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RECENT ADVANCES IN MITIGATING BIOFILMS ON MEDICAL DEVICES

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Abstract: Poor prognosis, patient distress, increased morbidity/mortality, antibiotic resistance and increased financial burden to patients and healthcare systems are some of the consequences of biofilm-related infections that arise from contaminated medical devices. The complex tri-dimensional architectural intricacy of biofilms has become an inevitable challenge to existing treatment options. It has also largely affected the development of *in vitro* models that help in the study of biofilm composition, formation, prevention, and therapeutic targets for eradicating biofilms. Newer biofilm models which were recently developed, enjoyed limited success in mitigating the limitations encountered by the traditional simpler models. More in-depth studies are needed to consider them relevant and accurate. Implants are generally considered as high risk medical devices, as they are exposed to patients' tissues for a longer duration of time. Implants are reported to represent 65% of total implant-related infections. Because of this reason, most studies reported in the literature have focused on biofilm-related infections from implants. Considering the severity of such infections and the difficulty in treatment, novel effective strategies revolving around biofilm prevention in medical devices are seen to be the urgent need of hour. Recent studies have shown that rough edged surfaces had the greatest cellular adhesion. In addition, certain types of material were found to be most susceptible to biofilm growth such as titanium alloy discs, polymethyl methacrylate (PMMA), polyethylene (UHMW-PE), stainless steel (SST), aluminum, hydroxyapatite (HA) and polyethylene (PE). Newly developed implant coating techniques and nanomedicine-based strategies are promisors to prevent biofilm occurrence, although risk-benefit concerns still need to be considered. Therefore, comprehensive studies are needed to address the existing limitations. There is also a need for innovative techniques that can test biocompatibility and efficiency of the products to ensure they are effective and safe to the patients.

Keywords: Biofilm, microbial control, medical devices, implants, surface, coating.

Introduction

Hard-to-treat infections caused by biofilm contamination on medical devices contribute to poor prognosis, patient distress, increased morbidity/mortality, device dysfunction, and a huge financial burden to both patients and healthcare systems (Ronin et al., 2021; Moris et al., 2022). The difficulty in dealing with biofilm-related infections relates to the complex tri-dimensional biofilm structure, which is essential for microbial resistance and a successful pathophysiological process. Biofilms are communities of microorganisms attached to a substrate in which microbial cells are surrounded by an extracellular matrix comprising self-produced polymeric substances (EPSs) (Wang et al., 2022; Costa et al., 2022; Lu et al., 2022). The EPSs consist of polysaccharides, proteins, lipids, and extracellular DNA that contribute towards an enhanced microbial accretion, biofilm virulence, and antimicrobial resistance (Costa et al., 2022). The biofilm structure further creates a microenvironment for social interaction within the colony where cells survive for longer periods, tolerate changes in living conditions, and escape from the immune system in the external environment (Wang et al., 2022). Therefore, they resist infiltration of host immune cells and most antibiotics (Yuan et al., 2022; Liu et al., 2022). Due to this phenomenon, biofilm-caused infections promote prevalence of antibiotic-resistant microorganism, and they require prolonged use of antibiotics at concentrations of 1000–1500 times higher than what is needed to kill planktonic infections (Moore et al, 2022; Ronin et al., 2021).

Biofilm prevention in medical devices

The challenges with *in vitro* models

Among all medical devices, implants represent a higher risk of contamination, as they remain in contact with patients' tissues for a

longer time, when compared to other medical devices (WHO, 2015). Bacterial biofilms represent 65% of total implant-related infections (Ho et al., 2015). Because of the increased interest on characterization, diagnostics, and prevention of biofilm-related infections from implants, several studies have been reported in the literature regarding its scope.

Due to the complexity in treating such infections, it has become an urgent need to focus on effective prevention and therapeutic measures (Lu et al., 2022). Several efforts have been dedicated towards the elucidation of biofilm formation and towards the development of biofilm models. Most studies reported in the literature reveal *Staphylococcus* as the most common genus of microorganism as the causative organism for infections from medical devices (Gundtoft et al., 2017; Triffault-Fillit et al., 2019; Wang et al., 2018). *Staphylococcus aureus* is a Gram-positive bacterium, present in various environments including human skin microbiota, and it can develop biofilms and multi-resistant strains (Pestrak et al., 2020). Because of this, *Staphylococcus*-based biofilm models are the first choice for investigational studies of implants.

Jothipandiyana et al., (2022), highlighted the clinical importance of *Acinetobacter baumannii* biofilms in orthopedic implants. As this biofilm is modulated by quorum sensing, the research group studied the activity of thiazolinyl-picolinamide based palladium (II) complexes (quorum sensing inhibitors) against biofilm development and obtained promising positive outcomes.

Several notable studies and reviews soon emerged in the literature revolving around the relationship between the EPS matrix and the implant environment and their roles in implant-related infections as a possible therapeutic target in biofilm prevention (Costa et al., 2022). Biofilm systems are complex which make them difficult to be reproduced in laboratory settings which in turn have led to limitations in the existing techniques. The use of pure homogenous standard strains, with standardized cell sizes do not reproduce the constitution of the wild formation of biofilms (Vyas et al., 2022). To reduce bias in the study's conclusions, an alternative is to combine different methodologies to have a better understanding and to discuss the outcomes. This is also useful to complement previous studies in the literature with alternative approaches or to conduct collaborative studies. Recently developed innovative *in vitro* models have been designed to better represent the environments of biofilm-associated infections, such as the three-dimensional organoid model by Wu et al. (2021), CF sputum medium model and an *in vitro* CF epithelial cell model by Cornforth *et al.* (2020), that are considered to be reasonable advances in this field. Although, caution is required when selecting and applying such *in vitro* models, still more studies are needed to consolidate and determine relevance and accuracy of these models in practice (Vyas et al., 2022).

The influence of medical devices constitution and design

Moore and collaborators studied the relationship between a variety of surface types and materials of orthopedic implants such as titanium, polyethylene and stainless steel in *Staphylococcus aureus* biofilm formation and attachment. They found that rough edged surfaces had the greatest cellular adhesion than smooth surfaces on a single implant and across all implants, suggesting that implant roughness, as well as large-scale surface features, may be at greater risk of biofilm colonization (Moore et al., 2022). Ho and collaborators noted that biofilms tend to attach to titanium alloy discs, polymethyl methacrylate (PMMA), polyethylene (UHMW-PE), stainless steel (SST), and aluminum (Ho, et al.,2015). Additionally, Gupta et al., 2020 demonstrated that rougher surfaces, such as hydroxyapatite (HA) and polyethylene (PE) materials, had a higher tendency of biofilm spread than titanium and 316L SST (Gupta et al., 2020).

Surface modification and coating

Diverse methods have been developed such as coating the implants to prevent the growth of bacterial biofilm on these surfaces. However, few studies had pointed to the risks involved with the selecting of drug-resistant species when implants were coated with antibiotics. Coating titanium–aluminum–niobium metal alloy with silver reportedly have limited effects. (Feng et al., 2016; Kuehl et al.2016, Oliveira et al, 2018). Moreover, nanomedicine approaches by engineering innovative multifunctional bionic coating systems on the surface of implants, are innovations that are increasingly becoming attractive. (Yuan et al., 2022).

Jothipandiyana et al. (2022) showed positive outcomes with Titanium plates with novel thiazolinyl-picolinamide based palladium (II) complexes (quorum sensing inhibitors) against Acinetobacter biofilm.

Fang and collaborators (2022) designed an antibacterial phototherapeutic system by combining polydopamine (PDA)-black phosphorus nanosheets (BP NSs)/ZnO nanowires (NWs) on titanium (Ti) substrates to manage infections. They combined this technique with photothermal effect and showed that the antibacterial activity was potentialized as PTT which dissipates biofilms to ZnO and in turn acts as a bactericidal agent. They achieved a 99.5 % eradication ratio of biofilm *in vivo*, which is much better than that of PTT or ZnO NWs alone. (Fang at al., 2022).

Yuan et al., (2022) proposed to coat titanium implants with BPs@HA composite (a hydroxyapatite (HA)-coated metal implant covered with 2D black phosphorus nanosheets (BPs) *in situ*. *In vitro* and *in vivo* studies have showed excellent outcomes against biofilm and have demonstrated accelerated fracture healing, resulting in osteogenesis.

Liu et al., 2022 proposed an antibacterial polypeptide coating that can be easily applied to titanium implants by immersion for 5 minutes at room temperature. This was observed to possess excellent *in vivo* adhesive property which may prevent implants from forming biofilms. Their findings revealed that antibacterial coating does not drive antimicrobial resistance upon long-term utilization and it effectively prevents biofilm formation.

Another approach found in the literature against biofilm growth is the perioperative administration of active substances such as the study reported by Wang et al. (2022). They observed that tranexamic acid protected the implants against implant-associated infection by reducing biofilm formation in infected tissues.

Physical removal of biofilms

Moris et al., 2022 tested different physical techniques (sonication, Digest-EUR®, mechanized bead mill, combination of sonication plus Digest-EUR®) to dislodge biofilms from medical implants made of silicone, piccline. The implants included peripheral venous catheter and endotracheal tube. They showed that the

sonication procedure was statistically superior to all the other treatment.

Microrobotic medicine has been getting much attention lately. Mayorga-Martinez et al., 2022 demonstrated the efficient eradication of dental biofilm on titanium dental implants via swarming magnetic microrobots constructed with ferromagnetic (Fe_3O_4) and photoactive ($BiVO_4$) materials through polyethylenimine micelles.

FINAL CONSIDERATIONS

Biofilm-related infections from medical devices are a huge challenge, due to the complexity of its structure. It is challenging and difficult to reproduce the biofilm *in vitro*, as a model to study biofilm development and potential therapeutic targets. Considering the severity and the difficulty in such treatment modalities, strategies around biofilm prevention in medical devices must be in focus. Recent studies have shown that rough and edge surfaces had the greatest cellular adhesion. Although eliminating biofilms from all such surfaces may cause loss of function of the medical device, as the design of a device is strictly related to its performance. There are also evidences that some materials are most susceptible to biofilm growth such like titanium alloy discs, polymethyl methacrylate (PMMA), polyethylene (UHMW-PE), stainless steel (SST), aluminum, hydroxyapatite (HA) and polyethylene (PE). Although these outcomes must be carefully assessed for the risk-benefit balance, and in addition, a change in the material or design of the product may lead to loss of device function putting patients in risk. For example, although a smooth surface is less susceptible to biofilm growth, it also promotes host cellular adhesion and proliferation, which is needed for implant fixation.

A similar risk-based approach must be considered when assessing developed implant coating techniques and nanomedicine. While most have been shown to be promisors to prevent biofilm occurrence, negative outcomes such as the probability of antibiotic resistance, increased toxicity and no significant results must be considered. It is necessary to deliver efforts to test biocompatibility and efficiency of the proposed products and to follow all applicable steps for clinical research.

Therefore, it is crucial to promote collaborative and complementary studies to overcome a specific model's limitations and to have enough data to ensure robustness and accuracy of the proposed new methods and products.

More than developing new products with enhanced properties against biofilm, prevention takes a critical role in microbial control during aseptic and sterilization processes at the manufacturing site and along the supply chain. It is important to involve a multidisciplinary team to develop a strategy to protect the product and also to ensure that safe and efficient products are delivered to improve patient lives.

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Declaration of competing interest

The authors declare that they have no competing interests.

Authorships

Adriana C. M. Lirio contributed to the literature review and wrote the article. Daniela Dal Molim Ghisleni, Dinesh Kumar Chellappan, Kamal Dua and Terezinha J. A. Pinto provided critical revision and final approval of the finalized manuscript. All authors have read and approved the final manuscript.

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