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# Biofilm. IMDs. Quorum Sensing: A Review

Abbas Obaid Farhan Al-Janabi
*Department of Microbiology, College of Medicine, University of Anbar, Iraq*

**KEY WORDS**
Biofilm
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Quorum sensing

**Abstract:** Biofilm is a castle or shield of microbes in nature, human and animals. Contamination of our ground water sources pose concerns for the future of our potable water supplies; this threat is accentuated by the stability that biofilms of these contaminants bring into equation. Biofilms are believed to be associated with human infections including chronic, recurrent and device-related infections such as Urinary catheters, endotracheal tube, artificial joint prostheses, Intrauterine (IUDs), artificial heart values and contact lenses, therefore, treatment of biofilm infections has become an important focus in modern medicine. As planktonic susceptibility testing, via. the Minimal Inhibitory Concentration (MIC) test, provides little guidance in the selection of antimicrobials to treat biofilms, a change in paradigm is required to determine appropriate treatment of biofilms and for the discovery of next-generation antimicrobials. Finally, we now recognize that MIC values provide us with little relevant information on how to treat biofilm infections. Clearly, a new paradigm for treatment biofilm is needed and the microbial biofilms as Enemies for human and animals but in other hand some of advantage biofilms conceder as friends with us.

**Corresponding Author:**
Abbas Obaid Farhan Al-Janabi
*Department of Microbiology, College of Medicine, University of Anbar, Iraq*

## INTRODUCTION

Biofilm is a thin coating containing biologically active agents which coats the surface of structures such as teeth or the inner surfaces of catheter, tube or other implanted or indwelling device. It contains viable and non-viable microorganisms that adhere to the surface and are trapped within a matrix of organic matter (for example, proteins, glycoproteins and carbohydrates)[1]. Microorganisms attack to surfaces and develop biofilms[2]. Biofilm-associated cell can be differentiated from their suspended counterparts by generation of an Extracellular Polymeric Substance (EPS) matrix, reduced growth rates and the up and down regulation of specific genes. Attachment is a complex process regulated by diverse characteristics of the growth medium, substratum and cell surface[3]. An established biofilm structure comprises microbial cells and EPS has a defined architecture and provides an optimal environment for the exchange of genetic material between cells. Cells may also communicate via quorum sensing which may in turn affect biofilm processes such as detachment. Biofilms have great importance for public health because of their role in certain infections diseases and impotence in a variety of device-related infections[4].

Greater understanding of biofilm processes should lead to novel, effective control strategies for biofilm control and resulting improvement in patient management. The technology can also be used to introduce new novel products such is the case of wound contact films where new antimicrobial agents can be incorporated[5, 6].

Microbiologists have grown bacteria as suspension cultures in rich media, in order to optimize cell yield. This planktonic mode of growth also became part of the standard assay on which all existing antimicrobials were selected and developed, and continues to be the basis for the selection of antimicrobials for specific patent treatment. We now recognize that in most environments including our bodies, bacteria typically exist as adherent microcolonies termed biofilms which afford bacteria a number of growth advantages including an inherent lack of susceptibility to antimicrobials. This antimicrobial tolerance differs from classical genetic resistance in that this reduced susceptibility disappears when the biofilm is returned to planktonic growth. Biofilm tolerance is multifactorial which includes the spatial and structural parameters of the biofilm as well as the increased phenotypic diversity within the biofilm population.

Biofilms are believed to be associated with approximately 60% of human infections including chronic[7], recurrent and device-related infections, therefore, treatment of biofilm infections has become an impotent focus in modern medicine[8]. As Planktonic susceptibility testing, via. the Minimal Inhibitory Concentration (MIC) test, provides little guidance in the selection of antimicrobials to treat biofilms, a change in paradigm is required to determine appropriate treatment of biofilms and for the discovery of next-generation antimicrobials[9]. Biofilms are micro colonies of one or more species of bacteria or fungi typically growing adherent to abiotic or abiotic surface. Biofilms form to allow bacteria to maintain themselves in a niche of their choosing rather than being washed away by the shear force of running water in the natural environment or the movement of body fluids and mucins in the body. Biofilms provide a more energy-efficient means of growth, capturing nutrients as they flow past and easily expelling waste. They also provide a more secure environment for sustainability, making it difficult for phagocytes, found both in nature and as part of the immune system, to eradicate the biofilm.

Also, as a biofilm, bacteria and fungi are less susceptible to antimicrobials, allowing them to be more tolerant than their planktonic brethren to antibiotics found in nature and those used clinically. Bacteria exist in a nature biofilm that may be formed from many species as in a consortium formed on the face of a rock in a stream or those found in the mouth, as part of our dental plaque. Chemical signals regulate the interactions between membrane of the biofilm just as hormones regulate the cell of our body. For example, under specific stress conditions appropriate signaling may lead to an increase in phenotypic diversity within the biofilm to accommodate the stress or these signals may cause bacteria to revert to their more motile planktonic phenotype and leave the biofilm to establish new micro colonies that will give rise to a mature biofilm[10].

**Biofilms in nature and health:** Bacteria exist often as multi species biofilms in nature which may allow pathogens to survive in nature away from their natural host where they may serve as a nidus for reinfection. Examples of this are enteric organisms that form biofilms in during-water pipes or in wells. Following an original contamination event, biofilms allow for sustainability of these population which then serve to shed further organisms inti potable water supplies, even after the apparent clearance of the original contamination event. Contamination of our ground water sources pose concerns for the future of our potable water supplies; thus, threat is accentuated by the stability that biofilms of these contaminations bring into the equation[11].

**Biofilms in the food products:** Food-bone outbreaks of infections are often associated with biofilms formed on the surfaces of food processing planks knives and processing equipment. The inherent resistance of biofilms to many biocides used in the cleaning process allows these bacteria to multiply and contaminate food products[12].

**Biofilms in hospitals:** Nosocomial infections within healthcare facilities often result from pathogens surviving in the environment as biofilms. Biofilms may facilitate carriage by patients, hospital staff or visitors as for example in colonization of nasal passages by *Methicillin-resistant Staphylococcus aureus* (MRSA). Biofilms may facilitate carriage by patients, hospital staff or visitors as for example in colonization of nasal passages by *Methicillin-resistant Staphylococcus aureus* (MRSA). Biofilms may also become associated with hard surfaces, drains or water pipes within the tactility.

Infections may also be associated with instruments or devices used in the hospital such as the contamination of endoscopes by biofilms where they are responsible for the passage of infections organisms from one patient to

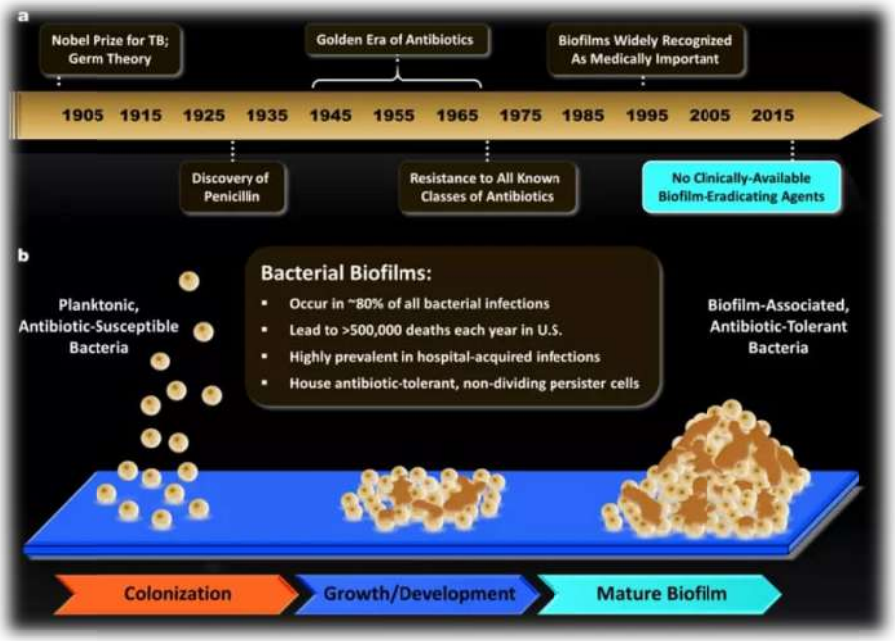


Fig. 1: Bacterial biofims

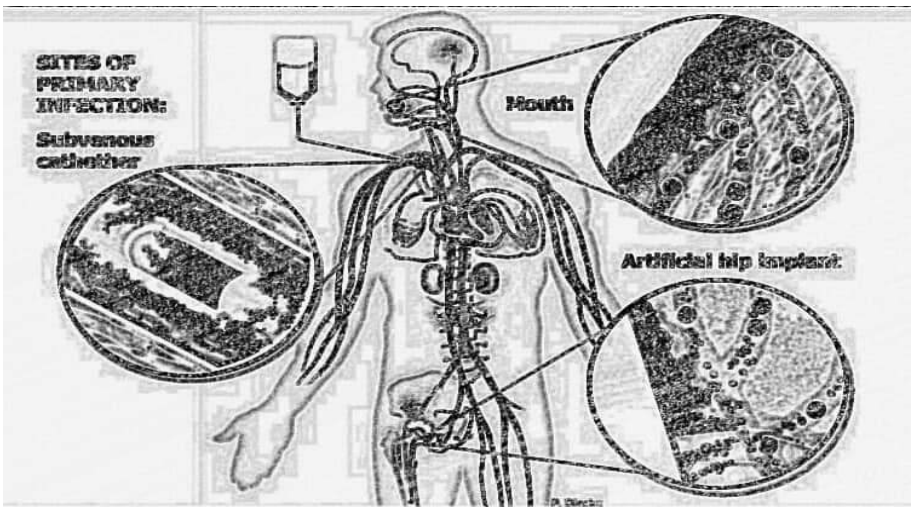


Fig. 2: Biofilm formation on the medical devices in human body

another. Whether biofilms from on animate or inanimate surfaces, their recalcitrant nature makes it difficult to remove them from the environment[13] (Fig. 1).

**Biofilms formed on Indwelling Medical Devices (IMDs):** Medical devices have become an essential aspect of patient care with tens of millions of implantable or indwelling medical devices (such as catheters, endotracheal tube, artificial joint prostheses and so on) Fig. 2 used each year in patients worldwide. However, despite the evolution of medical devices and biomaterials from which they are manufactured, their use in vivo is significantly compromised by their seemingly ubiquitous propensity to succumb to microbial colonization and biofilm formation, otherwise known as medical device-associated infection.

Immediately after implantation, the device surface becomes modified by the adsorption of host derived

proteins, extracellular matrix proteins, coagulation products, etc., depending on the site. This 'conditioning film' renders the surface of the device favorable for microbial adhesions and is often followed by rapid primary attachment of microorganisms to the material surface and biofilm formation[14]. The microorganisms responsible for causing medical device-associated infections may be either from exogenous (careers, visitors, healthcare environment) or endogenous sources (via. the migration of microorganisms from normally colonized body sites). Although, site dependent, the main causative organisms medical device-associated nosocomial infections are frequently normal skin biota including *Staph. aureus* and coagulase-negative staphylococci, predominantly *Staph. epidermidis* which is the most common causative organisms of infections related to intravascular catheters and other implanted medical devices. A number of other key microorganisms have been shown to be significant causative organisms of medical device-related nosocomial infections including *Pseudomonas aeruginosa* (Ventilator-Associated Pneumonia, VAP), enterococci, *Escherichia coli* (Urinary tract infection UTI, septicemia) and Proteus species such as proteus mirabilis (UTI, device encrustation)[15].

As least half of all case of healthcare-associated infections are estimated to be due to biofilm-mediated, medical device-associated infections with medical device use now regarded as the greatest external predictor of healthcare-associated infections. The development of medical device-associated infections generally necessitates the complete removal and replacement of the device with the level of clinical intervention depending on the nature and site of the device implantation. Systemic antibiotics (often a combination therapy of two or more antimicrobial agents) represent the conventional approach to the treatment of device associated infections; however, give the high degree of tolerance to antimicrobial challenge that is a feature of biofilm populations, eradication proves extremely difficult and infection relapses frequently occur. This has led to the development of a range of anti-infective and antimicrobial biomaterials for use in device manufacture, though the long-term efficacy of these devices in the reduction of medical device-associated infection is an area of considerable debate[16]. Healthcare-associated infections typically occur at four main body sites (urinary tract, respiratory tract, surgical sites and bloodstream infections), three of which (UTI, pneumonia, bloodstream infections) are commonly associated with the use or indwelling device. Indeed, around 95% of nosocomial UTIs reported are linked to the use of urological devices (mainly urinary catheters) and more than 85% of nosocomial respiratory infections (mainly VAPs) are device-related. Central venous catheters pose the greatest risk of mortality due to catheter blood stream infections with incidences in the USA ranging from 10 000-500 000 cases annually, resulting in more than 25 000 deaths per years. Although, these represent the most common device-associated infections, it is worth noting that all types of implantable medical device are susceptible to infection: for example, peritoneal catheter infections in peritoneal dialysis, orthopedic implant infections and biofilm formation on prosthetic heart values. In addition, to patient morbidity and mortality, device-associated infections impose significant financial burdens on healthcare providers, related primary to increased hospitalization time and associated care costs. Despite this, the use of and dependence on implantable, indwelling medical devices increases annually, correlated to an increasing ageing population in industrialized nations[17-19].

**Architecture of biofilm:** The hypothesis that the extracellular matrix acts as the gatekeeper for the penetration of antimicrobials into the biofilm has engendered many studies and a great deal of controversy. When biofilms were first visualized using both transmission and scanning electron microscopy, the dehydrated matrix seen in these original micrographs led to the belief that biofilms were very flat and dense structures where the compact and highly charged matrix a round the biofilm would prevent penetration of antibiotics into biofilm, hence, this diffusion barrier would render them resistant to antimicrobial treatment (Fig. 3).

Stabilization of the matrix and cross-sections through the biofilm revealed a very different picture of the biofilm where cells were seen to exist within a very hydrated matrix containing channels to allow for nutrient transfer into biofilm and the diffusion of water out. The matrix is now believed to be composed of bacterially derived carbohydrate, the composition of which is dependent upon the bacterial species, nutrient availability and the growth conditions of the biofilm.

Recently, it has been established that DNA is an important component of the matrix which may be specifically transported into the matrix. The role of DNA in the matrix is only now being deciphered. It has been shown to play a role in the conformation of the carbohydrate and hypothesized to serve as a gene pool for the diversity seen within the biofilm. The highly anionic charge of this matrix could be hypothesized to still play an important role in preventing charged antibiotics from effectively entering the biofilm and

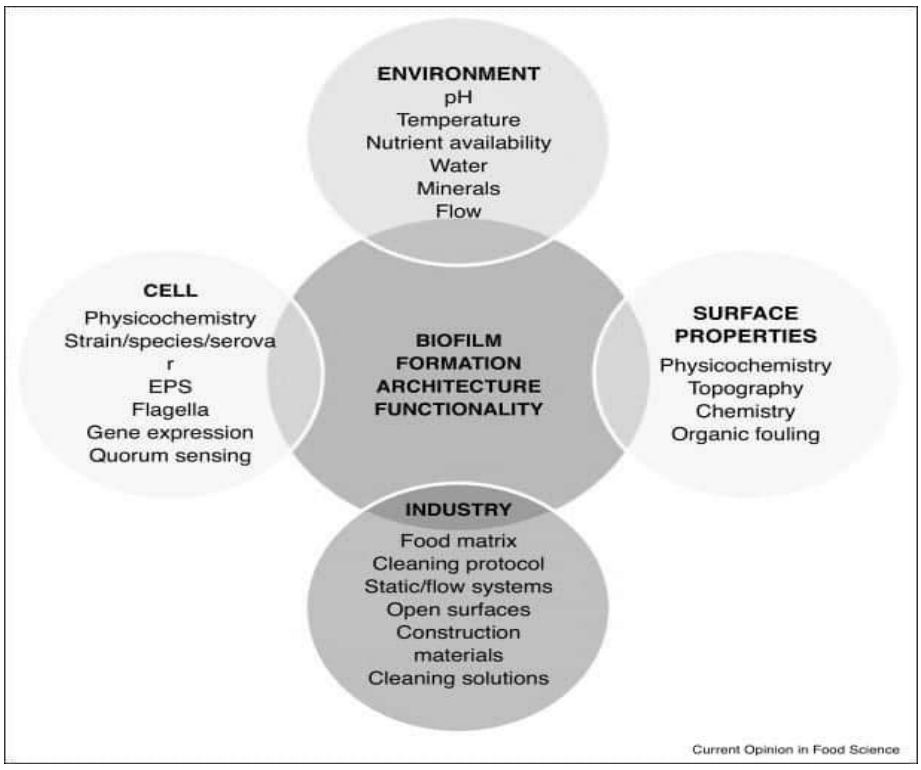


Fig. 3: Biofilm formation architecture functionality

thereby still act as a primary inhibitor of antibiotic killing as was originally proposed. Several studies of antibiotic penetration into biofilms demonstrated that the charge of the antibiotic could affect its penetration. For example, fluoroquinolones (ciprofloxacin, ofloxacin) that are not highly charged easily penetrate the matrix while the penetration of charged aminoglycosides (tobramycin, gentamicin) is delayed. These studies have not, however, the importance of the matrix in the resistance of biofilms. The rapid entry of fluoroquinolones, for example, may be only in to water channels of the biofilm and not into areas where cells of the biofilm are found while the delay in entry of aminoglycosides may affect the rate of entry but may not effect final concentration significantly enough to alter susceptibility of the biofilm. Further, penetration of antimicrobials alone may not be as key an issue as physiological state of cells which is also affected by the structure and organization of the biofilm. The diffusion into the biofilm of multiple factors, not limited to just the antibiotics themselves, may impact the biofilm's physiological state, there by affecting the efficacy of antibiotics against the biofilm[20, 21].

**Physiology of biofilm:** The physiological state of the biofilm is also affected by its organizational structure, as diffusion of oxygen, nutrients and waste will ultimately affect all properties associated with growth and sustainability of the biofilm. Sophisticated experiments based on microelectrode probing of the biofilm and confirmed by dye distribution confocal microscopy assays have established the presence of oxygen and pH gradients within the biofilm. Gradients of nutrients and end products are also implicated in defining the different growth properties throughout the biofilm which as described above has been linked to antibiotic susceptibility[22, 23] (Fig. 4).

**Biofilm resistance and cellular signaling:** Our perspective of the microbial lifestyle has changed from one where bacteria exist mainly as solitary independent planktonic populations to one where bacteria form adherent communal populations of bacteria organized into microcolonies called biofilms. This shift in lifestyle suggests the presence of specific signaling between cells to allow them to organize these complex structures. Many different genes have been identified that can alter biofilm formation or antimicrobial susceptibility but two global signaling pathways have come to the forefront as biofilm regulators in many different species of bacteria. (Fig. 5).

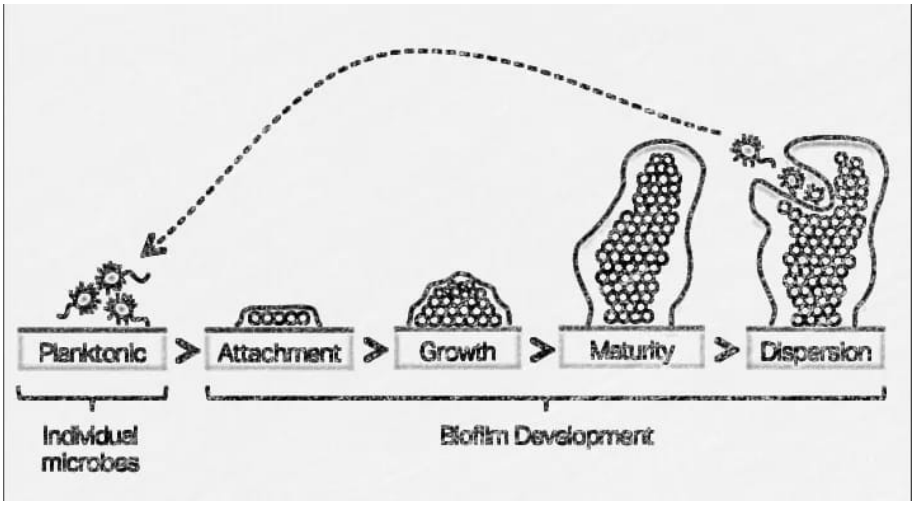


Fig. 4: Development of bioflm

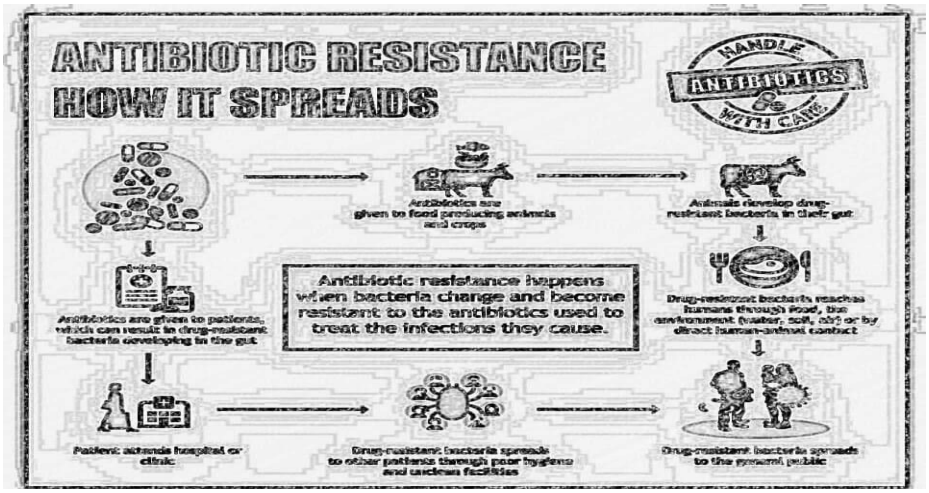


Fig. 5: Biofilms and antibiotics resistance

Although, models of biofilm formation have been proposed that do required cell signal molecules, the importance of the following molecules in biofilm formation and antimicrobial resistance is well established and has even led to attempts to develop signal antagonists for treatment of biofilm disease or to create greater efficacy of existing antimicrobials by returning biofilms to a planktonic-liked level of susceptibly[24, 25].

**Quorum sensing:** Quorum Sensing (QS) has been recognized as a key regulatory process associated with biofilm formation and antibiotic susceptibility. Well studied in Vibrio Fischeri, QS involves an enzyme Luxl that produces a small signaling molecule or autoinducer, that diffuses out of the cell. Upon reaching a threshold concentration the autoinducer will diffuse back into the cell where cellular transcription is altered when the autoinducer binds the transcription regulator LuxR and initiates QS-specific gene expression. In gram-negative organisms the autoinducer is typically an Acyl-Homoscrine Lactone (AHL) but in some organisms multiple QS systems exist. For example, in *Ps. auruginosa* signaling involve interactions of tow distinct AHL, compounds, produced by the Luxl Homologues Lasl and Rhll, respectively, that interact with their cognate receptors LasR and RhiR. Yet a third signal system, PQS, also active in *Ps. aeruginosa*. In gram-positive bacteria QS is typically carried out by autoinducing peptides (Fig. 6). As QS is an integral step in biofilm formation and

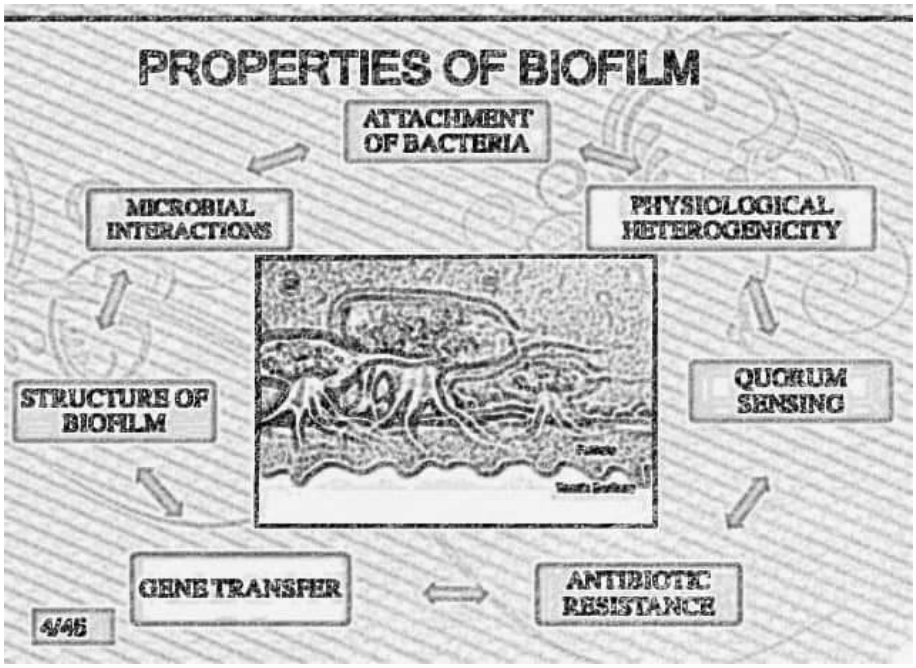


Fig. 6: Properties of biofilm

antibiotic tolerance, it has become a target for a new therapeutics. Inhibitors of the QS signal pathway, assayed for the ability to either block biofilm formation or the expression of QS-depending genes, may provide new approaches to treatment of biofilm disease[26, 27].

**Treatment of chronic biofilm infections:** As already stated, chronic, recurrent and device-related infection are now recognized to be associated with biofilm formation. Biofilms, as, discuss above, possess multiple Mechanisms that render them less susceptible to antibiotic treatment than the same isolate in the planktonic mode of growth the antibiotic, we have today were all selected for efficacy against planktonic cultures and all our diagnostics are based on planktonic assays.

## CONCLUSION

Finally, we now recognize that MIC values provide us with little relevant information on how to treat biofilm infections. Clearly, a new paradigm for treatment biofilm is needed[28, 30].

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