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Implant materials and prosthetic joint infection: the battle with the biofilm

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- Prosthetic joint infection (PJI) is associated with poor clinical outcomes and is expensive to treat.
- Although uncommon overall (affecting between 0.5% and 2.2% of cases), PJI is one of the most commonly encountered complications of joint replacement and its incidence is increasing, putting a significant burden on healthcare systems.
- Once established, PJI is extremely difficult to eradicate as bacteria exist in biofilms which protect them from antibiotics and the host immune response.
- Improved understanding of the microbial pathology in PJI has generated potential new treatment strategies for prevention and eradication of biofilm associated infection including modification of implant surfaces to prevent adhesion of bacteria.
- Much research is currently ongoing looking at different implant surface coatings and modifications, and although most of this work has not translated into clinical medicine there has been some early clinical success.

Keywords: biofilm; implant; material; microbiology; prosthetic joint infection; surface coating

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Introduction

Prosthetic joint infection (PJI) is one of the most feared complications of arthroplasty surgery due to its resistance to therapy with existing antibiotics.[1] It is a major cause of failure in arthroplasty, being the leading cause of revision within the first five years following surgery, and it is also the leading cause of failure following revision surgery.[2] Prosthetic joint infection is reported to occur in around 0.5–2.2% of cases undergoing primary arthroplasty, and the incidence is higher after revision surgery where it has been reported to contribute 30% of failures.[3–5] Due to the already large and increasing volume of arthroplasty surgery being performed annually, with over 250,000 operations per year alone in the UK, the number of patients affected by PJI is expected to rise.[5–7] The true incidence of PJI is likely to be even higher than that recorded (by up to 40%) in arthroplasty registries as a proportion of patients who at the time of revision surgery appear to have failed by aseptic loosening go on to be diagnosed with infection on the basis of intraoperative samples.[8]

Prosthetic joint infection is associated with poor clinical outcomes, prolonged hospital admissions, and complex revision operations which are associated with their own complications; septic revision surgery has a five times greater mortality when compared to aseptic revision and the re-infection rate can be up to 20%.[9–11] There are over 1000 operations per year recorded on the UK National Joint Registry for PJI following TKA alone, and this figure does not include non-revision operations for PJI.[5] Revision for PJI is between two and three times as expensive as revision for aseptic failure.[12,13] The cost of resolving PJI in knee and hip arthroplasty, taking into account revision surgery, extended length of stay, high-cost long-term antibiotics and new high-cost replacement prostheses, has been estimated to be approximately £100,000 per patient.[14]

Risk factors for prosthetic joint infection

Given the prevalence of PJI, the impact on patients and the cost to healthcare systems, in recent years there has been a growing international collaboration to tackle all aspects of the disease. This has included the adoption of an international definition for PJI which includes a combination of physical signs as well as microbiological, histological and biochemical findings.[15] There have also been large cohort studies using registry data, as well as extensive work to understand existing data to determine what risk factors predispose to PJI in arthroplasty. These factors have been broken down into patient, surgical and

healthcare factors.[16,17] Male gender, young age, high body mass index (BMI) and the presence of medical co-morbidities, particularly diabetes, increase the risk of PJI.[16] At the surgical level, the surgical indications that increase the risk of revision for PJI include fractured neck of femur and avascular necrosis.[16] In total hip arthroplasty, the lateral approach appears to increase the risk of PJI whereas the use of ceramic heads at the bearing surface appears to reduce it.[16] Maybe counterintuitively, it appears healthcare system factors, such as experience and grade of surgeon, have little impact on risk of revision for PJI.[16]

Micro-organisms in PJI

The most common micro-organisms responsible for PJI are Gram-positive staphylococcal species, namely *Staphylococcus aureus* and coagulase-negative staphylococci such as *S. epidermidis*.[18] However, the species of bacteria responsible for PJI, which can be Gram-positive or Gram-negative and mono- or poly-microbial, vary depending on the time elapsed since surgery to presentation, the joint replaced and the geographical location; *Staphylococcus aureus* causes most PJI in the US whilst *S. epidermidis* causes the most in Europe.[18]

Infections tend to be classified into time of onset from surgery; early (< 3 months), delayed (between three and 12–24 months) and late (later than 12–24 months).[19] Early onset and delayed onset infection are thought to occur due to direct contamination at the time of surgery, with early onset being caused by more virulent micro-organisms, such as *S. aureus*, and delayed/later onset being caused by a more indolent species such as *S. epidermidis* or *Cutibacterium acnes*.[18,19] Late onset PJI is frequently due to haematogenous spread from a distant source of infection, usually the skin, respiratory, dental or urinary infections, although it can be caused by direct contamination at the time of surgery by an extremely indolent micro-organism.[18,19] More recently, a new temporal classification dichotomizes infections into two groups: early infection, being less than one month from surgery or as a result of acute haematogenous spread, with symptoms for less than three weeks; and chronic infections which have been symptomatic for more than three weeks.[20] Cases of early infection and acute haematogenous spread have been shown to be amenable to debridement and implant retention, as opposed to the gold standard treatment of two-stage revision, and give acceptable rates of PJI clearance and likely correlate with a less established PJI more amenable to antibiotic therapies.[20,21]

Biofilms

Once bacteria have gained access to the surgical site they can exist in suspension, biofilm or invasive (intracellular) forms.[22] Suspended, single-cell bacteria are the most easily identified and can be cleared by the immune system and antibiotics. Biofilms are three-dimensional colonies of bacteria which are often associated with prosthetic material as abiotic surfaces offer a ready interface for biofilm attachment and maturation, and as such play a crucial role in PJI.[22] Biofilms are not only formed on the prosthesis but, in the context of PJI, can be found on bone cement, the bone itself, and fibrous tissue; detached clumps can be found in the synovial fluid.[23,24] Intracellular bacteria, only recently identified in the context of PJI, are able to enter, survive and even proliferate within host cells, typically within 'non-professional phagocytes' such as endothelial and osteoblast cells, hiding from the immune system and antibiotics.[18,25] The similarity of the bacterial phenotypes in both biofilm bacteria and invasive intracellular bacteria, such as *S. aureus'* small-colony variants, suggests that the intracellular pathogens may arise from the biofilm.[22,25] Ultimately, in order to eliminate the infection, the bacteria within the joint fluid, on the implant surface or sub-surface tissue must be fully eradicated; if insufficient washout, debridement or explantation occurs there is every likelihood of bacterial repopulation.[22]

The importance of the biofilm cannot be understated and its presence helps to explain the difficulty of treating PJI.[18] The bacterial biofilm is a structured aggregation of microbial cells encased in a self-produced extracellular slime, known as the extracellular polymeric substance (EPS), which shields the microbes from the host's environment and antibiotics. It colonizes the implants and from there propagates further infection.[26] There is growing evidence that in nature 99% of bacteria reside in biofilms, and staphylococcal species (specifically *S. aureus* and *S. epidermidis*) are known to readily form biofilms.[22] Three-quarters of all biofilm-related infections on medical devices are formed by *S. aureus, S. epidermidis* or *Pseudomonas aeruginosa*.[22]

The establishment of a bacterial biofilm on an implant surface occurs in stages; there is an initial adhesion of the free-floating bacteria in suspension to the abiotic implant surface (or onto the biotic protein layer that forms on the implant surface almost instantaneously when implanted), followed by cell aggregation, biofilm maturation, and the final stage, of cellular detachment, which can occur allowing cells and biofilm fragments to shed and attach at distant sites to cause further infection.[18,26] The free-floating bacteria, which include individual cells or small cellular aggregates, usually originate from biofilms on the skin or other contaminated surfaces and display a similar phenotype to bacteria found in biofilms. Planktonic bacteria, which are phenotypically different from biofilm bacteria, inoculate the surgical field much less commonly. The bacterial biofilm communities exhibit emergent properties; that is, properties that are different and not predictable

from study of the planktonic form but are better understood when examined in the context of the organization and architecture of the biofilm.[27]

Extracellular polymeric substance (EPS) is a self-produced matrix that encases the cells of the biofilm, binding them to the surface and each other, and composed mainly of polysaccharides, proteins, lipids and extracellular DNA.[27] The EPS not only forms a physical barrier but permits the diffusion-limited transport of chemicals, including antibiotics, into and out of the biofilm.[22] The enclosed structure within the EPS, high cell density and the proximity of constituent cells allows the biofilm bacteria to communicate through chemical ('quorum sensing') or electrical signals which can modulate gene expression within the bacterial cells allowing diversity within the biofilm and the ability to adapt to a changing environment.[27] The close proximity of cells within biofilms is also conducive to horizontal gene transfer, allowing the sharing of virulence genes as well as genes for antibiotic resistance.[22] Another consequence of the biofilm structure is that peripheral bacteria consume nutrients, leaving central bacteria lacking metabolic resource. This nutrient deprivation and other stressors cause the bacteria to enter a dormant metabolically inactive 'persister' state.[28] Both persister and small-colony variant (SCV) populations (SCVs show decreased metabolic rate giving rise to small sized colonies when cultured) can survive high concentrations of antibiotics due to their metabolic inactivity.[25]

Once established it is extremely difficult to eradicate and at times to even identify biofilm-related implant infections. The minimum biofilm eradication concentration (MBEC) is generally 100–1000 times greater than the minimum inhibitory concentration of planktonic bacteria for a given antibiotic.[29] The resistance to antibiotics is due to limited antibiotic penetration through the biofilm, antibiotic degradation in the 'inhospitable' regions of the outer biofilm, the function of the EPS to act as a 'sink' by binding and degrading antibiotics, the inherent resistance of persister cells, and the diffusion-limited transport which creates an antibiotic concentration gradient, therefore exposing a sub-population of biofilm bacteria to sub-lethal concentrations which is known to increase antibiotic tolerance.[22] Biofilms also utilize conventional resistance mechanisms to antibiotics, such as β-lactamases, upregulated expression of efflux pumps in order to remove intracellular antibiotics, and the capacity for horizontal gene transfer.[22]

The biofilm is also successful at avoiding the host immune system. Foreign abiotic material and postoperative scar tissue are relatively inaccessible to the immune system given their limited blood supply.[22] Polymorphonuclear leucocytes are unable to phagocytose biofilm bacteria due to restricted access to the bacterial cell within the EPS, and granulocytes become 'frustrated' and less effective in the PJI environment.[30] Antibodies in the adaptive immune system are much more effective against free-floating or early biofilm bacteria compared to those within the mature biofilm.[31] The impaired immune response in the presence of foreign material accounts for the 1,000,000 times smaller bacterial dose necessary for abscess formation in vivo.[32]

The identification of biofilm bacteria by conventional culture techniques is difficult, as many biofilm bacteria are in a metabolically quiescent state and as a result are difficult to culture in nutrient-rich culture media used for identification. The success of classical culturing techniques to identify biofilm bacteria can be as low as 30%.[33]

Surface modification and biofilm formation

It is clear that PJI occurs due to a complex interplay of numerous factors including bacterial load, micro-organism-specific factors, host factors, surgical technique, and the perioperative environment, but what is common to all implant related infections is the colonization of the surgical site, especially the foreign implant material. Much work has been done to better understand the interplay between the micro-organisms and the implant surface, and the aim of current research in this area is to modify the implant surface in order to minimize bacterial adhesion, inhibit biofilm formation and provide effective bactericidal action.[34]

The point of initial adhesion of the bacterial cells up to the point of irreversible binding and early biofilm formation has been identified as a potential therapeutic 'window of opportunity' to eradicate PJI before it has established a biofilm. At this point the bacteria are still susceptible to conventional antibiotics and immune attack.[35] The initial bacterial adhesion stage is mediated by a combination of host factors, microbial factors, and exposure time, but also other implant-related factors such as surface charge, hydrophobicity and topography.[36] The adhesion process can be divided into two phases: reversible and irreversible adhesion.[35] The reversible stage creates a less stable attachment and is brought about by non-specific adhesion of bacteria to the abiotic implant surface as well as interactions between specific lectins or adhesins (bacterial cell surface molecules) and proteins found on the conditioning layer which forms instantaneously on the implant surface.[18,37] The initial planktonic bacterial attachment to the abiotic implant surface is mediated by non-specific forces, including Lifshitz–van der Waals, Lewis acid-base and electrostatic forces, and depends on the implant's surface properties and those of the bacteria which can be variable depending on species, strain, and population heterogeneity.[18] In reality, the implant surface is almost instantaneously covered in extracellular matrix proteins and immune protein components on

implantation. This process is determined by the surface chemistry and wettability of the implant, and the newly formed protein conditioning layer acts as a plentiful source of bacterial adhesive ligands.[18,38] Therefore the main mechanism for bacterial adhesion to implants is via the cell surface molecules which facilitate site-specific surface binding; typically in the case of *S. aureus* and *S. epidermidis* the targets are collagen and fibronectin.[18] The irreversible adhesion phase is mediated by molecular and cellular interactions associated with expression of biofilm-specific gene clusters in the reversibly attached bacteria. This leads to a phenotypic change in the bacteria and ultimately early biofilm formation.[39]

The surface properties of orthopaedic implant materials have been investigated to determine the surface factors that promote or inhibit bacterial adhesion and, despite limitations, it does appear that generally the more inert a surface, the less likely it is to directly adhere bacteria or host conditioning proteins which then in turn adhere bacteria.[38,40] Surface factors investigated include chemical structure, surface roughness, hydrophilicity, Z potential and surface free energy, and they have all been identified as having an influence on bacterial adherence and early biofilm formation.[37] Given the multitude of variables it is extremely unlikely that any one combination of surface properties would universally deter all bacteria under all conditions; however, it does appear in general that rougher surfaces promote biofilm formation. This phenomenon is likely to be due to the increased surface area for bacteria or host protein adhesion and that micro pores are easily inhabited by bacteria but not larger leucocytes.[18,38] The converse also appears true, that smoothness down to the nanometre level is associated in vitro with the lowest adhesion of both Gram-positive and Gram-negative bacteria.[38] Other materials that appear to deter bacterial adhesion exhibit hydrophilic, highly hydrated and non-charged surfaces, although in nature anti-adhesion surfaces can be super-hydrophobic.[35]

All commonly used orthopaedic materials are susceptible to colonization by biofilm-forming bacteria including cobalt-chromium, titanium, polyethylene, polymethyl methacrylate (PMMA) and ceramics.[26,41] In vitro studies have shown ceramics to have advantageous physical-chemical surface properties to discourage biofilm formation when compared to other implant materials demonstrating reduced bacterial adhesion and slower biofilm development.[42] Clinically there has been evidence of an anti-infective effect of ceramic bearings compared to polyethylene; in an infected total hip arthroplasty retrieval study higher bacterial counts were observed on polyethylene liners compared with ceramic liners.[43,44] The protective benefit of ceramic bearings against PJI has also been demonstrated in large cohort studies, most notably in a recent well powered and controlled assessment of the UK National Joint Registry, which demonstrated a protective benefit of ceramic bearings against PJI after two years.[16,45] This delayed effect may suggest that the advantageous surface properties may confer only part of the protection against PJI; the tendency for bioceramics to undergo little surface degradation, compared to metals and polymers, may be a factor as they maintain their surface smoothness into the medium to long term.[42]

Given the propensity of traditional orthopaedic materials to become colonized with bacterial biofilms, an area of active research is antimicrobial surface implant coatings which could potentially minimize or prevent bacterial adhesion, inhibit biofilm formation and have a bactericidal effect.[35] The ideal antimicrobial surface coating would be biocompatible with the host, have strong evidence of anti-infective efficiency (tested both in vitro and in vivo in an appropriate model for PJI), would not compromise the fixation of the implant (either in the cement mantle or the osseointegration), would demonstrate durability of the anti-infective effect and be mechanically stable to withstand the forces applied in both the intraoperative placement an postoperative period.[35]

There are a plethora of potential antibacterial coatings and surface modifications which have been investigated or hypothesized for orthopaedic implants. In order to improve understanding and permit comparison the different technologies have been classified into modalities: passive surface finishing/modification; active surface finishing/modification and local carriers and coatings.[34]

Passive surface finishing/modification (PSM)

These surfaces do not release bactericidal agents to the surrounding tissues, but are aimed at preventing or reducing bacterial adhesion through surface chemistry and/or surface structure modification.[34] As described, surface characteristics play a crucial role in bacterial adhesion and subsequent biofilm formation; at present the majority of research on PSM has occurred in the in vitro setting and not yet translated into the clinical setting.[34] One example is the ultraviolet irradiation of titanium dioxide which increases its wettability, decreasing bacterial adhesion without affecting osseointegration.[46] The application of polymer coatings, including hydrophilic polymethacrylic acid, polyethylene oxide, or protein-resistant polyethylene glycol, to the surface of titanium implants results in significant inhibition of bacterial adhesion.[34] Hydrophobic and super-hydrophobic surface treatment technologies have also shown to have an antibacterial adhesion effect.[47] Pure titanium coated with cross-linked albumin reduced bacterial adherence in a rabbit model.[48] Another approach, gleaned from the study of antimicrobial surfaces in nature, is to modify the implant surfaces at the nano scale to decrease bacterial adherence or to mechanically lyse microbial cells on surface contact.[49] Nanopatterning of

the implant surface, typically titanium or titanium alloy, which is created by modifying surface finishing techniques, for example using hydrothermal treatment, to create nanopores of different sizes or the fabrication of nanotube arrays or nanowires, has demonstrated efficacy in vitro at deterring biofilm formation.[49–53] The most recent strategy is to create complex self-assembled mono- or multilayers which also have excellent anti-adhesive properties.[34] One concern of anti-adhesive coatings is that they may impair osteoblast function and osseointegration leading to early mechanical failure. However, the inclusion of bioactive molecules such as arginine–glycine–aspartic acid (RGD) peptides and sericin could restore or even improve this, and nanopatterned materials have been shown to promote the organization and proliferation of fibroblasts and osteoblasts at their surface.[34,49,50,52] New 'race to the surface' models have been introduced to ascertain in vitro the interplay between osseointegration and bacterial colonization.[54]

Active surface finishing/modification (ASM)

Active surface finishing/modification are coatings that feature pharmacologically active pre-incorporated bactericidal agents, such as antibiotics, antiseptics, metal ions, or organic molecules. They may be either contact killing or drug eluting and can be degradable or non-degradable.[34] The bactericidal function can be achieved by interfering with cell respiration or division, cell wall formation or the bacterial signalling network as well as inhibition of the transition from free-floating bacteria in suspension to bacterial aggregates in the biofilm.[34]

Silver coating is the most commonly used metal coating and functions as dissolved silver cations are biochemically active; they interfere with bacterial cell membrane permeability, bacterial cell metabolism and are responsible for the formation of reactive oxygen species.[34] Much research has centred on finding a balance between efficacy and toxicity of silver; however, silver coatings have demonstrated efficacy and safety in clinical studies in the use of megaprostheses (which represent a useful model given their high overall rate of infection).[55,56] Other metals and non-metallic elements, such as hydrogen, chlorine and iodine, have been investigated in vitro. Selenium, bound covalently onto the surface of titanium alloys, has demonstrated efficacy in reducing adhesion of staphylococci but not of osteoblasts.[57] Iodine-coated titanium megaprostheses have demonstrated clinical efficacy in a clinical series with excellent results.[58]

Another technique is the use of antibiotic-hydroxyapatite coatings, but concerns exist over the clinical effectiveness of surface-bound antibiotics, including their effectiveness against only specific sensitive bacteria, the potential for resistance and their limited ability to only interact with bacteria directly adjacent to the implant.[34] However, in the trauma setting positive results have been reported with the use of antibiotic-loaded D-poly-lactate acid/gentamycin-coated intramedullary nails.[59]

Local carriers or coatings (LCC)

Local carriers or coatings, which may be biodegradable or not, are applied at the time of the surgical procedure or immediately prior, and can be applied to the implant itself and or the peri-implant environment.[34] A key benefit is that they can be used in conjunction with a conventional implant. Antibiotic-eluting PMMA bone cement has been long established in orthopaedic practice.[60] Clinical studies have demonstrated that antibiotic-loaded PMMA can decrease the rate of PJI and the revision rate for supposed 'aseptic' loosening when combined with systemic antibiotic administration at the time of implantation.[61] However, PMMA was not specifically designed for this task; antibiotic elution may not reach the MBEC and sub-therapeutic doses may even be responsible for the creation of antibiotic resistant/tolerant bacterial variants.[34] A biodegradable alternative to antibiotic loaded PMMA is the use of biocompatible hydrogels which have been designed with desired drug elution properties (high short-term postoperative antibiotic concentrations when the implant is most likely to become infected) and can be loaded with antibiotics intraoperatively.[62] Defensive antibacterial coating (DAC), composed of covalently linked hyaluronan and poly-D,L-lactide, undergoes complete hydrolytic degeneration within 72 hours, which releases its pre-loaded antibiotics, has shown efficacy and safety in a multicentre randomized controlled trial for the plate osteosynthesis of closed fractures following trauma.[63] Most recently, a small sized clinical study assessed the benefits of DAC antibacterial hydrogel coating on cementless implants at second stage (conversion from antibiotic-loaded spacer) revision for prosthetic hip infection and observed a trend towards better infection control (with no recurrence of infection in the treated group despite a 14.8% recurrence in the control group [$p = 0.11$]) and a reduction of average hospital stay.[64]

Conclusions

The microbial pathology of PJI is becoming better understood and the role of the bacterial biofilm is central in understanding the recurrence and recalcitrance of this condition. The adhesion of bacteria to the implant surface and establishment of the early biofilm has been identified as a therapeutic target to halt PJI before it has had a chance to become established. While much basic science research has been undertaken on implant surface technology and bacterial adhesion, we await validation in clinical studies. These technologies have the potential to lead to novel clinical treatments and better outcomes for patients with PJI.

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