Antimicrobial Materials in Arthroplasty

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Abstract With an increase in the number of total joint arthroplasty procedures being performed, the number of surgical site infections (SSI) and peri-prosthetic joint infections (PJI) are also expected to increase. In addition to portending significant morbidity and mortality, the growing number of prosthetic associated infections also presents a significant social and economic burden. There are current antimicrobial resistance strategies available for clinical use and more are being developed and are in the laboratory development and testing phases. However, resistance to treatment include limited implant host interface vascularity that contributes to the inability of systemically administered antibiotics to effectively reach and exert a full effect where most needed. Recognition of the limitation of systemic antibiotics and the growing problem presented by PJI have led to more recent efforts focused on local antimicrobial control at or around surgically implanted materials. Current and developing methods of achieving prophylactic local antimicrobial control in arthroplasty include using antibiotic loaded bone cement, intrawound antibiotic powders, antiseptic lavages, biocompatible antimicrobial delivery devices and coatings, and modified implants.

Keywords Prosthetic · Joint · Infection · Biofilm · Antibiotics · Antimicrobial · Antiseptic · Implants · Delivery devices · Chitosan · Hydrogel · Surface · Metal · Coatings

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Introduction

Hip and knee arthroplasty are proven to be successful in clinical practice. They have led to high survivorship and resulted in reduced pain, function, and improved quality of life with low morbidity and mortality [1–3]. For these reasons, the number of joint replacement procedures continues to rise, with the number of total hip arthroplasty (THA) procedures slated to increase 71% and total knee arthroplasty (TKA) 85% by 2030 [4]. Despite reduced rates of revision performed for aseptic loosening and wear due to advances in components design and improved surgical technique, the rate of peri-prosthetic joint infection (PJI) remains unchanged, making it a very common mode of failure in total joint arthroplasty (TJA) [5, 6]. Revision for PJI is performed in less than 2% of primary TJAs [7] and up to 20% of revision arthroplasties, including limb salvage surgery [8]. With anticipated continued growth of total joint procedures performed, so too will the numbers of PJI [9]. PJI is associated with significant morbidity, increased rates of mortality, and costs associated with PJI are projected to exceed $1.6 billion by 2020 [10, 11]. The estimated PJI cost for sensitive organism PJI is over $60,000, while resistant organisms (e.g., methicillin-resistant organisms) is greater than $100,000 for per case [12, 13]. For these reasons, current and future efforts focused on preventing and/or eradicating PJI are paramount.

Current Methods of PJI Prevention

The first step in reducing PJI is prevention. Current methods have focused primarily on reducing risk through control of the operative environment and patient factors. In the operating room, foot traffic control, laminar flow, air filtration systems, hooded surgical gowns, good sterile techniques, and surgical efficiency have been adopted to minimize the opportunity for microbial contamination of the surgical field [14, 15]. Patient focused factors include administration of systemic perioperative antibiotics, presurgical skin cleansing, nasal methicillin-sensitive and methicillin-resistant *Staphylococcus aureus* decolonization, and selecting patients who have undergone modifiable risk factor optimization [16, 17]. Likewise, despite efforts to minimize these patient-related risk factors, host disparities leading to increased PJI susceptibility are not always identifiable or modifiable. In fact, only the use of perioperative systemic antibiotics is supported by consensus recommendation and is considered standard of care [18]. Unfortunately, regardless of efforts to maintain a sterile operating room (OR) condition, bacterial and fungal bioaerosols cannot be completely eliminated from the surgical environment. Various pathogens have been found on inanimate OR surfaces, as one study demonstrated that 16.6% of 283 objects sampled from 35 operating rooms of teaching hospitals in the USA were positive for pathogens [19].

Biofilm and Limitations of Systemic Preventative Strategies

Device-associated infections are generally assumed to occur due to a low numbers of contaminating bacteria that occurs during the operative procedure. Implanted material has been shown to allow establishment of infection with an inoculum (10–100 bacterial colony forming units (CFU)) that is ~10,000 times lower than that required for its establishment in the absence of an implant [20], suggesting that the host response to the hardware to defend is compromised. Specifically, upon placement, implants are rapidly coated with serum proteins such as albumin, fibronectin, and fibrin[ogen], proteins that are critical for osseointegration but unfortunately provide an ideal surface for bacterial adhesion. The presence of the implant further complicates the situation as this foreign body causes activation of the immune system and an inflammatory response, neither of which can adequately eradicate the adherent bacteria [21]. Finally, the bacteria use the proteinaceous matrix as well as secretion of its own biofilm proteins [22, 23] to encase the adherent bacteria within a bacterial biofilm that further protects microorganisms from surveillance by host immune cells and antibiotics [24].

Bacterial colonization is the process from microbial adhesion to establishing a mature biofilm layer that takes only a few hours [25]. Biofilm bacteria tend to be metabolically indolent and are comprised of a high percentage of persisters [26, 27]. This suppressed metabolic state decreases the consequences of antibiotic treatment as antibiotics are targeted at rapidly growing cells, including functions such as cell wall synthesis, protein synthesis, or DNA replication. Thus, bacteria contained within a biofilm have 10 to 1000-fold less antibiotic susceptibility than free floating planktonic bacteria in culture [23, 28]. Importantly, due to avascularity of implanted material and subsequent impaired blood circulation in the bone environment, only low drug concentrations are delivered to the bone-implant interface with the result that systemic antibiotic treatments are usually ineffective at eliminating bacterial biofilms [29]. To date, there is no systemic treatment capable of rapid and complete biofilm destruction, which leaves local control and contaminated implant extraction as some of the few viable options for the treatment of PJI [30]. Infection prevention is key, as treatment is difficult due to pathogen colonization of implants, pathogen recalcitrance to antibiotic treatment when adhered to implants, and pathogen persistence in tissue despite removal of the implant.

Focus on Local Control

Microbial colonization of implanted material furnished the theory of a proposed "race for the surface," in which bacteria and host cells compete for implant survivorship [31]. While this concept is not entirely accurate, as host peri-implant osseointegration or fibrous tissue encapsulation does not eliminate survivorship of bacterial micro-colonies, it has focused efforts on providing local antimicrobial control. The goal of local prophylactic control is to keep microbial infections from occurring at

or around the site of implantation. Local drug delivery can reduce bacteria concentration around implants and potentially prevent bacterial adherence. Compared to intravenous antibiotics, local antibiotic delivery offers higher drug concentration in relevant tissue and reduced systemic toxicity. Potential methods of achieving local peri-implant microbial control in TJA include use of antibiotic loaded bone cement (ABLC), antibiotic powders, antiseptic irrigation, biocompatible delivery devices and coatings, and modified implants.

Antibiotic Bone Cement

Discovery of antibiotic elution from polymethylmethacrylate (PMMA) bone cement into the tissue surrounding implants resulted in the use of antibiotic-loaded bone cement (ALBC) for infection prophylaxis in TJA [32]. Elution from ABLC shows an initial sharp peak of antibiotic release followed by decreased but constant release observed over the following days to week; a retrieval study demonstrated that gentamicin and vancomycin loaded hip spacers continued to release a reduced but constant concentration of local antibiotic 3–6 months after implantation [33]. While a multitude of antibacterial and antifungal pharmacologic agents can be added to bone cement, preferred characteristics include: thermal stability, powder form, antimicrobial efficacy over a wide spectrum, antimicrobial effect at low concentrations, high PMMA elution, minimal disruption of bone cement mechanical properties, and low risk of delayed hypersensitivity or allergy [34] (Table 1). Due to their wide spectrum coverage, including most organisms associated with PJI, vancomycin and gentamicin

Table 1 Antibacterial and antifungal pharmacologic agents that can be added to bone cement

Type of antibiotic	Activity against	g/40g PMMA
Vancomycin	Gram-positive bacteria, including methicillin-resistant organisms	0.5–4
Cefazolin	Gram-positive infections, limited gram-negative coverage	1–2
Erythromycin	Aerobic gram-positive *cocci* and bacilli	0.5–1
Linezolid	Multidrug-resistant gram-positive *cocci* such as MRSA	1.2
Meropenem	Gram-positive and gram-negative bacteria, anaerobes, and *Pseudomonas*	0.5–4
Tobramycin	Gram-negative bacteria (*Pseudomonas*)	1–4.8
Gentamicin	Gram-negative bacteria (*E. coli*, *Klebsiella*, and *Pseudomonas aeroginosa*). Aerobic bacteria	0.25–4.8
Ceftazidime	Gram-negative bacteria (*Pseudomonas*)	2
Cefotaxime	Gram-negative bacteria, not against *Pseudomonas*	2
Ceftaroline	Gram-negative bacteria, not against *Pseudomonas*	2–4
Ciprofloxacin	Gram-negative organisms (*Enterobacteriaceae*)	0.2–3
Colistin	Gram-negative bacteria	0.24
Aztreonam	Gram-negative bacteria	4
Amphotericin deoxycholate	Fungus	200
Voriconazole	Fungus	300–600

have broad clinical application in orthopedics. The literature surrounding the practice of prophylactic ALBC to prevent infection is controversial, as some studies support this practice while others have suggested that this strategy is not ideal as a prophylactic measure [35, 36]. Prolonged exposure to antibiotics does not provide any additional benefit and may lead to systemic toxicity, reduced mechanical properties of cement, and can contribute to microbial antibiotic resistance [37, 38].

Antibiotic Powder

The increase in drug-resistant organisms is due to the overutilization of antibiotics, which highlights the importance of reducing antibiotic exposure and minimizing unnecessary antibiotic prescriptions. Guidelines support systemic antibiotic perioperative prophylaxis administration within 60 min before surgical incision to prevent SSI (ASHP guidelines). However, there are no guidelines for administration of local antibiotics. The purpose of using topical antibiotics is achieving a high antibiotic concentration at the surgical site while minimizing the adverse effects associated with systemic exposure [39]. Systemic antibiotics show decreased surgical wound infection when administered within 1–2 h before incision; locally applied antibiotic powder requires less time for activity onset and achievement of high local concentrations at the desired site [40, 41]. A potential disadvantage of topical antibiotics is that the typical application occurs prior to closure to prevent dilution or removal with irrigation of the surgical bed. This limits their use in isolation, as without coadministration of preoperative systemic antibiotics, the late timing may provide inadequate prevention although isolated administration has not been conducted in any clinical studies to date.

Despite limited systemic bioavailability and diminished risk for adverse events, documented complications of local antibiotics in powder form including culture negative seromas, ototoxicity and transient hearing loss, nephropathy, and anaphylactic circulatory collapse have been reported with use in spine surgery [42, 43]. Other concerns regarding high concentrations of locally administered antibiotics include the effect on osteoblast physiology and the potential for accelerated bearing surface wear [44]. High local vancomycin concentrations <1000 mg/L have minimal effect on osteoblast-like cells, with osteoblast cell death at concentrations >10,000 mg/L of vancomycin [45, 46]. Tobramycin or cefazolin concentrations <200 mg/L do not affect osteoblast cells, where 200–400 mg/L alters cell replication, and >10,000 mg/L causes cell death [47]. Combined systemic cefazolin and local gentamicin has shown the greatest efficacy in in vivo animal model studies when compared to topical antibiotic options alone or with other combinations of systemic and topical antibiotics [48]. Few studies have evaluated the use of topical intrawound antibiotics for TJA infection prophylaxis, since it is not a commonly adopted practice. However, a retrospective study reporting on 125 consecutive patients who underwent THA compared intravenous antibiotics alone to intravenous antibiotics and 2 g of locally applied topical vancomycin. The placement of the powdered vancomycin resulted in markedly fewer infections in THA patients [49]. The growing antibiotic resistance and possible formation of culture negative seromas accentuate the need to develop alternative local antimicrobial strategies.

Antiseptic Irrigation

There are currently no set standards for wound irrigation for SSI prevention at the time of primary TJA, as there is a lack of evidence and minimal high-level studies [50]. Currently used solutions include 0.9% saline, antiseptics (e.g., povidone–iodine complex, chlorhexidine, or hydrogen peroxide), antibiotic solutions (e.g., bacitracin/polymyxin), and castile soap. Antiseptics are favored over antibiotics, as they have less likelihood of resistance due to the fact that they target various aspects of microbial cell biology with different mechanisms of action [51].

The commonly used povidone–iodine complex, formed by association of iodine with povidone (a synthetic carrier polymer), has no microbicidal activity [52]. In an aqueous medium, the povidone–iodine complex releases free iodine (the antimicrobial component) to reach an equilibrium; as the iodine-consuming germicidal activity proceeds, the povidone–iodine reservoir releases more free iodine [53, 54]. Iodine exhibits microbicidal activity by oxidizing nucleotides, respiratory chain cytosolic enzymes, and bacterial cell membrane fatty/amino acids. This oxidation causes their denaturation [55]. In terms of cytotoxicity, a recent study showed that povidone–iodine complex enhanced wound healing via tumor necrosis factor beta (TGF β) with increased granulation and enhanced neovascularization [56]. Thus, povidone–iodine complex offers favorable efficacy due to its ability for biofilm penetration, activity across a broad spectrum of bacteria, fungi, protozoa, and viruses, and decreased resistance development. Its lack of cytotoxicity as evidenced by its lack of adverse effects on wound healing and its anti-inflammatory properties are an added benefit as prolonged inflammation contributes to extracellular matrix defective remodeling and can cause failure of reepithelialization and development of chronic wounds [57]. Intraoperative flushing of the surgical site with povidone–iodine complex (0.35% dilution) has resulted in reduced TJA infection rates [58].

Chlorhexidine (CHD) is being used in multiple healthcare applications, since it has a broad-spectrum of antimicrobial activity and a fast onset of action. Applications including hand and oral hygiene, skin preparation, and impregnation into surgical meshes, catheter sites, and wound dressings at various concentrations [59]. CHD has a faster onset of action compared to povidone–iodine complex against more microorganisms and has been shown to be less cytotoxic when applied to healthy tissue [60]. CHD is a frequently used bactericidal antiseptic that acts through disruption of microbial cellular membranes [61]. Several in vitro and in vivo animal studies have sought to investigate the safety of CHD-based irrigants, evaluating the effects of its exposure on different anatomic structures including arteries, veins, and collagen. These studies have not found any toxicity at low concentrations and have demonstrated no effects on mechanical properties of collagen-based structures such as tendons [62, 63]. There are no known reports of CHD resistance despite long-term use. Mounting evidence may suggest that antiseptics should be used preferentially instead of systemic and topical antibiotics, however further investigation is needed to make that determination.

Modified Implants

While antibiotic powders and antiseptic irrigations offer options for treating the peri-implant local environment, emerging technologies involving implant surface modification facilitate both peri-implant and direct implant surface antimicrobial activity. The overall goals of these modifications are prevention of bacterial adhesion and formation of biofilm while avoiding conditions that may foster acquisition of antibiotic resistance. These implant surface modifications permit different strategies to display active molecules and/or prevent bacterial adhesion.

Two main strategies are implemented to produce activated implants. A selected drug or biomolecule can be mixed with the substrate of the bulk device, or it can be grafted onto the surface to produce biomolecular loaded coatings. Surface coatings require the apposition of a certain substance onto a desired object, adding layers to the existing surface. Some surface coatings consist of a biodegradable delivery from which bioactive agents are released. Examples of such bioactive delivery devices are bioactive glasses, hydrogels and chitosan. A variety of techniques including direct chemical coupling, dip coating, layer by layer (LBL), and electrophoretic deposition (EPD) are used to produce implant surface coatings. The aim of implant mediated antimicrobial activity is to prevent primary microbial adhesion by repelling or killing planktonic microbial cells. Coating activity is active or passive depending on whether agents are locally delivered to surrounding tissue or prevent adhesion or function by contact killing [64, 65].

Topographies: Perhaps the most straightforward surfaces are those created by topographically modifying the surface on the nanoscale to prevent bacterial adhesion. These surfaces are inspired by naturally antimicrobial surfaces, such as shark skin that has 3D riblet microstructure, lotus leaves that have micro-size bulge shape, and gecko skin that has hair-like nanostructure [66–68]. The patterning has been explored for uses in catheters, and on metal surfaces where micro and nanotopographic modulations affect the ability of bacterium to adhere to the surface. While numerous designs exist, and even at least one company, these topographic surfaces are predominantly characterized ex vivo; at least one rat skin test found that the surfaces retained activity in the presence of at least wound fluid. In general, these surfaces are reported to decrease bacterial colonization by up to three logs [69]. In addition, surfaces have altered charge, roughness, porosity, and hydrophobicity to affect bacterial adhesion [70].

Antimicrobial Implant Surfaces

Example of active antimicrobial molecules that have been used to modify implant surfaces include a nitric oxide (NO) releasing material, antimicrobial peptides, antibiotics, antibacterial polymers, and inorganic antibacterial metal elements [24, 71]. Currently available and developing modified implants for orthopedic use have primarily involved applied strategies to titanium (Ti) substrates, and to a lesser extent

cobalt chrome (Co-Cr) and allograft bone [72]. Titanium and its alloys (Ti-6Al-7Nb, Ti-5Al-2·5Fe, and Ti-6Al-4V) are often used in orthopedics due to biocompatibility, corrosion resistance, and chemical and mechanical properties, and are therefore the focus of most research involving surface treatment. Due to the frequent use of press fit techniques in THA and growing use in TKA, with ultimate stability reliant on successful host implant in-growth or on-growth, modified implant strategies developed for use in the trauma setting may not be appropriately applied to the realm of arthroplasty. Therefore, the ideal antimicrobial arthroplasty implant should maintain its biomechanical properties, remain biocompatible, promote or be non-inhibitory toward osteoblast activity, and provides effective anti-infectivity [73–75]. We and others have explored the efficacy of using direct grafting to permanently render the biomaterial surface antimicrobial. Unlike controlled-release systems, antibiotics are not eluted from these surfaces and thus have the potential to remain antimicrobial during the osseointegration period. Direct grafting of vancomycin [76–78] on titanium, Ti-6Al-4V, and on allograft bone reduced adhesion by *S. aureus* and *S. epidermidis* [79, 80], with direct efficacy in small [45] and large [81] animal models of osteomyelitis. Similarly, antimicrobial peptides have been tethered to surfaces with retention of antimicrobial activity [82–85]. Perhaps of greatest interest is a report in which tissue plasminogen activator (tPA) was coated on polystyrene and examined in vitro and in vivo. The induction of fibrinolysis by tPA significantly reduced bacterial colonization [86].

More recently, vancomycin and complementary antibiotics was immobilized in the matrix of UHMWPE to render the bearing surfaces antimicrobial. With an eccentric clustering of the antimicrobial, elution of vancomycin occurred at bactericidal levels for >3 weeks. Importantly, gamma radiation of the implant for sterilization resulted in permanent immobilization of some of the antibiotics, leading to permanently antimicrobial UHMWPE components to prevent infection. It is noteworthy that these surfaces were also used to treat infection, as it had continued activity in a rabbit model of osteomyelitis, outperforming antibiotic-loaded bone cement [87]. These surfaces, however, remain in the development phase.

Hydrogels

Cross-linked polymers and hydrogels are often used for various biomedical purposes due to their biocompatibility, ability for local pharmacological agent delivery and capacity to produce specific elution patterns [88]. The broad structure of these polymers and hydrogels encourages cell survival and proliferation, has compositional similarities to extracellular matrices, and is readily resorbable. Poly-electrolyte hydrogels bearing amino acid residues approximates biologic tissue by permitting bioactivity, while also forming a physical barrier to bacterial adhesion. Ionic functional groups permit complex formation with drug molecules and/or metal ions. Aside from the primary role as an ion and drug delivery system, hydrogels ionic interactions also control the release kinetics into the environment. The kinetics of release is determined by the strength of the interaction between the hydrogel car-

boxyl group and drug amine group. Hydrogels are therefore utilized as an antibacterial coating that provides fast resorption and local protection in the short-term.

A current clinical use includes a hydrogel coating referred to as defensive antibacterial coating (DAC, Novagenit SRL, Mezzolombardo, Italy). Novagenit SRL, Mezzolombardo, Italy). The composition consists of hyaluronan that is covalently linked and poly-D,L-lactide, and undergoes hydrolytic degradation within 72 h in vivo. During the dissolution phase, the hydrogel completely releases a variety of antibacterials impregnated within the gel. In a prospective observational multicenter study, 380 patients were in the treatment group that received antibiotic loaded DAC coating applied intraoperatively to the surfaces of total hip or total knee prosthesis, or a control group. Although only short-term results were available, it demonstrated good safety and efficacy without local or systemic side effects, and there was a ten-fold reduction in early SSIs [89].

Chitosan

Chitosan (CTS) is a biocompatible, biodegradable polymer developed from renewable resources that are natural. It is derived from the deacetylation of chitin, which is a naturally occurring biopolymer that comprises the exoskeleton of crustaceans, can be found in fungal cells walls, and is found in abundance in other biological materials. The antibacterial and antifungal properties of chitosan are hypothesized to derive from the polycationic characteristics and are mediated by electrostatic forces between negative residues at cell surfaces and protonated amino groups (NH_3^+) in chitosan. The antimicrobial activity of CTS is influenced by the numbers of these protonated amines present in chitosan where these numbers increase with greater degrees of deacetylation, as well as its film-forming properties and cationicity. When formed as a film, CTS has selective permeability to CO_2 and O_2 gases, strong mechanical properties, and exhibits high permeability to water. This biopolymer is susceptible to accelerated angiogenesis, enzymatic degradation, limited fibrous encapsulation, increased cellular adhesion, and innate ability to deliver and link to growth factors [90].

The miscibility of the substance with which chitosan is blended can influence both the mechanical properties and surface morphology of the biologic film. In addition, chitosan-based films can be tuned when combining with other hydrocolloids or proteins, where antibiotics are often combined with CTS as a drug delivery system. Using chitosan–gelatin composites, ampicillin release could be rate-controllable by changing the polymer ratio within deposited films in an in vitro model [91]. CTS also functions well as a delivery device for other bioactive agents. For example, chitosan has been combined with gentamicin-loaded bioactive glass (CS/BG/GS), forming a composite coating that transforms a brittle glass coating to a more compliant structure [92]. Similar to ALBC, release kinetics show an initial burst followed by slower release. Within 5 days, the CS/BG/GS composite released 40% gentamicin but maintained sustained release over a period of 8 weeks. This inhibited in vitro bacterial growth for 2 days, led to cellular proliferation up to

10 days. Finally, CTS has been combined with the poly anionic polymer hyaluronic acid (HA) and applied to Ti; this coating showed decreased adherence of *S. aureus* and *E. coli* in vitro. It is thought that coatings consisting of hydrophilic CTS and HA inhibit bacterial adhesion, which is typically greater on hydrophobic materials [93].

Metal Ion Coating

Zinc, copper, silver, gold, and magnesium nanoparticles (NPs) are clusters of atoms that range from 1 to 100 nm. These NPs exhibit antimicrobial activity by an ion release mechanism that has intrinsic antimicrobial properties. These can serve as agents for antimicrobial implants [94]. Metal ions are bactericidal, especially silver and copper ions, which is secondary to the oligodynamic effect, which is the noxious effect that these metal ions have against living cells [95]. Copper exposure to microorganisms can permeate membrane integrity and can lead to cell death. Furthermore, copper can cause hydrolysis and displace cell organelles. Copper also contributes to viral inactivation or cell death by altering protein structure to change their function or forming complexes with proteins. Due to affinity for DNA, copper can break hydrogen bonds within DNA, which leads to cross-linking within the strands and opens the double helix resulting in DNA destruction [96]. An in vivo animal study simulated an *S. aureus* PJI to evaluate the antibacterial effect of a spacer (Ti6A14V) coated with 4× Cu-TiO2. This coating used a sol–gel substrate to integrate and deliver copper ions. In the presence of copper ions, there was a significant reduction in bacterial growth rate, with the highest reductions (4×) found in the copper TiO2-coating group. In addition to desirable antibacterial activity, coatings integrated with the implant coating were also found to have good durability. In particular, it was noted that this antibacterial Cu-TiO2 coating had good efficacy against MRSA, a particularly problematic microorganism responsible for a growing number of PJI [97]. However, some bacteria expressed copper tolerance genes, minimizing its potential efficacy [98].

Silver (Ag) is the most prevalent antimicrobial metal used in applications within biomedical science, and its activity has been known for many years. Antibacterial activity is attributed to the solvated ionic or nanoparticle form as opposed to bulk material [99]. The benefit of elemental NPs is the large surface area to volume ratio, thus amplifying release of ions and the consequent antimicrobial effect. In addition, the shape of the silver nanoparticle appears to be important [100]. As these ions are gradually released from surface coatings into the surrounding tissue, they become hydroxylated to form highly reactive components, including reactive oxygen species [101]. These cause bacterial cell membrane oxidation and result in greater cell permeability and death. Despite their antimicrobial activity, silver ions are not routinely applied to implants due to concerns of cytotoxicity with resultant decreased biocompatibility [102]. The use of silver NP loaded polymers show a burst of silver release for the first 3 days and decreased release over the subsequent 2 days [103]. However, due to high shear forces between the implant and bone surfaces in arthroplasty, polymer coatings do not adequately meet mechanical requirements given the force of load bearing

implants. An alternative is incorporation of silver into inorganic coatings like glass or ceramic, which demonstrate antibacterial activities against gram-positive and -negative bacteria in vitro with no remarkable cytotoxicity [104, 105]. Recently, HA coatings doped with silver NPs implanted in an animal model showed osseointegration similar to conventional HA implants, indicating good osseointegrative properties [106]. Enhanced silver loaded Ti showed successful in vitro inhibition of *S. aureus* growth with maintenance of good cellular activity [107]. Selected delivery devices along with layering techniques have been used to control the release of silver ions while maintaining cyto-compatible concentrations.

Silver Clinical Use-Case Series

More importantly, there are several reports on in vivo clinical application of silver coatings with respect to arthroplasty-related implants. Silver coating of Modular Universal Tumor and Revision System (MUTARS) megendoprosthesis (implantcast, Buxtehude, Germany) is accomplished by galvanic deposition of elementary silver on the surface of the titanium–vanadium prostheses. The first prospective case series included 20 patients with bone tumors (humerus, tibia, and femur) that were treated with an implant with this specific coating. There were no local or systemic toxic side effects of the silver coating. Blood silver levels never exceeded 56.4 (0.056 μg/mL) parts per billion (ppb), which is considered non-toxic, and there were no aberrant liver and kidney laboratory parameters. There were no signs of foreign body reaction or chronic inflammation in histological analysis [108]. A separate 51 patient case series that received a proximal tibia or proximal femur replacement using a tumor endoprosthesis with a similar silver coating found an infection rate of 5.9% (3 of 51 patients) in the silver group after 5 year follow-up compared to a historical control of uncoated implants in the same hospital with a 17.6% (13 of 74 patients) infection rate [109]. Another case series of 32 patients reported on the use of silver coated megendoprostheses in those undergoing soft tissue or bone resection surgery (26 patients) or revision arthroplasty (6 patients), of which 7 patients (23%) developed local argyria, which is a local reaction to silver often manifest in the skin. Silver levels were similar between patients with and without argyria with regards to serum levels and aspirated postoperative seroma. There was no association with the length of prosthesis, which was an indicator of how much silver was present. There were no elevated liver or kidney serum levels, and no significant difference in hemoglobin and leukocytes with or without argyria. Four out of seven patients with local argyria had peripheral neurological deficit, with two present prior to surgery, and the remaining two with no details on potential cause given [110].

Further clinically used silver coatings are produced by anodization of Ti alloy substrate with absorption of low amounts of silver within an aqueous solution; these are used in the *Agluna* tumor prostheses (Accentus Medical Ltd., Oxfordshire, United Kingdom). In contrast to the galvanized silver implants, a retrospective review of 394 consecutive patients that underwent resection and endoprosthesis

placement for bone tumors showed 12.4% PJI in the anodized-silver treated group compared to 7.5% in the non-silver group; however, the patients that received silver had a higher baseline risk of infection [111]. However, in this study, patients who received the anodized silver prosthesis were assigned to this treatment group based on elevated preoperative risk for infection. This may reflect different local silver concentrations thus different antibacterial effect, as it may relate to the method of silver-Ti substrate incorporation.

Custom made endoprostheses (Stanmore Implants Worldwide Ltd., Elstree, United Kingdom) are made with on ionic silver "stitched" into the titanium alloy surface by titanium alloy anodization with silver absorption from an aqueous solution [112]. The surface modification is directly integrated into the substrate, then silver is added by an ion exchange reaction where 5 μm circular features are formed. The maximum amount of silver allowed on a typical endoprostheses is 5 mg.

A retrospective case-control study compared 85 patients that received a silver-coated tumor prosthesis (2006–2011) to 85 patients that received the same prosthesis without a silver coating (2001–2011) with a 12-month minimum follow-up. The indications for tumor prosthesis implantation included 50 primary reconstructions, and 120 revisions for infection (79 one-stage revisions and 41 two-stage revisions). There were significantly less post-operative infections in the silver group (11.8%) compared to the non-silver group (22.4%, $p = 0.03$). For those that developed subsequent infection, debridement, antibiotic treatment with implant retention (DAIR) was successful in the seven infected patients who received a silver implant, whereas only 6 of 19 patients (31.6%) in the non-silver group ($p = 0.048$) were successfully treated with DAIR. When performing two-stage revision for infection, the silver group had an overall success rate of 86% versus 57% in the matched control group ($p = 0.05$). There were no implant specific adverse events, including argyria [112].

Non-metal Element Coating

Non-metal elements, such as chlorine, hydrogen, oxygen, or iodine, are commonly used in medicine given their antimicrobial properties. However, they are rarely used as antibacterial coating technologies in orthopedics due to their inadequate mechanical properties. An in vitro study of selenium covalently bound onto a Ti surface prevented *S. aureus* and *S. epidermidis* adhesion without impact on osteoblast activity [113].

Iodine is an ideal bioactive molecule, as it rapidly kills bacteria, fungi, mycobacteria, viruses, and spores. While the exact mechanism is unknown, it is known that iodine can penetrate into microorganisms and leads to cell death by attacking key groups of nucleotides, proteins, and fatty acids [114]. Aqueous solutions are often unstable, as there are at least seven iodine species that exist in a complex equilibrium; of those different species, molecular iodine (I_2) is mostly responsible for antimicrobial efficacy [115]. The problems with aqueous solutions were overcome when iodophors were developed with "iodine carriers" such as povidone–iodine complex. In addition, an electrolyte-based process has been used for iodine coating

of implants for limb salvage and megaendoprostheses. A prospective case series that followed 222 patients that received iodine coated implants were evaluated for post-operative infections, compromised status (bone tumor cases), degenerative disease, limb deformity, fractures, or non-unions with an average follow-up of 18.4 months. This series reported on a variety of implants, but included 10 hips and 4 knee prostheses. The author distinguished between "preventative" and "therapeutic" cases. One patient had a suspected iodine allergy, although all patients underwent preoperative patch testing for potential iodine allergy. Thyroid serum levels and thyroid function were evaluated and found to be unaffected. Mechanical implant failure occurred in two cases without further specification, and overall no implant loosening and good radiographical bone integration were reported. Of the 158 patients who received iodine coated implants preventatively for an immune compromised state in the setting of tumor resection, only three cases of acute infection (1.9%) were noted, of which all three were reportedly treated with DAIR without recurrence of infection at latest follow-up [116].

Synthetic Peptide Coatings

Antimicrobial peptides are an alternative strategy for infection prevention, as they do not rely on bacteria metabolic activity for efficacy. However, the native antimicrobial peptides suffer from problems of suboptimal efficacy and systemic toxicity which have been largely circumvented through the design of synthetic peptides. These engineered cationic amphipathic peptides (eCAPs) bind to bacteria then create pores in the bacterial membranes of gram-positive and -negative organisms. One eCAP WLBU2 synthetic peptide maximizes antimicrobial activity while causing minimal toxicity in mammalian cells, and decreases biofilm mass compared untreated implants in a surgical implant infection animal model. It has been shown to have in vivo efficacy in a murine model against *S. aureus*, and in vivo efficacy against clinical strains of *S. aureus*. Unlike antibiotics, the property of antimicrobial peptides cell lysis is independent of metabolism. However, concern remains for maintenance of bactericidal action of antimicrobial peptides in vivo with exposure to protease activity. However, there is optimism that this can be overcome with carefully designed D-enantiomers such as WLBU2 [117], but these materials are not yet ready for clinical use.

Barriers to Development/Implementation

Due to the low prevalence of PJI, most studies evaluating effective treatments to prevent PJI cannot achieve statistical significance without requiring prohibitively large clinical studies. Because of this, most proposed therapies will have to be tested in cases of established infection such as revision for established PJI. Studies such as these will allow insight into the effects of the treatments on colonization of the

implant surface and subsequent reestablishment of infection. However, as mouse models suggest that bacteria colonize the bone matrix during infection [118], it is possible that the bar may be much higher for prevention of reinfection in these cases.

There are a plethora of suggested coatings for antimicrobial implants, indwelling catheters, and other readily infected materials, such as the ventilator tubes associated with assisted respiration. Many of the materials/composites lack the mechanical robustness required for orthopedic applications. Nevertheless, mechanical considerations aside, the progress of these surfaces into small and then large animal models has been slow. We would suggest that several factors figure into this. Firstly, it is well-accepted that implant-associated infections are due to formation of biofilms [119] and biofilms formed in vitro may lack important components of those formed in a particular tissue environment, further hampered by the fact that there is no "accepted" model for a physiological biofilm. Secondly, antimicrobial efficacy is severely attenuated against biofilm bacteria so that antimicrobial activity needs to be determined against biofilm bacteria—either those forming on the antimicrobial surface or on adjacent material. In this context, it is not clear the degree of inhibition that needs to be attained to have a surface that is antimicrobial, in vivo. In our studies, our vancomycin-modified surfaces achieved between 1 and 3 logs (94–99.9%) inhibition [79, 80] and this inhibition was sufficient to markedly reduce infection in a large animal model [81]. However, with 10^{7-8} bacteria in a biofilm, these reductions only bring the numbers of ~10^5 bacteria, more than enough bacteria to propagate the infection. More animal studies should be performed to determine reasonable reductions in bacterial colonization by antimicrobial surfaces. Furthermore, animal models may not mimic human chronic wound care, as human patients have various underlying medical conditions that cannot be replicated in the animal model that complicate healing [120].

Safety and efficacy properties of developed antimicrobial surface modifications are often first tested in vitro which is limited in its translation to in vivo animal and human environments. For example, cytotoxicity data from isolated cells may be more pronounced than an in vivo system that contains three-dimensional matrices and vascular systems [121, 122]. Certainly, the financial costs from research and development of modified implants and the many stages of testing, is not insignificant. While the biomaterial market is worth over $300 billion US Dollars and is increasing 20% per year [123], it remains important to balance the clinical need with the cost of development.

Conclusion/Summary

Implant-associated infections remain a problem that is increasing due to the growing number of prostheses being implanted, and efforts toward prevention are a continued area of interest. Implant modification strategies may play a future role in both preventing bacterial adhesion and biofilm formation, and eradicating implant associated infections. Despite the current challenges facing translational medicine

development of antimicrobial surface technology, with mounting worldwide pressure to diminish the incidence of PJI, continued efforts will be made. It is not unrealistic to expect to see multifunctional smart surfaces in the field of orthopedics in the foreseeable future. Implant modification remains a growing area of research with limited clinical implementation, which highlights the need for further translational science in this field.

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