The management of periprosthetic infections in the future
A REVIEW OF NEW FORMS OF TREATMENT

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The number of arthroplasties being undertaken is expected to grow year on year, and periprosthetic joint infections will be an increasing socioeconomic burden. The challenge to prevent and eradicate these infections has resulted in the emergence of several new strategies, which are discussed in this review.

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Despite many initiatives to reduce it over the years, the rate of periprosthetic joint infection (PJJ) remains at 1% to 2%.1

The most common pathogen is Staphylococcus aureus (S. aureus),2-4 which adheres to the prosthesis, duplicates and colonises the surface and becomes resistant to antibiotics, resulting in persistent and recurrent infections (Fig. 1).5,6 The key to this resilience is the formation of a protective membrane. The biofilm is composed of a matrix of polypeptides, polysaccharides and nucleic acids, forming a microenvironment enabling the bacteria to flourish and become inaccessible both to the patient’s immune system and to systemic antibiotics.7-9

In this review of the literature, we discuss current and emerging treatment strategies in order to reduce further the incidence of PJJ and report on novel and futuristic approaches to disrupt or inhibit biofilm formation.

Patients and Methods

We reviewed all papers with a full text or an abstract in English, published from 1970 to June 2014 using international databases such as PubMed/Medline, EMBASE and other non-indexed citations including Google Scholar. Keywords either alone or in various combinations were used to search for appropriate papers (Table I). Following the initial search, if a topic was identified that was deemed appropriate for inclusion, the review was expanded to include this.

Results

Theatre modifications. The internal environment of the operating room and its associated airborne bacterial count is extremely important. Surgical personnel are a major source of air contamination,10,11 and the presence of five people increases the bacterial count by 34 times12 due to their shedding pathogens from their skin, respiratory particles, hair and clothing.13

In the early 1980s, laminar airflow was introduced to reduce airborne contamination. This initially showed a significant reduction in PJJ.14,15 However, recent studies have revealed inconsistencies and that laminar flow has no clear benefit, and also there is a potential risk of increased PJJ.16-18

An alternative approach is the use of ultraviolet light, which disrupts bacterial DNA, preventing replication and contamination.19 During primary arthroplasty, one study demonstrated a rate of infection of 1.77% with laminar airflow, but only 0.57% with ultraviolet light (p < 0.001).20 Ultraviolet light can also eliminate bacterial contamination on solid surfaces. However, its use is not currently recommended due to the potential harm it may cause theatre staff, who are at an increased risk of eye damage and skin cancer if exposed,21-24 however, there may be other applications such as sterilising the operating room between patients or overnight,25 as the handles, lights, keyboards, floors and walls are additional sources of pathogens.26-29

Operative modifications. Prophylactic systemic antibiotics and antibiotic-impregnated cement have been shown to reduce rates of infection.30-32 The use of other adjuncts, such as pulsatile lavage33-35 and antibiotic-impregnated plastic adhesive drapes36-38 have had mixed reviews.

Modification of prostheses. The structure of the prosthesis varies between manufacturers, especially the composition of the surface, the texture and hydrophobicity.39-41 It is necessary for osseointegration to occur at the same time as reducing foreign body reactions and bacterial adhesion.42,43 Many novel strategies have
focused upon modifying the composition of the prosthesis in particular the use of metal ions (or nanoparticles).

The broad-spectrum antibacterial properties of silver are effective against many organisms, and are used in dressings and creams for chronic wounds and ulcers, vascular and bladder catheters and endotracheal tubes.

Silver ions bind to bacterial DNA and to sulphydryl groups in amino acids, resulting in the disruption of enzymes that control respiration and other critical cell functions. Silver ions are rapidly bactericidal to S. aureus in susceptibility-testing media to levels equivalent to high doses of tetracycline and vancomycin, but they cannot eradicate the biofilm (Fig. 2).

Silver encourages the release of iron from iron-sulphur clusters and the formation of hydroxyl radicals, when tested against Staphylococcus (S.) epidermidis, which is lethal to this bacteria. Silver has been applied to the prosthesis in a number of ways, including the incorporation of silver with ceramics, silver coating, or incorporating silver ions within the surface of the prosthesis (Fig. 2).

A custom-made implant with silver augmentation has been developed by Stanmore Implants Worldwide Limited (Elstree, United Kingdom). Mid-term results of 85 oncology patients with these implants showed lower rates of early PJI following a two-stage exchange arthroplasty using the silver implant (p = 0.03), but not following a single-stage or primary arthroplasty.

Patients exposed to higher levels of silver may develop local skin pigmentation due to exposure to silver (argyria), which may occur after two years. However, patients with local argyria did not develop neurological symptoms, renal or hepatic failure and had similar levels of silver in the blood and aspiration fluids to patients that did not develop argyria. In addition, resistance has been shown to develop in vitro following repeated exposure by Escherichia (E.) coli.

Other ions such as iron, zinc, titanium, and carbon can reduce microbial adhesion, proliferation and biofilm growth. They can also enhance the function of keratinocytes and osteoblasts.

Antibiotic prosthetic coatings. Hickok hypothesised that the role of antibiotic-bonded prostheses was in preventing bacterial adhesion to the prosthesis, thus reducing the biofilm formation and preventing its ability to harbour bacteria. Vancomycin has been used due to its action against gram-positive bacteria inhibiting the synthesis of structural proteins of the bacteria cell wall. Other antibiotics have been studied, such as gentamicin, ceftriaxone, kanamycin, tetracycline, doxycycline, levofloxacin and novel porphyrin antibacterial drugs, XF-70 and XF-73.

One method of emitting the antibiotics is through a ‘controlled-release system’ that enables it to be released over a period of several days to weeks. These systems are based upon biodegradable or non-biodegradable polymers as a prosthetic coating or a sleeve. Biodegradable polymers have a short period of release and may be beneficial at the time of surgery and in the early post-operative period. Non-biodegradable polymers, such as spacers used in two-stage revision procedures, release antibiotics for up to six weeks.

An alternative to the controlled-release system is the use of antibiotics which are covalently tethered to the prosthesis enabling longer-term action. Using animal models, vancomycin which was covalently tethered to a modified surface on a titanium plate showed no evidence of biofilm formation compared to controls when inoculated with S. aureus.
Furthermore, the investigators were able to demonstrate through immunofluorescence staining, that after three months of implantation, vancomycin homogenously covered the surface of the prosthesis, was stable and still active, and produced minimal disturbance of the titanium surface.72

Phage therapy may also have a role in PJIs. This involves the use of bacteriophages to target specific pathogens and kill them.74 In doing so, the phages multiply, increasing the number of cells present to target specific bacteria, which is unlike other antibiotic based delivery systems where the antimicrobial action soon reduces to a subtherapeutic level.74 A biodegradable polymer has been developed to incorporate linezolid, and a broad spectrum lytic bacteriophage that targets MRSA, in animal models.75 Applied to stainless steel Kirschner-wires, a significant reduction in bacterial adhesion was achieved compared with non-coated wires, without the development of resistant mutants.75 Phage therapy appears free of local tissue toxicity or adverse effects.76 The polymer presents a high concentration of bacteriophage and antibiotic around the prosthesis and such a combination can avert bacterial adherence, colonisation, biofilm formation and the entire infection process.75-78

**Antibiofilm prosthetic coatings.** Once adhered to the prosthesis, the bacteria become resistant to antibiotics and inaccessible to the immune system as a result of biofilm formation. This can delay bone healing and osteointegration, with subsequent loosening of the prosthesis.79

Within the matrix of the biofilm, antibiotic-specific enzymes may be present which limit the diffusion of agents into the biofilm.80,81 Within the biofilm, bacterial growth and division slows, if not stops altogether.82-84

Targeted therapy has been developed to interrupt the physical integrity of the matrix, such as deoxyribonuclease (DNase) I and Dispersin B.85 DNase I degrades extracellular DNA, known to cause firmness and stability of the biofilm and inhibit biofilm formation in vitro, making it more susceptible to various antibiotics.82,85

Dispersin B, a soluble beta-N-acetylglucosaminidase, targets intercellular adhesin produced by the biofilm.85 *In vivo* studies have found Dispersin B to have antibiofilm and antibacterial activity against *S. aureus*, *S. epidermidis*, and *E. coli* when combined with antiseptics, such as triclosan or chlorhexidine.86,87 Compounds secreted or extracted from selected marine microorganisms have natural compounds with antibiofilm and bacteriostatic activity88,89 and have the potential to be adapted as biological coatings (Table II).90-98

**Intra-operative applied therapies.** The most basic and commonly used method is cancellous allograft bone impregnated with antibiotics,99 however, more novel approaches have been used to administer antibiotics locally, such as a gentamicin-impregnated bovine collagen sponge.100 This sponge (or fleece) continuously releases gentamicin until fully resorbed within eight to 14 days, with a concentration peak within the first 48 hours.101,102 However, its role has declined due to a marked cytokine and cellular inflammatory response following insertion,103,104 with some studies identifying an increase in rates of infection.105 An alternative approach has recently been developed and is used at the bone–prosthetic interface. DAC (disposable antibacterial coating) enables a high concentration of antibiotics to be released over a short period of time demonstrating both antibiofilm and antibacterial properties. Composed of a biodegradable hydrogel, DAC is a combination of hyaluronic acid and polylactic acid, to which the microbe-specific antibiotic of choice is added.106 Spread on the uncemented prosthesis prior to insertion, it releases antibiotics at the prosthetic surface for up to 96 hours (Fig. 3).107 Initial in vitro tests confirmed its physical and chemical stability, safety and modes of action,108 whilst clinical studies are emerging showing its benefits.108
Within the wound, bone–prosthetic interface, or within bone dead space, a combination of pharmaceutical-grade calcium sulphate mixed with antibiotics enables a prolonged release of antibiotics (vancomycin). In either a fully absorbable pellet or paste form (Fig. 4), concentrations of vancomycin of > 1000 ug/ml last for over 30 days.109 This is comparable with previous attempts to add antibiotics to the soft tissue by irrigation110 or as a powder,111 which proved relatively unreliable in controlling local concentrations and distribution. The calcium sulphate beads are absorbed within three months.112

During wound closure, sutures must maintain their tensile strength long enough to enable the wounds to heal, but dissolve at such a time that prevents microbial colonisation of the suture material.113,114 In order to prevent colonisation, antibiotic-coated sutures have been developed. Vicryl Plus (polyglactin 910) sutures may be coated with triclosan, a broad-spectrum antiseptic effective against *S. aureus* and *S. epidermidis* including methicillin-resistant strains.115-117

**External antimicrobial therapy**

**Photodynamic therapy (PDT).** PDT is currently used in the treatment of cancer118 and age-related macular degeneration.119 A photosensitive molecule, or non-toxic dye, is administered topically or systemically and subsequently activated by low-intensity visible light.120,121 Antibacterial PDT has already proved successful in treating periodontal infections,122 and may be a new approach in treating PJIs.123

The efficiency of PDT is secondary to the endocellular concentration of the photosensitiser within the biofilm matrix124 and in the upregulation of neutrophil function.125 Experimental studies treating the non-infected joint with
PDT demonstrated significant protection once the joint was inoculated with infection.\(^{125}\)

Several barriers need to be overcome, however, to enable PDT to be used in clinical practice for the treatment of PJI. These include the accessibility and depth of the prosthesis for the appropriate penetration of light at the correct wavelength, the pharmacokinetics of the photosensitiser, its ability to accumulate at the site of infection, and also in the timing of irradiation.\(^{126}\)

**Magnetic and electric fields.** Iron oxide demonstrates activity against P J I s by causing disruption of the bacterial cell wall via direct mechanisms and the production of free radicals,\(^{127}\) enhanced by its magnetic properties.\(^{128}\) In animal models it was shown that a magnetic field directed iron oxide ions to a specific area, increasing both the local concentration\(^{129}\) and the penetration of paramagnetic ions into bacterial biofilms.\(^{59}\) Clinically, if the prosthesis was magnetically charged prior to insertion, or was accessible to externally placed magnetic fields, metal ions could be focused on areas demonstrating signs of infection, disrupting the biofilm, which could enable systemic antibiotics to penetrate the vulnerable biofilm layer and eradicate the infection.

Within orthopaedics, an approach has been used to anodise and charge nanotubular titanium using a voltage of 15 to 30 volts. *S. aureus* biofilm formation significantly decreased secondary to the formation of fluorine on the surfaces of the anodised titanium.\(^{130}\) Similarly bioceramic hydroxyapatite has been electrically polarised with marked deceleration of the growth of *S. aureus* and *E. coli* on a positively charged surface.\(^{131}\) Accordingly, the use of nanoparticles to create a charged surface following insertion may be a possibility following activation by a systemic or local agent.

**Shockwave treatment.** Unlike the manipulation of magnetic forces to prevent bacterial adherence and biofilm formation, ultrasonic and laser-generated shockwaves can transmit mechanical energy, disrupt bacterial adhesion and dislodge biofilm.\(^{132}\) The disrupted biofilm enables greater exposure of the pathogen to systemic or local antibiotics. *In vivo* studies using 24 hours of ultrasonic treatment combined with gentamicin acting on established *E. coli* biofilms have demonstrated a reduction of viable bacteria.\(^{133}\) However, practical applications of shockwave may be limited. Shockwave lithotripsy is currently used in the treatment of renal calculi and its success is dependent on targeting a specific small area.\(^{134}\) If used in PJI, the whole prosthesis will need to be included in the field of treatment, and it may not be tolerated, especially if the therapy lasted for 24 hours.

**Discussion**

Novel strategies have shown promising results in the treatment of PJI, however, most of these therapies are still in preclinical development. The tests demonstrate that bacteria can adhere to the surface of the prosthesis, but this is not sufficient to cause infection, which requires persistent adhesion, colonisation and a lack of host clearance.\(^{135}\) In addition, *in vitro* bacterial adhesion assays have many translational issues as non-physiological media are used and the observed decreases in bacterial load, however significant in the laboratory, may be clinically irrelevant. Furthermore, *in vivo* infection models tend to use healthy young animals and the strains selected for these experiments may bear little resemblance to those implicated in human infection.\(^{136}\)

Infection exists as an epidemiological triangle, between the pathogen, the wound and the host. We found no papers that presented novel experimental findings relating to enhancing the host’s interaction with the pathogen, particularly investigating or modulating aspects of the patients immunity.

*S. aureus* is a human commensal, adding the risk of infection to every incision, despite skin antisepsis. Bacteria cannot be fully eradicated from the skin without formal sterilisation. Greater understanding is required of the patient’s predisposition to developing a PJI in order to explain why some patients develop infection whilst others do not, despite identical peri-operative precautions and comorbidities.

The evolving field of human genomics may have a role in our understanding of a patient’s susceptibility, and in improving host resistance. Several mechanisms have been identified which limit the responses of the host’s T-cells to proteins expressed by bacteria. These may be modulated by drugs to amplify or suppress the host’s responses,\(^{137,138}\) as used in the treatment of cancer.\(^{137,138}\) If applied to bacterial infection, those who use such attempts at modulation need to bear in mind that tissue destruction may, equally if not more, be driven by excessive inflammatory responses as much as by the organisms themselves.\(^{139}\) Other gene products and intracellular pathways may emerge and may be found to be useful in the control of PJI.

Infection is variable, unpredictable and its causes are multifactorial, resulting from interactions between the surface of the prosthesis and the bacteria, the acute foreign body response of the host to colonisation and soft-tissue pathogen reservoirs around the implant.\(^{135}\) These novel therapies, if transferrable to clinical practice, hold the key to reducing further or eliminating the currently low, but certainly not negligible, rates of PJI.

**Author contributions:**

D. A. George: Researched and analysed the data, Wrote the manuscript.

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F. S. Haddad: Edited and approved the manuscript.

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**References**


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