Novel Antibiotic delivery and Novel Antimicrobials in Prosthetic Joint infection

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Prosthetic joint infection (PJI) is rare occurring in 0.5-2% of hip and knee arthroplasties, nevertheless the large numbers of arthroplasties undertaken means that more than a thousand patients are affected each year in the UK alone. Concern regarding multi-drug resistant organisms makes national headlines with recent reports confirming resistance to colistin, a polymyxin. This is currently a ‘reserve antibiotic’, although already used in PJI.

Despite the strict aseptic and antiseptic precautions that are routinely performed, including patient preoperative decolonisation, surgeon’s hands and patient’s skin disinfection, sterile instruments and operating theatres with laminar flow, the use of prophylactic antibiotics in the perioperative period remains a critical part of avoiding infection in primary arthroplasty. The bacteria causing infection often originate from the patient’s own skin, as well as that of the operating theatre personnel. As there is no way to completely eliminate risk, innovative solutions are required to prevent and treat orthopaedic infections.

Novel Antibiotic Delivery

Local antibiotic delivery can achieve a much higher concentration than achievable systemically, maximising efficacy, minimising toxicity and potentially reducing the risk of resistance. Infusion pumps have been used to deliver antibiotic locally into infected prosthetic joints. Such infusions are used along with one or more surgical debridements and exchange of any modular components. Treatment with infusion is suitable for some acute infections.

Devices loaded with antibiotics which elute into the joint space or an infected area have advantages. Antibiotic release
is continuous and depending on the vehicle substance can last for weeks to months.

Antibiotic loaded polymethylmethacrylate (PMMA) cement is well established in arthroplasty, primary and revision, and osteomyelitis. The antibiotic loaded PMMA cement within the bone cavity and/or joint can act as a barrier to the elution of antibiotics. The antibiotic loaded cement can also act as a foreign body, upon which microbes produce a biomembrane or biofilm, protecting them against the antimicrobial activity of the antibiotics. The PMMA cement is also non-resorbable and a second surgical intervention to remove cement is necessary.

Biodegradable vehicles represent an alternative to PMMA cement. They gradually resorb and may even act as a matrix for bone growth. With their degradation, additional release of antibiotics occurs, prolonging their action and not allowing biomembrane formation on their surface. Cancellous bone autograft, or morsellised bone allograft, impregnated or soaked in antibiotic solution can also be utilised, although the elution is very short-lived. Impregnated osteoinductive biomaterials show rapid release of antibiotics and aid new bone formation; calcium sulphate is used commercially and calcium phosphate is under investigation. Calcium hydroxyapatite combined with an antibiotic can be used for coating non-cemented implants, creating an antibacterial coating. Covalently tethered antibiotics, such as vancomycin, on titanium can also serve the same purpose. This technology holds great promise in developing so called “smart” implants, which may well demonstrate self-protective attributes against infection. Bioactive glass is another example of a biomaterial which can be impregnated with antibiotics.

Collagen, fibrin and thrombin are all naturally occurring materials which can be fabricated into a mesh-like structure creating a scaffold or allowing the direct binding of antibiotics which are released as the structure is broken down, usually within days. Their use is more common outside orthopaedic surgery, but their biocompatibility and quick degradation are valuable properties. On the other hand biodegradable surgery, but their biocompatibility and quick degradation are valuable properties. On the other hand biodegradable synthetic polymers, mainly from glycolide and lactide, have been used in orthopaedics for several decades as a suture material. Modifying their structure by selection of copolymers, crystalline structure and molecular weight controls their degradation and also antibiotic release. Synthetic polymers could be used as antibiotic carriers; unfortunately they are not suitable because of their quick loss of integrity and mechanical properties.

Other antibiotic delivery systems include plaster of Paris, which can act as a vehicle for many antibiotics. It is well tolerated and easily absorbed by tissues. There are also several gel-like carriers, such as hyaluronic acid or mono-olein-water gel, which can be loaded with antibiotics. Antibacterial hydrogel coating of non-cemented press-fit implants as a short-term prophylactic method in animal models has also been trialled. Various biomaterials derived from marine organisms, with differing grades of porosity, show the potential to act as osteoconductive bone substitutes, making them promising candidates for antibiotic delivery systems in the future.

**Novel Antimicrobials**

The real threat of multi-resistant bacteria has forced us to look for different strategies and options for treating and preventing implant related infection. New and novel non-antibiotics with antimicrobial properties should be considered. An example is Chitosan, which is used in military medicine as a field dressing to promote thrombus and reduce blood loss. It is also anti-septic, aids healing and is biocompatible. When loaded with gentamicin it seems to be useful in the treatment of orthopaedic infections.

Many drugs whose primary role is in non-infectious disease, from neurotropic to antihypertensives, possess antimicrobial properties. Some of these drugs are routinely used in orthopaedics either as general or local anaesthetics, painkillers and anti-inflammatory drugs. Studies looking at infection rate and the usage of these particular drugs for anaesthesia and pain relief would be interesting.

The antimicrobial action of two different substances combined does not automatically guarantee synergistic action. One study has shown that bupivacaine and gentamicin combine to give a synergistic antimicrobial action against Staphylococcus aureus. It has also been shown that some antidepressants and their isomers have a synergistic effect when combined with conventional antibiotics. The same had been found for magnesium and zinc against a variety of human pathogens.

Bioactive antimicrobial peptides are proteins formed by the non-specific humoral mechanisms of eukaryotic and prokaryotic organisms. These peptides have antimicrobial activity and their derivatives have been produced synthetically. They can be used...
be used in combination with hydroxyapatite to coat implants. They have the potential for clinical application.\textsuperscript{51-54} Several other substances and metallic elements were tested \textit{in vitro} and in animal models. Silver, copper, iodine and chlorhexidine have the potential to be incorporated into the outer nano-layers of prostheses, and have shown evidence of antimicrobial action.\textsuperscript{55,56} They can be added onto the titanium, stainless steel and calcium phosphate surfaces of orthopaedic implants.

Changing the surface properties of implants is an area of focus to try and prevent, or reduce, biofilm infections.\textsuperscript{57} Among metals with antimicrobial activity, silver has excellent antimicrobial activity and low toxicity.\textsuperscript{58} Hardee et al introduced silver-coated femoral and tibial megaprostheses in sarcoma patients and compared the results with uncoated titanium prostheses over a five year period. The infection rate in this series was reduced from 18\% in the uncoated to 6\% in the silver-coated group.\textsuperscript{59} The use of silver-coated, extendable endoprostheses has also been reported with some success.\textsuperscript{60} The mechanism of the bactericidal action of silver is still unclear. Although when silver ions penetrate into cells, the DNA is condensed and loses its ability to replicate, leading to cell death. Silver ions may also inactivate proteins by reacting with the thiol groups in cysteine residues.\textsuperscript{61-63} Silver nanoparticles have been shown to penetrate bacteria, react with proteins and DNA, interrupting the respiratory chain and cell division, leading to cell death.\textsuperscript{64}

Successful treatment of PJIs is ultimately all about clearing bacteria in biofilms. Bacteria embedded in extracellular polymeric matrix form a biofilm which attaches to the surface of a prosthetic joint. Biofilm-associated bacteria are highly resistant to antibiotics. Bacteria in biofilm behave differently, especially in their response to antibiotic treatment. The complicated structure of biofilm with extracellular polymeric matrix may prevent antibiotics from reaching the bacteria. Bacteria in biofilm also slow their physiological turnover, making them more resistant to the antibiotics, which target active cellular processes.\textsuperscript{65}

Within the biofilm, bacteria are protected from antimicrobial killing and host responses rendering PJIs difficult to eradicate.\textsuperscript{66} Any strategy to prevent the attachment of organisms to the surface of the implant, prevention of their proliferation or stopping molecular communications between the organisms may help in the battle against PJIs.\textsuperscript{67}

Although, not yet fully understood, several techniques have been recently described which have the potential to supersede our reliance on antimicrobials. Acetic acid (AA), or vinegar, has been used in the management of infection since the time of Hippocrates, and is one such novel chemical debridement agent. AA has a bactericidal spectrum covering gram-positive and -negative organisms. It is frequently used to treat ear and complex wound infections. \textit{In vitro} analysis has demonstrated complete eradication of mature gram-positive and gram-negative biofilms at physiologically tolerable concentrations of AA. The proposed mechanism is not due to its acidity and proton dissociation, but due to the non-dissociated form.\textsuperscript{68,69} Another chemical agent that has been used for millennia in the treatment of infection is honey. Medical-grade honey has broad spectrum antimicrobial characteristics with activity against gram-positive and -negative, and multi-resistant organisms.\textsuperscript{70} Bee defensin-1, hydrogen peroxide and methylglyoxal (in Manuka honey) have been suggested as having antimicrobial activity; although understanding of the antimicrobial mechanism is incomplete.\textsuperscript{71,72}

### Conclusion

Many of these novel antimicrobial agents and carriers for them show promise. Nevertheless, they have often only been tested \textit{in vitro} and we need to exercise caution in extrapolating the results from the laboratory bench to the clinic. In the age of antibiotic resistance with the daunting prospect of the post-antibiotic era, we need to maximise the effectiveness of current antibiotic delivery but also investigate the potential of alternative, novel antimicrobial therapies.
References


