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Review Article

New developments in combating infection from biofilm forming bacteria of orthopedic implants

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ABSTRACT

Orthopedic device related infections (ODRI's) represent a difficult to treat situation owing to their biofilm based nature. Biofilm infections once established are difficult to eradicate even with an aggressive treatment regimen due to their recalcitrance towards antibiotics and immune attack. The definitive treatment to eradicate the infections once a biofilm has established is surgical excision of the implant and thorough local debridement, but this carries a significant socioeconomic cost, the outcomes for the patient are often poor, and there is a significant risk of recurrence. The aim of the study was to provide a comprehensive insight into the newer anti-biofilm interventions (non-antibiotic approaches) and a better understanding of their mechanism of action essential for improved management of orthopedic implant infections.

Keywords: Biofilm, Orthopeadic implants, Bacteria, Infections

INTRODUCTION

Orthopedic implants have become an indispensable component of modern medicine as they have improved the quality of life of many individuals worldwide and continue to do so. However, the introduction of a foreign body (i. e.; orthopedic implant in this case) along with damage to the skin barrier during the surgical procedure may predispose the body to infection allowing bacteria to adhere to the implant surface and form a biofilm.

Early orthopaedic implants were engineered to purely transmit and resist mechanical forces necessary to perform their function whilst remaining biologically inert; however, modern implants also have the ability, through the local delivery of molecules and surface coatings, to enhance bone healing and osseointegration whilst reducing the foreign body reaction and the risk of infection.[1] Moreover, biofilm infections pose an extremely difficult situation to treat. Although the reasons may be many but primarily the major cause of concern is the fact that biofilm bacteria acquire the ability to become resistant to the action of antibiotics as well as host immune responses. It has been reported that biofilmbacteria are up to 1,000 times more recalcitrant to most of the antibiotics employed.[7]

Implant-related infection occurs following approximately 5% of all elective and emergency orthopaedic procedures and is a serious surgical complication. Treatment often results in revision surgery, which has high levels of associated morbidity and financial costs; some cases result in amputation and death.[2-6]

Orthopaedic implant-related infection cannot be simply prevented by implant design and implant surface characteristics; instead, it must be considered in the wider context of prevention strategies including patient, surgical, and healthcare factors; however, the implant surface has the potential to be the final line of defence against microbial attack. For the purposes of this review, a bibliographic search was carried out on Pubmed using the search string: (biofilm orthopedic implants), resulting in

821 articles, of which 125 papers were finally analysed because they were directly related to novel strategies to prevent and treat biofilm-forming bacteria on orthopaedic implants.

BIOFILM

A bacterial biofilm is a colony of sessile bacteria irreversibly anchored to the implant surface and contained within a self-produced matrix known as extracellular polymeric substance (EPS), containing mainly polysaccharides, lipids, proteins, and extracellular DNA.[10,11] Bacterial biofilms display emergent properties: that is, properties that are not predictable from study of the planktonic cells from which they emerge.[12] These properties give the biofilms a significant survival advantage, making them extremely resilient to host immune or conventional anti-microbial therapies; they have been shown to be up to 1000 more resistant to antibiotic eradication, which ultimately results in the recalcitrance and recurrence of biofilm-related implant infection.[13-16] A biofilm is a complex three-dimensional aggregation of microorganisms, which can be single or multiple species, embedded within the EPS, which has its own internal architecture and nutrient circulation.[6,15] Biofilm antibiotic resistance and tolerance mechanisms differing depending on the antimicrobial agent, the bacterial strain and species, the age and developmental phase of the biofilm, and the biofilm growth circumstances.[17-21]

BACTERIA

The most common bacteria responsible for orthopaedic BRII are gram-positive staphylococcal species namely *Staphylococcus aureus* (*S. aureus*) and coagulase-naegative staphylococci such as *Staphylococcus epidermidis* (*S. epidermidis*), although multiple gram-positive and negative organisms have been found to be responsible for BRII, and the infection can be caused by a single organism or be polymicrobial.[22] Acute aggressive implant infections are often caused by more virulent pathogens such as S. aureus where more indolent chronic infections are typically caused by commensal bacterial that form part of the skin's microbiome, such as *S. epidermidis*, where their role in opportunistic biofilm-associated implant infection is well established.[24]

NEW DEVELOPMENTS IN BIOFILM PROTECTION

Phage therapy

Lytic bacteriophages (or simply 'phages') are bacterial viruses which attack bacteria, multiply within them, and finally destroy them.[25-27] Phage therapy represents an ideal approach against implant infections and the reasons are many-fold. Firstly, from a clinical standpoint, phage therapy is safe with no reports of any adverse effects or local tissue toxicity. They do not affect eukaryotic cells even at higher concentrations.[28] Secondly, phages possess self-reproducing ability (auto-dosing), and giving them an advantage over the other antibiotic based therapy that requires repeated dosing. Thirdly, because of the fact that phages have co-evolved over time with bacteria, they have developed an innate ability to penetrate biofilm and lyse the embedded bacteria within the biofilm matrix.[29] Their unique capability towards prevention of formation as well as disruption of formed bacterial biofilms (through action of phage enzymes) even by resistant strains makes them an attractive alternative option against orthopedic implant infections that is worth exploring.

Great efforts have been made to devise materials and coatings that prevent or retard bacterial adhesion and hence the formation of biofilms. Bacterial adhesion to surfaces is controlled by physicochemical factors (including surface chemistry, topography, and roughness), bacterial properties (including bacterial hydrophobicity, surface load, and cell size), and environmental parameters (including flow rate, temperature, and pH) The ideal implant surface would be one that minimises bacterial adhesion, inhibits biofilm formation, and confers an effective bactericidal action surfaces that appear least attractive to bacteria tend to exhibit hydrophilic, highly hydrated, and non-charged properties.

Ceramics

Ceramics have been shown to display advantageous physical-chemical surface properties to deter biofilm formation in vitro compared to other implant materials demonstrating reduced bacterial adhesion and slower biofilm development, and there has also been clinical evidence of increased bacterial counts on polyethylene liners compared with ceramic in biofilm related infection.[30-33]

Nanopatterning

Modifying the surface finish at the nanometer scale typically on titanium or titanium alloy implants, including the creation of surface nanopores using hydrothermal treatment has demonstrated efficacy in vitro at deterring biofilm formation. The chemical modification of implant surfaces by the application of polymer coatings to the surface of titanium implants results in a significant inhibition of bacterial adhesion. In a recent study, both these techniques were combined, a nanopatterned coating, mimicking shark skin was subsequently coated with a peptide-based coating and then inoculated with *E. coli* and *S. epidermidis*; both surfaces on their own demonstrated efficacy compared to a control smooth surface.[34]

Metal ions as nanoparticles against biofilm bacteria

Nanoparticles (NP's) are another promising alternative for use against orthopedic implant infections. The most commonly used inorganic metal ion coating is silver, other less popular one include gold nanoparticles (AuNP), zinc,

magnesium, copper, selenium, titanium and NO releasing silica NP's. These nanoparticles can be used as implant coatings in hydrogels or polymers for surface preparation of implants and prosthesis to improve osteointegration and reduce biofilm formation. Also, nanoparticles can be surface modified and used in conjugation with conventional antibiotic molecules as drug delivery systems for improved antibacterial outcomes at implant sites. However, with a silver coating, there is a risk of host silver toxicity; locally elevated silver concentrations are toxic to osteoblasts, and this may be implicated in osteolysis prosthesis loosening.[35-38]

PREVENTION OF BIOFILM THROUGH SURFACE IMPLANT MODIFICATIONS

These include surface modifications to decrease bacterial adhesiveness. This can be achieved by applying a layer of inert polymers with inherent anti-adhesive properties. For example, polyethylene glycol (PEG) based coatings were able to reduce bacterial adhesion of *S. aureus* and *E. coli*, showing a significant anti-adhesion effect of around 8-folds.

To further improve regarding the concern that anti-adhesive coatings impair osseointegration, bioactive molecules such as bone morphogenetic protein-2 (BMP-2) and arginine-glycine-aspartic acid (RGD) peptides could be grafted on the anti-adhesion surface in an attempt to restore and improve osteogenesis.

Tethering of antibiotics to the implant surface

Newer approaches include covalent attachment of antibiotics to implant surfaces. These tethered antimicrobial agents are firmly attached and therefore no bulk tissue toxicity occurs.

The covalent modification of titanium surfaces has been achieved using different antibiotics such as vancomycin, tetracycline, daptomycin and gentamycin.

For example, vancomycin has been covalently attached to a Ti alloy surface (Vanc-Ti) and this was able to significantly reduce colonization of the implant surface by *S. epidermidis*.[39]

Local drug delivery system

Nowadays, there are the new 'cementless' implant coatings wherein biodegradable polymers are loaded first with the antibiotic (plasma spraying, gel-dip coating, electrochemical deposition) and then these antibiotic-polymer mixtures are coated onto the implant surface, also called an active coating. These coatings work as local antibiotic delivery systems and deliver high doses of antibiotics on the implant surface as well as into the nearby tissue spaces thus taking care of bacterial adherence on the implant as well as in the surrounding implant tissue.

Hydrogel carriers

A recent strategy has been to design hydrogels with the desired drug elution properties, i.e., high short-term post-implantation antibiotic concentrations above the level that can be achieved by intravenous delivery at a time when the implant is at most risk of colonisation, and which can be loaded with the desired antibiotic regime intra-operatively.

One example is a defensive anti-bacterial coating (DAC) that consists of covalently linked hyaluronan and poly-D, L-lactide that undergoes complete hydrolytic degeneration within 72 h, which releases its pre-loaded antibiotics.[40]

CONCLUSION

Orthopeadic device related infections represent a challenging situation due to the biofilm based nature of these infections as well as to the increasing involvement of antibiotic resistant pathogens as the causative agents. The ideal implant material or surface coating would be able to perform its function whilst being immune to bacterial colonisation and super compatible with the host tissue. Numerous strategies, have been developed and are being interrogated to determine their potential clinical efficacy. However, there are certain limitations and challenges associated with each therapeutic approach that need to be addressed in order to move these strategies from experimental technologies to effective clinical treatments. At present, the only treatment strategy to eradicate the infection is implant removal, but novel strategies, using vastly different technologies, are offering potential solutions to purge the implant of infection whilst remaining *in situ*.

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REFERENCES

1. Filipović U, Dahmane RG, Ghannouchi S, Zore A, Bohinc K. Bacterial adhesion on orthopedic implants. Adv Colloid Interface Sci. 2020;283:102228.
2. Moriarty TF, Schlegel U, Perren S, Richards RG. Infection in fracture fixation: can we influence infection rates through implant design? J Mater Sci Mater Med. 2010;21(3):1031-5.
3. Kapadia BH, Berg RA, Daley JA, Fritz J, Bhave A, Mont MA. Periprosthetic joint infection. Lancet. 2016;387(10016):386-94.
4. Vastag B. Knee replacement underused, says panel: useful option when nonsurgical therapies fail. JAMA. 2004;291(4):413-4.
5. Lamagni T. Epidemiology and burden of prosthetic joint infections. J Antimicrob Chemother. 2014;69(1):5-10.
6. Saeed K, McLaren AC, Schwarz EM, Antoci V, Arnold WV, Chen AF, et al. 2018 international

consensus meeting on musculoskeletal infection: Summary from the biofilm workgroup and consensus on biofilm related musculoskeletal infections. J Orthop Res. 2019;37(5):1007-17.
7. Mah TF, O'Toole GA. Mechanisms of biofilm resistance to antimicrobial agents. Trends Microbiol. 2001;9(1):34-9.
8. Donlan RM, Costerton JW. Biofilms: survival mechanisms of clinically relevant microorganisms. Clin Microbiol Rev. 2002;15(2):167-93.
9. Costerton JW. Overview of microbial biofilms. J Ind Microbiol. 1995;15(3):137-40.
10. Flemming HC, Wingender J, Szewzyk U, Steinberg P, Rice SA, Kjelleberg S. Biofilms: an emergent form of bacterial life. Nat Rev Microbiol. 2016;14(9):563-75.
11. Mottola C, Matias CS, Mendes JJ, Melo-Cristino J, Tavares L, Cavaco-Silva P, et al. Susceptibility patterns of Staphylococcus aureus biofilms in diabetic foot infections. BMC Microbiol. 2016;16(1):119.
12. Poilvache H, Ruiz-Sorribas A, Sakoulas G, Rodriguez-Villalobos H, Cornu O, Bambeke F. Synergistic Effects of Pulsed Lavage and Antimicrobial Therapy Against Staphylococcus aureus Biofilms in an in-vitro Model. Front Med (Lausanne). 2020;7:527.
13. Macià MD, Rojo-Molinero E, Oliver A. Antimicrobial susceptibility testing in biofilm-growing bacteria. Clin Microbiol Infect. 2014;20(10):981-90.
14. Nishimura S, Tsurumoto T, Yonekura A, Adachi K, Shindo H. Antimicrobial susceptibility of Staphylococcus aureus and Staphylococcus epidermidis biofilms isolated from infected total hip arthroplasty cases. J Orthop Sci. 2006;11(1):46-50.
15. Ibrahim EH, Sherman G, Ward S, Fraser VJ, Kollef MH. The influence of inadequate antimicrobial treatment of bloodstream infections on patient outcomes in the ICU setting. Chest. 2000;118(1):146-55.
16. Ito A, Taniuchi A, May T, Kawata K, Okabe S. Increased antibiotic resistance of Escherichia coli in mature biofilms. Appl Environ Microbiol. 2009;75(12):4093-100.
17. Alhede M, Kragh KN, Qvortrup K, Allesen-Holm M, van Gennip M, Christensen LD, et al. Phenotypes of non-attached Pseudomonas aeruginosa aggregates resemble surface attached biofilm. PLoS One. 2011;6(11):e27943.
18. Bowler LL, Zhanel GG, Ball TB, Saward LL. Mature Pseudomonas aeruginosa biofilms prevail compared to young biofilms in the presence of ceftazidime. Antimicrob Agents Chemother. 2012;56(9):4976-9.
19. Haaber J, Cohn MT, Frees D, Andersen TJ, Ingmer H. Planktonic aggregates of Staphylococcus aureus protect against common antibiotics. PLoS One. 2012;7(7):e41075.
20. Arciola CR, Campoccia D, Montanaro L. Implant infections: adhesion, biofilm formation and immune evasion. Nat Rev Microbiol. 2018;16(7):397-409.
21. Achermann Y, Goldstein EJ, Coenye T, Shirtliff ME. Propionibacterium acnes: from commensal to opportunistic biofilm-associated implant pathogen. Clin Microbiol Rev. 2014;27(3):419-40.
22. Biswas B, Adhya S, Washart P, Paul B, Trostel AN, Powell B, et al. Bacteriophage therapy rescues mice bacteremic from a clinical isolate of vancomycin-resistant Enterococcus faecium. Infect Immun. 2002;70(1):204-10.
23. Matsuzaki S, Yasuda M, Nishikawa H, Kuroda M, Ujihara T, Shuin T, et al. Experimental protection of mice against lethal Staphylococcus aureus infection by novel bacteriophage phi MR11. J Infect Dis. 2003;187(4):613-24.
24. Chhibber S, Kaur S, Kumari S. Therapeutic potential of bacteriophage in treating Klebsiella pneumoniae B5055-mediated lobar pneumonia in mice. J Med Microbiol. 2008;57(Pt 12):1508-13.
25. Sulakvelidze A, Alavidze Z, Morris JG. Bacteriophage therapy. Antimicrob Agents Chemother. 2001;45(3):649-59.
26. Khalifa L, Brosh Y, Gelman D, Coppenhagen-Glazer S, Beyth S, Poradosu-Cohen R, et al. Targeting Enterococcus faecalis biofilms with phage therapy. Appl Environ Microbiol. 2015;81(8):2696-705.
27. Sorrentino R, Cochis A, Azzimonti B, Caravaca C, Chevalier J, Kuntz M, et al. Reduced bacterial adhesion on ceramics used for arthroplasty applications. J Eur Ceram Soc. 2018;38:963-70.
28. Hexter AT, Hislop SM, Blunn GW, Liddle AD. The effect of bearing surface on risk of periprosthetic joint infection in total hip arthroplasty: a systematic review and meta-analysis. Bone Joint J. 2018;100-B(2):134-42.
29. Lass R, Giurea A, Kubista B, Hirschl AM, Graninger W, Presterl E, et al. Bacterial adherence to different components of total hip prosthesis in patients with prosthetic joint infection. Int Orthop. 2014;38(8):1597-602.
30. Pitto RP, Sedel L. Periprosthetic Joint Infection in Hip Arthroplasty: Is There an Association Between Infection and Bearing Surface Type? Clin Orthop Relat Res. 2016;474(10):2213-8.
31. Dolid A, Gomes LC, Mergulhão FJ, Reches M. Combining chemistry and topography to fight biofilm formation: Fabrication of micropatterned surfaces with a peptide-based coating. Colloids Surf B Biointerfaces. 2020;196:111365.
32. Suzuki T, Fujibayashi S, Nakagawa Y, Noda I, Nakamura T. Ability of zirconia double coated with titanium and hydroxyapatite to bond to bone under load-bearing conditions. Biomaterials. 2006;27(7):996-1002.
33. Lazarinis S, Mäkelä KT, Eskelinen A, Havelin L, Hallan G, Overgaard S, et al. Does hydroxyapatite coating of uncemented cups improve long-term survival? An analysis of 28,605 primary total hip

arthroplasty procedures from the Nordic Arthroplasty Register Association (NARA). Osteoarthritis Cartilage. 2017;25(12):1980-7.
34. Noda I, Miyaji F, Ando Y, Miyamoto H, Shimazaki T, Yonekura Y, et al. Development of novel thermal sprayed antibacterial coating and evaluation of release properties of silver ions. J Biomed Mater Res B Appl Biomater. 2009;89(2):456-65.
35. Tsukamoto M, Miyamoto H, Ando Y, Noda I, Eto S, Akiyama T, et al. Acute and subacute toxicity in vivo of thermal-sprayed silver containing hydroxyapatite coating in rat tibia. Biomed Res Int. 2014;2014:902343.
36. Douthit C, Gudenkauf B, Hamood A, Mudaliar N, Caroom C, Jenkins M. Effects of powdered rifampin and vancomycin solutions on biofilm production of staphylococcus aureus on orthopedic implants. J Clin Orthop Trauma. 2020;11(1):S113-7.
37. Pitarresi G, Palumbo FS, Calascibetta F, Fiorica C, Di Stefano M, Giammona G. Medicated hydrogels of hyaluronic acid derivatives for use in orthopedic field. Int J Pharm. 2013;449(1-2):84-94.

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