., 2004). The bacteria assume the biofilm phenotype to survive the unpredictable environmental stressors on the plant surfaces. Commercial operations typically use triple-wash treatments and disinfectants to clean leafy vegetables (Lindow and Brandl, 2003).

But these conventional sanitation processes for cleaning leafy products reduce pathogen levels by an amount that is inadequate to ensure microbiological safety (Sapers, 2005). The cause for this inadequacy is attributable to strong microbial attachment via biofilms. To reduce the presence of biofilms on leafy products more thorough washing and sanitation strategies are necessary to overcome the substantive cohesive properties of biofilms (Mahami and Adu-Gyamfi, 2011).

Biofilms formed in food-processing environments are of special importance as they have the potential to act as a persistent source of microbial contamination that may lead to food spoilage or transmission of diseases. It is generally accepted and well documented that cells within a biofilm are more resistant to biocides than their planktonic counterparts. Numerous reports indicate that the antimicrobial efficacy of various

aqueous sanitizers is lower for biofilm-associated than for planktonic Salmonella spp. Nine disinfectants commonly used in the feed industry and efficient against planktonic Salmonella cells showed a bactericidal effect that varied considerably for biofilm-grown cells with products containing 70% ethanol being most effective (Moretro et al., 2009).

Other studies similarly indicated that compared to planktonic cells, biofilm Salmonella were more resistant to trisodium phosphate and to chlorine and iodine (Joseph et al., 2001). Listeria monocytogenes biofilms were more resistant to cleaning agents and disinfectants including trisodium phosphate, chlorine, ozone, hydrogen peroxide, peracetic acid (PAA) and quaternary ammonium compounds (Robbins et al., 2005). Lactobacillus plantarum ssp. plantarum biofilms showed increased resistance towards various organic acids, ethanol and sodium hypochlorite (Kubota et al., 2009).

Which disinfectant is the most effective in a particular situation depends on numerous factors including the nature of the attachment surface, temperature, exposure time, concentration, pH and bacterial resistance (Bremer et al., 2002).

Resistance is attributed to different mechanisms: a slow or incomplete penetration of the biocide into the biofilm, an altered physiology of the biofilm cells, expression of an adaptive stress response by some cells, or differentiation of a small subpopulation of cells into persister cells. Biofilm resistance to chlorine is still incompletely understood, but is at least partly because of hindered penetration of the biocide into the biofilm (Xu et al., 1996). Active chlorine concentrations as high as 1000 ppm are necessary for a substantial reduction in bacterial numbers in multispecies biofilms (formed by *L. monocytogenes*, *Ps. fragi* and *Staph. xylosus*) compared to 10 ppm for planktonic cells (Norwood and Gilmour, 2000).

The slow or incomplete penetration of the biocide into the biofilm is partly because of diffusion limitation in the exopolymeric matrix, but primarily because of neutralization of the active compound in the outermost regions of the matrix. The active chlorine species react with organic matter in the surface layers of the biofilm faster than they can diffuse into the biofilm interior (Xu et al., 1996).

In view of their resistance to traditional microbial control methods, biofilm-associated microbes cause humans to become more virulently ill for longer periods with limited treatment options leading to increase in mortality rates and increased cost of treatment. According to some estimates, the economic burden of infections arising from biofilms is $6 billion per year in the United States (O'Toole, 2002).

Biofilm and Drug Resistance

It is known that host immune system responds to bacterial infections by activating several signalling cascades, cytokines and expressing genes associated with stress management (Hartmann et al., 2014). However, host immune responses are not much effective against bacterial biofilms in comparison with their planktonic counterpart (Schultz et al., 2010). Many bacterial pathogens that are initially considered as strictly extracellular can persist inside the host by the formation of biofilm through the process of adaptation (De la Fuente-Nunez et al., 2013) that results in the evasion of the bacteria from innate immunity of the host. The evasion of biofilms from host innate response proves harmful to the host, as the inflammatory influx released by the body in response to the bacterial infection may damage the host tissues (Archer et al., 2011). Three hypotheses have been proposed to explain the possible underlying mechanism of antibiotic resistance of biofilm-associated bacteria.

The first hypothesis suggests that the antibiotic may not be able to penetrate completely into the biofilm (Stewart and Costerton, 2001). Sometimes, if the antibiotic gets degraded while penetrating the biofilm, the antibiotic action declines rapidly. Antibiotics may get adsorbed on the extracellular polymeric surfaces of the biofilm which can reduce the penetration of the antibiotic (aminoglycosides) (Shigeta et al., 1997). Sometimes, antibiotics which are positively charged in nature can bind to the negatively charged molecules of the biofilm matrix. This interaction thereby hampers the passage of the antibiotic to the biofilm depth (Nichols et al., 1988).

Secondly, the microenvironment of the biofilm changes rapidly that resulted in the malfunction of the antibiotics. In deep layers of the biofilm, there is no consumable oxygen left and the niche becomes anaerobic (de Beer et al., 1994).

It has been reported that a class of antibiotics namely aminoglycosides are not effective in anaerobic environmental condition (Tack and Sabath, 1985). It has also been reported that the amount of acidic waste accumulation inside a biofilm increases which changes

the pH of the environment that may reduce the action of some antibiotics (Stewart and Costerton, 2001). The accumulation of toxic waste or limitation of necessary substrate can lead the bacterial population to remain in a dormant, nongrowing form which can then protect the bacteria from certain antibiotics like cell wall inhibiting agents and penicillin (Tuomanen et al., 1986). There are zones within a biofilm which are metabolically inactive and this also advocates for this hypothesis. Under osmotic stress, biofilm population reduces the abundance of porins in the bacterial membrane that resulted in the considerable reduction in the transport of some antibiotics inside the cell (Stewart and Costerton, 2001).

The third hypothesis is still under some speculation. It has been hypothesized that a small population of the bacteria residing in a biofilm may adapt a protective phenotype (which is in parity with spore formation phenotype) that resulted in the development of drug resistance in biofilm population (Gupta et al., 2015).

Approaches for Biofilm Control and Prevention

Ideally, preventing biofilm formation would be a more logical option than treating it. However, there is presently no known technique that is able to successfully prevent or control the formation of unwanted biofilms without causing adverse side effects. The main strategy to prevent biofilm formation is to clean and disinfect regularly before bacteria attach firmly to surfaces (Simoes et al., 2006). The cleaning process can remove 90% or more of microorganisms associated with the surface, but cannot be relied upon to kill them. Bacteria can redeposit at other locations and given time, water and nutrients can form a biofilm. Therefore, disinfection must be implemented (Gram et al., 2007).

Biofilm detectors were already developed to monitor the surface colonization by bacteria and allow the control of biofilms in the early stages of development (Pereiraet al., 2008). Pereira et al. (2008) developed a mechatronic surface sensor able to detect biofilms in the early stages of development. This sensor was also able to detect the presence of cleaning products in a surface, identify when it was biologically and chemically cleaned and measure the rate of cleaning (Pereira et al., 2009).

Attempts have been made to devise fruitful strategies to control biofilms. The acid shock treatment on proteins expression and upregulation of stress-responsive proteins during acid tolerance in biofilm cells of Streptococcus mutans documented(Len et al., 2004). The acid is said to affect the physiology of biofilm cells of Streptococcus mutans(McNeill and Hamilton, 2004). The blocking of bacterial biofilm formation using catheter lock solutions in staphylococcal biofilm formation on abiotic surfaces, by a fish protein coating and synergistic activity of dispersin B and cefamandole nafate in inhibition of staphylococcal biofilm growth are some of the important works carried out in this field (Vejborg and Klemm, 2008)

Recent advances focus on bacteriophages as specific and effective therapeutic agents with lytic action against target bacteria. Thus, combination of antibiotics and bacteriophage application has been suggested as a valuable approach for biofilm control. The phage philBB-PF7A showed 63% to 91% activity for biomass removal in *Pseudomonas fluorescens*, an important food spoilage pathogen (Sillankorva et al., 2008). Phage specific for *Enterobacter* was demonstrated to control biofilm by depolymerase activity on polysaccharide. Similarly, in *Pseudomonas aeruginosa*, depolymerase enzyme reduced the viscosity of alginates and the EPS of the organism, thereby leading to dispersal of biofilm.The dual approach of impregnation of medical devices with phages and incorporation of phages in hydrogel coating of catheter has proven its efficacy, especially in *Staphylococcus epidermidis* (Del Pozo et al., 2007). The vulnerability of pathogenic biofilms to *Micavibrio aeruginosavorus* and *Bdellovibrio bacteriovorus* attack has been documented (Kadouri et al., 2007). However, recent studies have shown the dispersal of films by using genetically engineered bacteriophages (Lu and Collins, 2007).

It has been suggested that further understanding of the composition and function of extracellular matrix proteins may hold the key to controlling biofilm infections and that proteins specifically expressed by biofilm bacteria may be useful targets of therapeutic interventions. Evidence from the aforementioned reasons indicate that consumption of leafy vegetables and fruits or the use of indwelling medical devices or a kitchen cutting board or a sink may increase the incidence of biofilm-associated infections. It is important to note that these infections may not be only difficult to treat but may also enhance the spread of antibiotic resistance genes among microbes such that when they infect humans they become difficult to treat with conventional antibiotics. Additionally, avirulent strains of microbes in a biofilm can become virulent due to reception of resistant genes. The spread of

biofilm-forming commensals should therefore have humans to become more virulently ill for longer periods of time. Unfortunately, host immune systems do not easily counter act biofilm associated diseases neither do biocides including antimicrobials. As a consequence, biofilm associated infections may persist for a long period of time (i.e., progress from an acute to a chronic infection), thus posing a daunting public health challenge (Mahami and Adu-Gyamfi, 2011).

To reduce biofilm-associated infections there is the need for government agencies with a mandate for safeguarding public health and environment to develop and adopt appropriate health risk assessments and biofilm-specific guidelines that are protective of both public health and the environment. Further studies are required in the evaluation of various biofim control strategies for either preventing or remediating biofilm colonization of surfaces, and development of new methods for assessing the efficacy of these treatments. Research should also focus on the role of biofilms in development of antimicrobial resistance, biofilms as a reservoir for pathogenic organisms, and the role of biofilms in chronic diseases (Mahami and Adu-Gyamfi, 2011).

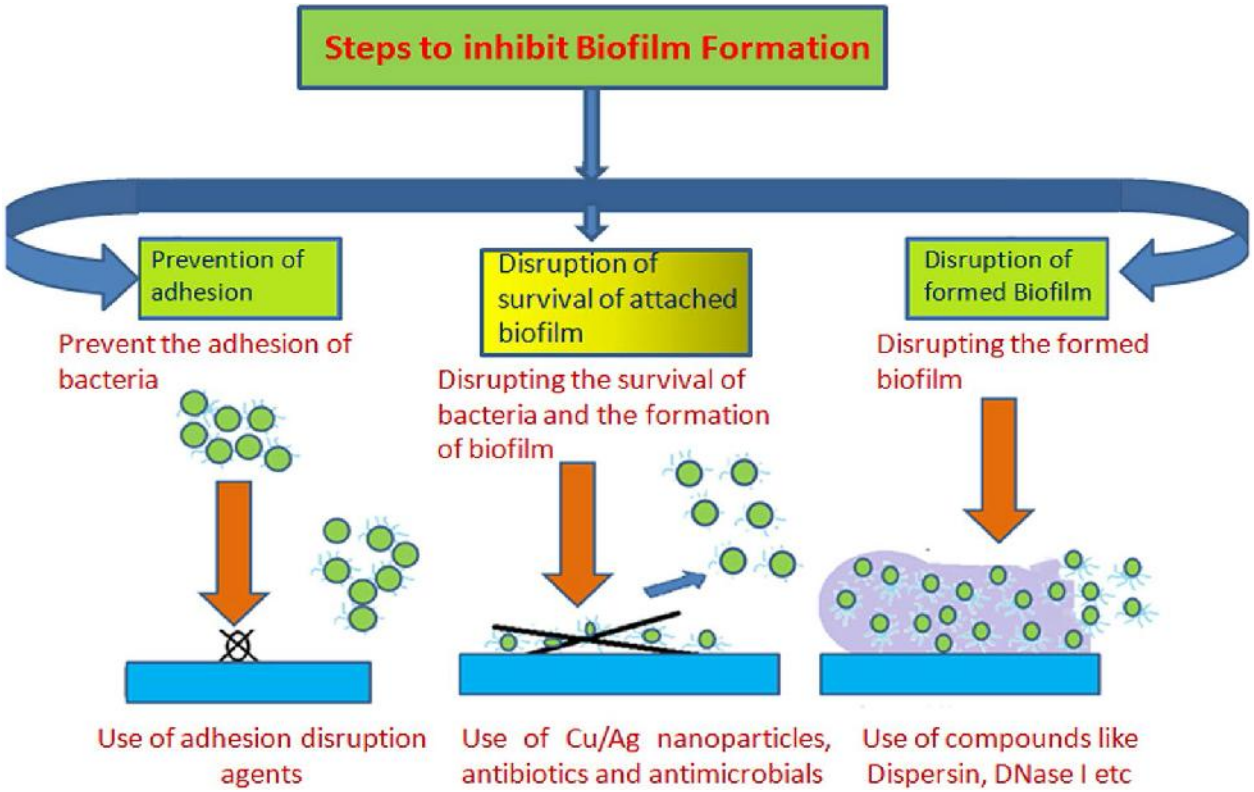

Figure 3: Strategies for prevention of biofilm formation on implant surfaces by use of three different approaches: source: (Gupta et al., 2015)

Use of nonadhesive coatings over surfaces to inhibit the microbial attachment to the surface, Use of nanoparticles and antibiotics to disrupt the survival of attached bacteria and Use of compounds like dispersin and DNase to disrupt preformed biofilm (Gupta et al., 2015).

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