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MICROBIAL BIOFILM ASSOCIATED HUMAN INFECTIONS ON MEDICAL DEVICES: APPROACHES FOR PREVENTION AND TREATMENT

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ABSTRACT
Biofilms, a group of microbes, are present on the surface of medical devices. These pathogens are very difficult to eradicate and therefore they associate with major morbidity and mortality of human patients. The present article highlights the importance of microbial biofilms with approaches for prevention and treatment of them in human healthcare.

KEYWORDS: Biofilm, Medical device, Bacterial infection.

INTRODUCTION
Microbial infections of biofilm play a pivotal role in human health. Implantable medical devices have improved the lives of many human patients.[1] But the medical devices may be accompanied by microbial infections depending upon the location and duration of use of implanted device in human. These biofilm infections are very difficult to eradicate and causes for the failure of implanted devices. Various studies have been reported that biofilm formation by microbial infections on implanted devices causes major morbidity and mortality among patients.[2] Therefore at present microbial biofilm in human has become a pressing issue. The present article initially center on the importance of biofilm in human health, further highlights on the biofilm formation to dissemination and finally the approaches for the prevention and treatment of biofilm in human health.

1. Importance of biofilms in human health
Microbial infections are usually form biofilm in human which are normally source from skin flora of host and/or the physician and the environment. Approximately 75% of nosocomial infections are of biofilm origin.[3] These infections [commonly *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Enterococcus* species, *Pseudomonas aeruginosa*, *Escherichia coli*, *Proteus mirabilis* and *Candida* species] can cause dysfunction of medical devices [commonly central venous and urinary catheters, heart valves, orthopedic devices, intraocular contact lenses, dental implants] [Table 1][3,4] and produce systemic and chronic diseases [Table 2][5,6] in patients. Generally biofilm infections show some clinical manifestations such as fucoids sputum with cystic fibrosis, recurrent identical pathogens with central venous catheter, recurrent of same pathogens with urinary catheter, chronic pain with joint prostheses, recurrent wound infection with chronic wound and intermittent fever and identical pathogens with prosthetic heart valves or pacemaker.[7] The biofilm infections are very difficult to eradicate and therefore the prevention of the formation of biofilms in human is very serious clinical problem.

2. Biofilm formation to dissemination
The process of biofilm formation consists of many steps starting with attachment to surface that lead to formation of microcolony and after maturation ending up with detachment.[8] The biofilm formation influences by some factors such as texture & the surface charge of the substratum, temperature, pH, nutrients & velocity of medium and hydrophobicity of cell surface etc.[3] After attachment of microbes on the surface they produce extra polysaccharide substances which form stable microcolony. Mature microbes start communication each other by production of autoinducer and intercellular signaling or quorum sensing. Gram-negative bacteria release autoinducer called acrythromoserine lactones whereas gram-positive bacteria release oligopeptides. These autoinducers can regulate the expression of genes related to virulence.[8] Because of the depletion in nutrients and production of different saccharolytic enzymes, the microbe disperses and moves in the bloodstream and spreads the infections. Early phase of immune response helps to control the excessive propagation of microbes but latter it is not capable of eradicating infections which results to tissue damage and tends to become chronic.[9]

3. Approaches for prevention and treatment of biofilm infections in human

There are three strategies for the prevention of biofilm formation on medical devices[10] i.e. Inhibition of microbial adhesion to the device surface, interference with the signal molecule communications of microbes during biofilm development and disaggregation of biofilm matrix.[10]

The surface properties of implanted devices are one of the important approaches to prevent biofilm formation. For example antibiotic coating devices provides surface antimicrobial activity in orthopedic and orthodontic applications.[11] However, antibiotics impregnate catheters prevent biofilm formation but they can lead to antibiotic resistance.[2] Coating of Heparin[10] and silver nanoparticle[2] and hydrophilic polymers [hyaluronic acid and poly-N-vinylpyrrolidone][10] prevents bacterial adhesion to medical devices. Blockage of cell to cell communication [Quorum sensing] is a novel approach to inhibition of biofilm formation. Ribonucleic acid-III-inhibiting peptide inhibits staphylococcal infections associated with orthopedic implants and urethral stents.[10,12] Disaggregation of the biofilm matrix using an enzyme is another antibiofilm approach. Treatment with dispersin B followed by a protease is capable to eradicate staphylococcal biofilm. However, detachment by enzymatic treatment depended on the nature of the biofilm constituents.[13]

Treatment of biofilm infections is currently very complicated. The one of the important reason is that microorganisms of biofilm are highly resistant to antibiotic treatment in human. Various studies demonstrated that the minimum inhibitory concentration for biofilm bacteria is approximately 10-1000 times higher than the planktonic bacteria. The possible reasons for antibiotic resistance are limited antibiotic penetration, horizontal gene transfer etc.

In view of above generally the strategies can be divided into two i.e. involve a medical device or not. If not involve medical devices, long term treatment with then combinations of antibiotics [different killing mechanisms] can some time eliminated the infections. If the medical device is involves, removal of device is necessary for a successful outcome.

Antibiotic combination therapy [characters of antibiotics, tolerance and resistance of biofilm] is generally recommended for the treatment of biofilm infections. In general macrolides, lincosamides, tetracyclines, rifamycins, quinolones, nitroimidazole, sulfonamide and oxazolidinones penetrate better in tissues and cells than beta-lactam, aminoglycosides, glycopeptides and polymyxin.[7]

A novel approach for the treatment for the biofilm is using the electric current and ultrasound adjunctively with antimicrobial therapy. This approach may be very useful in clinical practices.

Table 1: Microorganisms associated with medical implants devices.

Microorganism	Medical device
Staphylococcus aureus, Klebsiella pneumoniae, Enterococcus faecalis, Proteus mirabilis, Candida albicans.	Central venous catheter utilizes to deliver generally medicines, fluids, or nutrients for long period of time. Both the outer part of catheter and the catheter lumen can become contaminate with microorganisms of biofilm.
Staphylococcus epidermidis, Klebsiella pneumoniae, Enterococcus species, Proteus mirabilis, Pseudomonas aeruginosa, Escherichia coli and other gram negative bacteria.	Urinary catheter uses to collect urine during surgery, measure urine output and prevent urine retention in intensive care unit patients. Severe complications such as injury to the urinary bladder, block urine flow may occur due to formation of biofilm.
Staphylococcus aureus, streptococcus species, Candida species, Enterococcus species.	Replacement of diseased valves with prosthetic heart valves reduces the morbidity and mortality associated with native valvular disease. Biofilm microorganisms may be attached and develop on components of *valves* and surrounding tissues of the *heart*, leading to *prosthetic valve* endocarditis.
Pseudomonas aeruginosa, Escherichia coli, Stapylococcus aureus.	Through contact lance, the cornea may be exposed to microbes which lead to severe ocular infections.
Klebsiella pneumoniae, Escherichia coli, Pseudomonas aeruginosa Acinetobacter species.	Endotracheal tube insert into the trachea through the mouth or nose to maintain an unobstructed passageway especially to deliver oxygen or anesthesia to the lungs. The presence microbes on ventilator and endotracheal tube contribute for the development of biofilm and the result occurrence of pneumonia.
Staphylococcus aureus, Candida albicans, Streptococcus species.	*Dental implants* provide people with the strength and stability require to eat all the foods. The biofilm infections can cause dental implant failure.
Staphylococcus epidermidis, Pseudomonas aeruinosa, Enterococcus species Staphyloccus aureus.	Numerous joint prostheses uses in orthopedic practice and the joint infections may causes of implant failure leading to pain and repeated surgeries etc.

Table 2: Biofilm associated human diseases.

Microorganism	Disease
Pseudomonas aeruginosa, Haemophilus influenzae, Staphylococcus aureus.	Cystic fibrosis in the lung causes the formation of thick and sticky mucus which blocks airway and makes it hard for patient's to breath.
Staphylococcus epidermidis, Staphylococcus aureus, Streptococcus species, Corynebacterium species, Enterococcus species and Candida species.	In Prosthetic valve endocarditis, biofilm disrupt or block the artificial cardiac valve that results in diminished flow, turbulence or even leaking.
Streptococcus species, Staphylococcus species, Pneumococci species, Candida species, Aspergillus species and some gram negative bacteria.	Native valve endocarditis inflammation of the inner tissues of the heart valves. The risk factors are rheumatoid vascular disease, congestive heart disease, and age-related degenerative heart disease.
Streptococcus pneumomoniae, Haemophilus influenzae, Moraxella catarrhalis, Staphylococcus epidermidis, Pseudomonas aeruginosa	Otitis mediais, a chronic ear infection, involves the inflammation of the mucoperiosteal lining causes ear pain.
Porphyromonas gingivalis, Fusobacterium nucleatum, Pseudomonas aerobicus	Periodontitis, gum infections causes damage to the soft tissues as well as the bone that support the teeth.
Staphyloccus aures	Osteomyelitis is a disease of bone in which microbial infection can become chronic and cause a loss of blood supply to the affected bone that can lead to the eventual death of the bone tissue.
Pseudomonas aeruginosa, *Staphyloccus* aureus.	In chronic wounds delay healing of wounds.

CONCLUSION

From all these information we have observed that biofilm formation on indwelling medical devices greatly affects human health. Current therapeutic approaches for the prevention of biofilm formation are limited. Further, antibiotic treatment alone is often inadequate and subsequent resistance to antibiotic is slow but serious threat to public health. Despite the advances made in the development of novel antibiofilm therapy, urgent development is required to identify cost efficient alternative therapy. Advances in this field will require interdisciplinary collaborative efforts among medical practioners, scientists and engineers in design and testing of innovative surfaces to combat medical devices associate infections.

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