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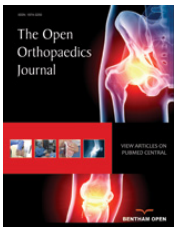

REVIEW ARTICLE

Biofilm and the Role of Antibiotics in the Treatment of Periprosthetic Hip and Knee Joint Infections

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Abstract: An increasing demand for lower limb arthroplasty will lead to a proportionate increase in the need for revision surgery. A notable proportion of revision surgery is secondary to periprosthetic joint infections (PJI). Diagnosing and eradicating PJI can form a very difficult challenge. An important cause of PJI is the formation of a bacterial biofilm on the implant surface. Our review article seeks to describe biofilms; their definitions and formation, common causative bacteria, prophylactic and therapeutic antibiotic therapy.

Keywords: Antibiotics, Biofilm, Periprosthetic joint infection, Total hip arthroplasty, Total knee arthroplasty.

INTRODUCTION

With an increasingly ageing population and rising levels of obesity, an increase in the number of lower limb primary and revision arthroplasties can be anticipated [1]. Prosthetic Joint Infection (PJI) is a common indication for hip and knee revision surgery, constituting 15% of all revision hip and 25% of all revision knee procedures [2]. PJIs are distressing to the patient, who may undergo multiple surgeries with prolonged hospital stay and suffer the side effects of long term antibiotic treatment. Furthermore, patients report a poorer quality of life and levels of function in comparison to those who undergo uncomplicated primary procedures [3]. PJI management has significant financial implications with an estimated cost of €32,000 per patient for revision surgery; approximately 3.6 times greater than that of the primary surgery [4]. PJIs are therefore greatly feared amongst patients and the operating surgeons.

In Sir John Charnley's *era*, an incidence of 9.5% of PJI was observed in the United Kingdom (UK). This has now decreased to 2% in primary total knee arthroplasty (TKA) and 0.45-0.57% in primary total hip arthroplasty (THA) [5]. The incidence of PJI after revision arthroplasty is far higher [6]. Risk factors for PJI can be classified as patient or surgery related. Poultsides *et al*. [7] reported that independent risk factors for surgical site infection (SSI) related to the patient included male sex, ethnicity, age<44, liver disease, excess alcohol intake, coagulopathy, chronic lung disease and complicated diabetes. From a surgical viewpoint, a careful analysis of perioperative methods led to the implementation of various measures to improve infection control. This included the introduction of laminar air flow and prophylactic antibiotics, minimizing the number of staff present intraoperatively and limiting unnecessary entry and exit into the operating room and improving surgical times [8, 9].

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PJI management is challenging for a number of reasons. Until recently, there has been no consensus as to what constituted a PJI and this in turn hindered correct diagnosis and further treatment. The confusion is further complicated by the fact that no single investigation accurately confirms a PJI. The recent Musculoskeletal Infection Society classification [9] has sought to rectify this. Surgical treatment is guided by confirmation of the causative organism and its characteristics which may not always be feasible. It is crucial to understand the patient's pre morbid function, prior medical history including any immunocompromised condition and expectations for further surgical treatment. PJI should be dealt with urgently as there is only a short period during which the biofilm, a product of the infecting bacteria may still be in a nascent form and thus easier to eradicate. Once established, the biofilm is difficult to eliminate and confers a number of advantages to the bacteria at the expense of the host.

The aim of this review is to discuss biofilms and their role in PJI including pathogenesis as well as the infecting bacteria and the role of prophylactic and therapeutic antibiotics.

IMPLANTS AND THE BIOFILM

The implantation of prostheses itself predisposes to infections and makes it more difficult to control already established infections. In Zimmerli's classic animal model experiment [10], a population of guinea pigs had subcutaneous, rigid and perforated polymethacralate and polytetrafluoroethylene tubes implanted. In those which had the tubes removed, no abscesses developed, whilst those in which the implants remained developed infection in 95% of the population. The same experiment also suggested a decreased ability for opsonization in the presence of the implant as well as decreased bactericidal properties of polymorphonuclear leukocytes (PMNLs). The avascular nature of the implant prevents the access of cells facilitating the immunological response to bacteria. Furthermore, the presence of the implant reduced the minimal dose of *Staph Aureus* required to form an abscess by 10,000 folds from 10^6 to 10^2. Surrounding the implant is an area described as the immuno-incompetent fibroinflammatory zone [11, 12]. Within this zone, any cellular immune responses initiated result in the formation of superoxide radicals and cytokine mediated activity causing damage to the surrounding tissues and bringing about implant loosening [12].

Biofilms play a crucial role in the pathogenesis of PJI and make its eradication difficult. They are described as a complex network of sessile bacteria organized in micro colonies, within a highly hydrated polymeric matrix [13]. The properties of sessile bacteria completely differ to that of planktonic bacteria, the free floating single celled organism. Susceptibility of the bacteria to antibiotics is reduced within the first 2 weeks of infection, owing to their sessile and slow growing nature. The bacteria receive nutritional support from the surrounding matrix which contains a glycocalyx of polysaccharides, protein and DNA. The high density of bacteria in a biofilm leads to the phenomenon of quorum sensing. Through this microorganisms can communicate with each other; regulating expression and production of virulence factors. This prevents biofilm eradication and potentially contributes to the destruction of surrounding tissues [14]. Antimicrobial agents as a result, become limited by their inability to penetrate the full thickness of the biofilm and diffuse adequately. Bacteria can be introduced intraoperatively, during implantation, or spread by hematogenous seeding. Gristina *et al*. [15] describes a "race for the surface" when both bacterial and host cells compete at the expense of one another in colonizing the implant surface. A biofilm is fully developed after four stages: adherence, accumulation, maturation and dispersal. The mechanism by which bacteria adhere to the implant is not completely understood. Bacteria contain adhesins, a cell surface component which facilitates adherence to the biomaterial. The specific group of adhesins involved in the facilitation of binding of the bacteria to the implant are called microbial surface component recognizing adhesive matrix molecules (MSCRAMMS). Each molecule is specific for different types of tissue and the adherence of the bacteria to the tissue [16]. The implant, becomes coated in serum proteins which include amongst others, fibronectin and collagen. The bacterial MSCRAMM recognizes the serum protein and binds to it accordingly. The most commonly examined MSCRAMM in *Staphylococcus Epidermidis* infections is a fibronectin binding protein called sDRG. The deletion of this protein prevents adherence of the bacteria in experiments performed both *in vitro* and *vivo* [17]. Two stages have been identified in bacterial adherence to an implant surface. The first which is reversible is known as the physico-chemical stage. Through this stage the bacteria is brought into contact with the implant surface via van der Waals forces, electrostatic attraction and gravitational forces. The second stage which is known as the molecular-cellular stage occurs when the bacteria attach irreversibly to the surface. These stages create a satisfactory environment for the production of biofilm. The subsequent deposition of the extracellular polysaccharide matrix provides nutrition to the bacteria whilst protecting them from the immunological response. The second stage varies according to the causative bacteria. For example, *Staphylococcus Aureus* binds to host proteins such as fibronectin, whereas *Staphylococcus Epidermidis* is more dependent on the type of prosthetic material [10, 14]. The most widely studied MSCRAMM with a critical role is polysaccharide intercellular adhesin (PIA). PIA is responsible

for the pathogenesis of the extracellular matrix which prevents successful antimicrobial action and promotes bacterium-bacterium adhesion [16]. It also inhibits neutrophil dependent bactericides and plays an important role in the architecture of the mature biofilm [17]. The mechanism by which biofilms modulate the actions of the innate immune system cells remains unknown. Scherr *et al*. [18, 19] reported that examination of the transcriptome, revealed a down regulation of 550 staphylococcal genes within an hour, upon exposure to macrophages. Interestingly, there was no phagocytic activity of the macrophages at the time of down-regulation whereas after 24 hours when the macrophages had died, the suppression of transcriptional activity ceased. This finding suggests an attempt by biofilms to conceal themselves from the host immune response. Biofilm response to neutrophils differs markedly. There is no reduction in the transcriptome analysis upon exposure to neutrophils which tend to invade the biofilm in greater numbers and display signs of phagocytosis whilst remaining viable [18, 19]. In spite of this, there is no reduction in bacterial burden observed *in vitro* or *in vivo* studies.

The actions of both neutrophils and macrophages broadly overlap. Macrophages portray phagocytic activity like neutrophils, yet in addition play an important role in adaptive immunity. They play a crucial role in cell signaling; alerting T cells to the presence of bacteria and propagating the adaptive immune response. It is not clear why the transcriptional action of *Staphylococcus Aureus* behaves differently with different phagocytic cell types, but it has been suggested that *Staphylococcus Aureus* can "hide" intracellularly in neutrophils.

As the biofilm increases in size, planktonic bacteria are released, subsequently forming secondary colonies [14].

MICROBIOLOGY

The most common organisms implicated in PJIs are Gram positives including *Staphylococcus Aureus* and coagulase negative *Staphylococci* (CNS) which cause 50-60% of all infections and are well known to form biofilms [16, 20].

Staphylococcus Aureus

This is a commensal organism, found most commonly within the nares and the skin flora. It is more virulent than CNS, with the ability to synthesize toxins and virulence factors and causes a variety of infections including endocarditis, osteomyelitis and PJIs and toxic shock syndrome. An overall 30% of the population is colonized with either methicillin sensitive or methicillin resistant strains and this has been reported as an independent risk factor for development of SSIs [21, 22]. *Staphylococcus Aureus* carriage has been classified into 3 groups: intermittent carriers with changing strains (60%), carriers of a single persistent strain (20%) and non-carriers (20%) [23]. An increase in *Staphylococcus Aureus* colonization is noted in insulin dependent diabetics, intravenous drug users and patients on dialysis. This is thought to be due to the regular skin punctures, which is further supported by the high colonization rates observed in otherwise medically well patients who administer allergy injections [21]. This high rate is also noted in patients with human immunodeficiency virus but the exact pathogenesis remains unknown [21].

Methicillin Resistant *Staphylococcus Aureus* (MRSA)

Originally reported in 1961 in the UK, MRSA was believed to be a nosocomial infection related to misuse of antibiotics which was confined to immunocompromised inpatients and patients with indwelling devices [24]. The methicillin resistant status of MRSA is conferred by the presence of a penicillin binding protein called PBP2A, coded for by the mecA gene on the staphylococcal chromosomal cassette [24]. This protein renders all beta lactam antibiotics inactive including flucloxacillin, co amoxiclav and piperacillin tazobactam. Other groups affected include cephalosporins (notably cefuroxime) and carbapenems (meropenem). More recently a community acquired strain of MRSA which is not related to hospital admissions, known as c-MRSA has been discovered. Analysis reveals a different genotype to hospital acquired MRSA. C-MRSA predominantly affects younger and healthier patients [25].

As with other staphylococci, both coagulase negative and positive, MRSA is a hardy organism; allowing it to survive outside of the human host. This stems from its ability to resist desiccation, changes in temperature, humidity and exposure to sunlight [26]. MRSA when mixed with dust for example is still viable up to a year after inoculation, allowing for an increased likelihood of the bacteria being transferred to a new host [26]. However, the main route of transmission for MRSA is by direct skin contact with colonized or infected patients, healthcare workers or by oro-nasal droplet spray. In an effort to prevent transmission, NICE has recommended frequent hand washing and emphasized this through several high profile awareness campaigns within the UK National Health Service [27]. With MRSA colonizing 5.3% of all patients admitted for elective orthopaedic surgery, efforts to address its transmission have also involved prophylaxis. Since April 2009, the Department of Health in the UK has screened all elective surgical admissions

attending general practitioners surgery and pre-operative assessment clinics for MRSA taking swabs from the nares, throat, groin and axilla. MRSA positive patients are treated with topical mupirocin 2%, administered nasally for five days and daily baths with 4% chlorhexidine. A 0.2% chlorhexidine mouth wash is also prescribed if the pharyngeal swab grows MRSA.

Murphy *et al*. [28] evaluated the relationship between MRSA colonization, after successful eradication, and subsequent SSI in patients admitted for elective lower limb arthroplasty. The study demonstrated that the overall rate of MRSA SSIs, in those with negative MRSA screens on admission, was 1.1% in THA and 0.4% in TKA. It was suggested that those with a positive MRSA screen have a significant risk of subsequent SSI, with MRSA being the most likely causative organism. The study raises important questions regarding antibiotic prophylaxis in those with a positive screen for MRSA. Given that implant surgery is high risk, conventional antibiotic regimens cannot be used and hence Murphy *et al*. altered their practice, adding teicoplanin to the usual cefuroxime regimen [28].

Staphylococcus Epidermidis

Staphylococcus Epidermidis is a coagulase negative bacterium known for its ability to mediate infection on indwelling devices. It is an opportunistic organism, previously thought to be harmless, and frequently found as a commensal on the skin and mucous membranes.

Its presence is suspected to prevent the attachment of more virulent organisms such as *Staphylococcus Aureus*. It is well known for its ability to form a biofilm. However, the exact pathogenesis is unknown but the most plausible hypothesis is that it has developed mechanisms to nullify the innate host response.

Other common pathogens include *Streptococcus* and *Gram Negative Bacilli* (GNB). Peel *et al*. [29] reported that GNB and enterococcal species are more likely to occur in polymicrobial PJIs. Biofilms are most commonly formed by staphylococci and streptococci, but the ability to form them has also been observed with *Pseudomonas Aeruginosa*, a bacterium colonizing most cystic fibrosis patients.

ANTIBIOTIC THERAPY

Prophylaxis

Prophylactic antibiotics are defined as those given before, during or after surgery to prevent infection. Current UK practice suggests that prophylactic antimicrobial agents should cover expected pathogens, take into account local resistance patterns and have a narrow spectrum whilst considering cost [30].

Historically prophylactic antibiotics have erroneously been suggested to cause a two fold increase in infective complications and thus were not initially used. However this was based on flawed research which was later discredited with Fogelberg *et al*. [31] demonstrating a fourfold reduction of infections in patients given perioperative penicillin, compared to a control group receiving no antibiotics. Meehan *et al*. [32] investigated the optimal time for prophylactic antibiotic administration in an animal model and reported that bactericidal action was most favorable when antibiotics were present within tissues prior to surgery.

Current guidance obtained from consensus between the Centre for Disease Control (CDC) and the American Association of Orthopaedic Surgeons (AAOS) recommends administration of prophylactic antibiotics an hour prior to incision and continuing antibiotics for 24 hours postoperatively [33]. Cephalosporins including cefuroxime and cefazolin are the most commonly prescribed prophylactic antibiotics as per AAOS recommendation due to broad spectrum coverage against penicillinase producing methicillin susceptible Gram positive staphylococci and streptococci. Alternatives for allergic patients include clindamycin and vancomycin [34]. Cefazolin, a first generation cephalosporin, also covers some Gram negatives such as *Proteus mirabilis, Escherichia Coli* and *Klebsiella* whereas cefuroxime, a second generation cephalosporin also covers *Haemophilus influenzae*, *Enterobacter* and *Neisseriae*. There are numerous benefits to using cephalosporins as they cover most organisms encountered in orthopaedic surgery. Furthermore, they have a proven evidence base, good safety profile and are inexpensive. The UK has recently however seen a trend away from using cephalosporins [35]. In 2011, Aujla *et al*. sent a questionnaire to 195 acute care trusts in the UK enquiring about antibiotic prophylaxis in elective and trauma patients and reasons if new regimes were adopted [35]. The most popular regimes used were cefuroxime alone, flucloxacillin and gentamicin, and co-amoxiclav. The reasons for adopting new regimes included the fear of Clostridium difficile infection secondary to cephalosporin use, the desire to reduce dependence on cephalosporins and local microbiology advice. Interestingly, Jenkins *et al*. [36]

reported only 1.7 episodes of Clostridium Difficile infection in 1000 cases of primary elective arthroplasties associated with using cefuroxime and a recent meta-analysis [37] did not show any clinical difference between using cephalosporins and flucloxacillin *versus* cephalosporins and teicoplanin. The study recommended that local availability and cost should determine antibiotic choice.

Treatment of PJIs

High quality prospective randomized trials dictating best antibiotic therapy for PJIs and duration of treatment is currently lacking. Thus antibiotics utilized are those which have been historically used and based on clinical experience. The Infectious Diseases Society of America (IDSA), cognisant of the problem, addressed this by provision of a consensus statement, using best available evidence [9]. Accordingly, the choice of an antibiotic should be based on the bactericidal effects of the antibiotic whilst providing excellent bone and soft tissue penetration. The bactericidal effects should target surface adhering, slow growing and biofilm producing sessile bacteria as well as planktonic forms. Furthermore, the antibiotic should be well tolerated by the patient whilst adhering to local antibiotic policy and considering cost. Antibiotic therapy was conventionally delivered intravenously to attain minimum inhibitory concentration. However, upon demonstration of clinical improvement, they can be switched to an appropriate oral equivalent closely monitoring clinical progress [9, 38, 39]. Biofilm eradication has been further complicated by emergence of resistant strains and therefore, newer antimicrobial agents have been devised and in turn resistant organisms have been reported. Some of the antibiotics with direct effect on biofilm formation are discussed in the following section.

Rifampin

Originally a cornerstone of anti tuberculosis therapy, rifampin manifested itself as an important agent in treating biofilm related infections. Zimmerli *et al*. [40] established the role of rifampin against staphylococcal infections in a randomized controlled trial examining rifampin effects in treatment of acute PJIs with a retained implant. Rifampin has high bioavailability (>95%) and action against organisms discovered within leukocytes and osteoblasts. Its action against slow growing bacteria has led the Société de Pathologie Infectieuse de Langue Française **(**SPLIF) to recommend it as a first line agent in PJIs [41]. It is worth noting though that there is a high risk of resistance when using rifampin alone and thus combination therapy is recommended. The most potent combination includes rifampin-fluoroquinolone which has demonstrated excellent clinical outcomes [40, 41].

Vancomycin

Vancomycin is a glycopeptide antibiotic used for prophylaxis and treatment of PJIs in penicillin allergic patients. Additionally, the AAOS recommends it for treatment of MRSA colonized patients and MRSA outbreaks. Recent evidence suggests that vancomycin may play a role in the prophylaxis and treatment of MRSA related PJIs after primary and revision arthroplasty surgery [42, 43]. It is disadvantaged however by its predominant intravenous use, the risk of red man syndrome and ototoxicity requiring therapeutic drug monitoring. Additionally resistance to vancomycin has been increasingly reported [42, 43].

Newer Antibiotics

Linezolid and daptomycin have emerged as alternatives to vancomycin and more conventional antimicrobials. Linezolid, a synthetic antimicrobial from the group of oxazolidinones has multiple advantages including high oral bioavailability and lack of cross resistance. It is effective against *Staphylococci*, *Enterococci* and multi resistant organisms such as MRSA and Methicillin resistant Staphylococcus Epidermidis (MRSE) [44, 45]. However, more recently there have been some reports on linezolid resistance as well [45].

Antibiotics have been utilized in treatment of various types of PJIs. For example, when a patient is medically unfit to undergo revision arthroplasty or is unwilling to undergo further surgery then antibiotics may be administered for long term suppression [39]. This is far from the gold standard of treatment but does have benefits such as avoiding the need for staged surgery and reduced costs. However, this strategy has specific indications including an organism which is susceptible to long term oral antibiotic suppression therapy and a prosthesis which is well fixed and functioning [46]. Table **1** includes some of the common antibiotics used for chronic suppressive therapy as suggested by the IDSA [47].

Table 1. Infectious Diseases Society of America (IDSA) guidelines on common antimicrobials used for chronic oral antimicrobial suppression therapy.

	Preferred Treatment	Alternative Treatment
MSSA	Cephalexin OR Cephadroxil	Dicloxacillin Clindamycin Amoxicillin-clavulanate
MRSA	Co-trimoxazole Doxycycline	N/A
Beta Hemolytic Streptococcus	Penicillin V OR Amoxicillin	Cephalexin
Enterococcus	Penicillin V OR Amoxicillin	N/A
Pseudomonas	Ciprofloxacin	N/A

MSSA: Methicillin Susceptible *Staphylococcus Aureus*, MRSA: Methicillin Resistant *Staphylococcus Aureus*

For single or two stage revision procedures, antibiotic treatment remains essential perioperatively to ensure that infection has been adequately controlled. Intravenous administration of antibiotics for 4-6 weeks is the rule. However, conversion to oral alternatives at around 2 weeks may be an option as long as clinical and serological markers have improved and after consultation with the local microbiology department [34]. The use of antibiotic laden bone cement (ALBC) has also been popularized in conjunction with intravenous antibiotics for prophylaxis and treatment of PJIs with the potential benefits of delivering a much greater local concentration of antibiotics than achieved with systemic therapy alone. In fact, Stockley *et al*. [48] reported a short period of systemic antibiotic treatment when ALBC was utilized in two stage revision surgery. The most commonly used antibiotics in ALBC include a combination of vancomycin with either tobramycin or gentamicin [49]. This provides a broad spectrum of coverage for organisms commonly encountered with PJIs whilst reducing the development of resistant strains [50]. When used in temporary spacers, antibiotic dosages up to 20 g per 40 g of bone cement can be achieved without reported systemic side effects. However, if used for prophylaxis in a single stage revision or during reimplantation at the second stage revision, the maximum dose recommended is usually 1 or 2 g per 40 g of bone cement to avoid mechanical weakening [51].

Table 2. IDSA Guidelines on antibiotic treatment for different types of PJIs.

	Staphylococcal PJI	PJI Due To Other Organism
Debridement and Retention of Prosthesis AND One Stage Revision	2-6 weeks of pathogen specific IV antibiotic in combination with rifampin 300-450mg orally twice daily Followed by 3-6 months rifampin + companion drug (3 months for a THA infection and 6 months for a TKA infection) Companion agents can include ciprofloxacin/levofloxacin Alternatives include co-trimoxazole/ doxycycline/1st gen cephalosporin in case of allergy If unable to use rifampicin, 4-6 weeks of pathogen specific IV antibiotics	4-6 weeks of pathogen specific IV or highly bioavailable oral antibiotics
Resection Arthroplasty with or without Second Stage Reimplantation	4-6 weeks of pathogen specific IV or highly bioavailable oral antibiotics	

IV: intravenous, THA: total hip arthroplasty, TKA: total knee arthroplasty

In acute infections, the timing of intervention is critical in order to prevent biofilm formation. However, there remains a lot of variables including timing from onset of symptoms, timing since the primary surgery, type of prosthesis, bacteria involved, debridement technique and irrigation fluid utilized which affect infection control and hence it is difficult to formulate a single treatment strategy which will fit all cases. However, the literature suggests that the earlier an infection is diagnosed and treated with aggressive debridement with exchange of modular parts in a well fixed implant in combination with appropriate antibiotic treatment, the better the chances of infection control [52 - 64]. It is also worth noting that biofilms may rapidly reform within 24 hours following debridement and therefore a patient may benefit from more than a single debridement alongside antibiotic therapy. However there will always be some surfaces to an in situ prosthesis which debridement techniques will not reach. On the other hand, recent research has suggested that multiple debridements may have a negative impact on the success of a subsequent two stage revision procedure if those debridements are to fail [65]. A rationale for antibiotic treatment post surgery according to IDSA

guidelines is summarized in Table **2**.

CONCLUSION

As demand for total joint arthroplasty increases, so will a corresponding increase in the incidence of PJI. Infections are difficult to diagnose and once diagnosed, difficult to eradicate. This is reflected in the significant financial burden placed on healthcare systems, and considerable emotional toils inflicted on our patients.

One of the principle causes of these issues is biofilm, a network of sessile bacteria enclosed in a polymeric matrix. Aided by the implants inherent lack of immunological surveillance and defense, biofilms evade both innate immunological defenses and iatrogenic antibiotics causing problems ranging from local pain and prosthesis loosening to systemic sepsis.

Orthopaedic surgeons have addressed the considerable challenge by increased vigilance with regards to perioperative techniques ensued. This is reflected by developments in operating room environment, pre-operative screening, pre-operative planning and the administration of antibiotics. Furthermore, upon diagnosis of PJI orthopaedic surgeons have sought consensus locally in multi-disciplinary team meetings with microbiology and infectious diseases colleagues, nationally in the formulation of guidelines and internationally, to understand best management including the role of antibiotics. However many questions remain unanswered with regards to diagnosis and accurate timely treatment of biofilms and PJI.

CONFLICT OF INTEREST

Each author certifies that he or she, or a member of his or her immediate family, has no commercial interest that might pose a conflict of interest in connection with this work.

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