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Implant Surface Technologies to Prevent Surgical Site Infections in Spine Surgery

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ABSTRACT

Spine surgeries are occurring more frequently worldwide. Spinal implant infections are one of the most common complications of spine surgery, with a rate of 0.7% to 11.9%. These implant-related infections are a consequence of surface polymicrobial biofilm formation. New technologies to combat implant-related infections are being developed as their burden increases; however, none have reached the market stage in spine surgery. Conferring antimicrobial properties to biomaterials relies on either surface coating (physical, chemical, or combined) or surface modification (physical, chemical, or combined). Such treatment can also result in toxicity and the progression of antimicrobial resistance. This narrative review will discuss "late-stage" antimicrobial technologies (mostly validated in vivo) that use these techniques and may be incorporated onto spine implants to decrease the burden of implant-related health care–acquired infections (HAIs). Successfully reducing this burden will greatly improve the quality of life in spine surgery. Familiarity with upcoming surface technologies will help spine surgeons understand the anti-infective strategies designed to address the rapidly worsening challenge of implant-related health care–acquired infections.

New Technology

Keywords: antibacterial implant surface technology, antibacterial coatings, antibacterial surface modification, biofilm, implant-related infections

INTRODUCTION

Spine surgery procedures are rapidly increasing worldwide because they can reliably improve a patient's quality of life, even among elderly patients.[1] However, spinal implant infection is among the most common complications after spine surgery, with an overall reported rate of 0.7% to 11.9%.[2] In fact, infection rates may even reach 47% in reconstructive surgeries in orthopedic oncology on materials similar to those used in spine surgery.[3] One of the most recent strategies to prevent postoperative infections is the perioperative optimization of patients.[4] This strategy has obviously reached limits as the burden of obesity and diabetes is rapidly worsening and will become an unresolved public health issue in the coming decades.[5,6] Older age, combined with the rapidly rising incidence of diabetes and obesity, are risk factors for infection in patients with high functional demands.[7]

Health care-acquired infections (HAIs) can develop in acute, subacute, or chronic modality and frequently cause chronic pain and disability. HAIs in the United States are gradually becoming a silent public health crisis that accounted for an estimated 2,000,000 infections, 90,000 deaths, and US$4.5 billion extra cost in 1992.[8] Treating these postoperative infections carries an enormous personal and financial burden. The full cost of medical device-related implant infections in the United States alone was estimated at up to $27 billion in 2009.[9] These staggering figures naturally call for medical device manufacturers, hospital systems, insurers, and government agencies to join their efforts to curb the incidence and severity of HAIs, which are, to date, largely driven by biofilm growth on products sold by the medical device industry. Titanium is a common metal in spine surgery implants but also a known substrate for polymicrobial biofilm formation, which is a prime factor of implant-related infections (IRIs).[10] Biofilm is an exopolysaccharidic matrix harboring bacteria with reduced antibiotic sensitivity and poor mechanical accessibility.[11] The literature now abounds with evidence showing that biofilm formation is the culprit behind infection control failure (antibiotic therapy, irrigation, and debridement) for IRIs.[12] Biofilm formation on foreign bodies, such as spine implants, also explains why infections are harder to treat when hardware is present. Common strategies to fight infections, such as handwashing, antibiotic prophylaxis, and

intraoperative irrigation, fail to address the principal weakness of the anti-infective strategy: an inert and large metal or plastic surface for which bacteria and host cells will compete in a "race for the surface".[13] Therefore, numerous surface technologies have been developed to reduce the burden of biofilm on surgical implants.

Surface technologies are not necessarily synonymous with coatings. Conferring antimicrobial properties to biomaterials relies on either surface coatings (physical, chemical, or combined) or surface modification (physical, chemical, or combined). Indeed, surface modification involves changing the very structure of the substrate. Coatings imply an apposition or spreading of a substance onto a substrate, hence forming an additional layer on the surface.[14] Antimicrobial technologies may display one or several features. As biofilms have appeared to play a central role in the pathogenesis of implant-related surgical site infection (SSI), preventing bacterial adhesion, inhibiting proliferation, inhibiting biofilm formation, or even killing bacteria with antimicrobial and biocompatible coatings or surface modifications is rapidly becoming one of the most pressing objectives in spine surgery. Several technologies have already reached market stage, notably in cardiovascular surgery.[15] None, however, are available as of today in the US market for spine implants.

The ideal surface technology should deliver the following qualities: efficacy, safety (nontoxicity and osteoconductivity), stability, sterilizability, and scalability (raw material production and application process). Some believe that any antimicrobial surface technology will also present local and/or systemic toxicity to humans. This is especially the case for eluting technologies with a narrow efficacy-toxicity window such as silver ions, iodine, or antibiotics. Antimicrobial resistance is also a challenge that is encountered with most conventional antimicrobial technologies. Therefore, despite a plethora of studies demonstrating the in vitro and in vivo efficacies of antimicrobial surface technologies on orthopedic or spine implants, very few antimicrobial implants have reached the commercial stage worldwide. Given the maturity of the available technologies and the unacceptable morbidity and mortality of IRIs, it is not unreasonable to consider that in this decade, there will be significantly more spine implants commercialized worldwide and possibly in the United States.[16] In this narrative review, we describe technologies that can be considered "late-stage" (mostly validated in vivo) that may be incorporated onto spine implants and hopefully decrease the burden of implant-replated HAIs.

REVIEW OF ANTIMICROBIAL SURFACE TECHNOLOGIES

Surface Coatings

Antibiotics

Gentamicin, amoxicillin, vancomycin, tetracycline, rifampicin, and levofloxacin have been successfully coated onto titanium. Of these, gentamicin and vancomycin are the most frequently used. Gentamicin is an aminoglycoside bactericidal broad-spectrum antibiotic. Its mechanism of action involves inhibition of bacterial protein synthesis by binding to 30S ribosomes. Vancomycin is a glycopeptide antibiotic that inhibits cell wall synthesis.[17] When gentamicin-coated implants were used in a rat osteomyelitis model with *Staphylococcus aureus*, 1 out of 20 rats showed evidence of implant contamination at the conclusion of the study. The single contaminated implant displayed reduced bacterial growth compared to negative control implants with no antibiotics. These gentamicin-coated implants also resulted in a decrease in the osteomyelitis score compared to controls, suggesting that the coating played a vital role in infection prevention.[18]

In the European market, the EXPERT Tibial Nail PROtect (DePuy Synthes, Raynham, MA, USA) is an orthopedic trauma titanium alloy nail coated with gentamicin sulfate.[19] A retrospective case series from the UK Major Trauma Centre demonstrated reassuring results in preventing postimplant infections in high-risk patients with aseptic nonunions. Patel et al cautioned against high costs of this specific product in the treatment of established osteomyelitis. In this study, all gentamicin-coated nails used in the context of fracture-related infection revision surgery were removed due to persistent infection or the need for further stabilization. Instead, they suggest that the cost of this technology can potentially be offset in the case of high-risk primary fracture fixations and aseptic nonunion revisions.[19]

Additionally, a defensive antibacterial coating was developed by Novagenit (Mezzolombardo, Trentino-Alto Adige, Italy) and used for an antibiotic-loaded hydrogel for implant coating (point-of-care use).[20] Forster et al described antibiotic-coated external fixator pins marketed by Smith & Nephew (Memphis, Tennessee, USA) using the OrthoGuard AB, which is a gentamicin-coated polyurethane sleeve.[21] Antibiotic-based coatings most frequently require elution to either inhibit bacterial proliferation or kill bacteria at a distance from the implant. These strategies, however, raise significant concerns regarding antibiotic resistance over time. Moreover, given the minimal amounts of

antibiotics used for thin implant coatings compared with antibiotic-loaded beads or even with direct deposition of antibiotic powder, lack of efficacy is typically a more concerning clinical outcome than toxicity.

Metal Oxide–Based Coatings

Zimmer (Warsaw, IN, USA) commercialized an orthopedic trauma nail (Natural Nail) in Europe treated with a metal oxide–based coating comprising gold, silver, and palladium, produced by Bactiguard AB (Tullinge, Sweden).[22] This alloy coating enables a galvanic effect that reduces bacterial adhesion and possibly biofilm formation. To this date, no clinical data have reported a reduction in infection against controls using this implant.

While the quantities of heavy metals are claimed to be low, it is known that buildup of metallic oxide nanoparticles increases the risk of toxicity to surrounding tissues.[23] The degree of toxicity depends on the specific molecule, dosage, and surface area on an implant, among other factors.[24] Glazer et al found that while gold nanoparticles exhibit no evidence of organ dysfunction in a rabbit hepatic tumor model, there was a nonspecific inflammatory response associated with the treatment condition.[25] In the case of silver nanoparticles, several in vitro and in vivo studies have exhibited evidence of cytotoxicity, genotoxicity, neurotoxicity, and reproductive toxicity. Silver nanoparticles disrupt the mitochondrial respiratory chain causing reactive oxygen species to accumulate, damaging DNA and ultimately leading to cellular apoptosis and necrosis.[26] Palladium complexed with coumadin, a proven antipancreatic cancer agent, has been shown to decrease diastolic left ventricular pressure, mean blood pressure, heart rate, and contractility in isolated rat hearts.[27] The long-term stability of the present metal oxide–based coatings in the human body is difficult to guarantee, raising concerns about the toxicity and long-term impact of this technology on implants.

Silver

Silver has a broad-spectrum antibacterial effect and has been utilized in medicine for decades. Silver adversely affects many parts of the bacterial cell and its metabolism, including inhibition of ribosomes, ATP production, membrane destruction, and DNA replication. Another attribute of silver, supported by literature, is the long and sustained effect with the prevention of bacterial biofilm formation.[28] Silver has shown the potential to exhibit antimicrobial efficacy at low concentrations, even against highly resistant bacteria, serving to minimize local toxicity and osteoblast inhibition. As worldwide bacterial resistance grows, there is a paucity of data showing silver-containing compound resistance, suggesting that silver-coated implants remain an intriguing technology.[29]

Several in vivo trials, mostly conducted in Japan, have demonstrated usually low-to-intermediate antibacterial effects, from 0.35 to 1.4 $\log_{10}$ colony-forming unit reductions.[30,31] In 2021, the first silver-coated spinal implant was brought to market by Kyocera for use in Japan. Resitage, a thermal sprayed silver-hydroxyapatite lumbar interbody cage, is currently the center of an ongoing prospective multicenter clinical trial.[32] Kyocera has made supporting in vivo rat studies available in which they demonstrate biocompatibility and efficacy against methicillin-resistant *Staphylococcus aureus* (MRSA) and its biofilm.[33]

In addition, the authors of a 2017 clinical trial in Turkey using a titanium-silver nanoparticle-dipped screw-rod system reported no infections in 50 patients, and undetectable serum/urine silver levels over a 1-year study period.[34]

Historically, the MUTARS (Modular Universal Tumor And Revision System; implantcast, Buxtehude, Germany) and other silver ion–coated titanium alloy endoprostheses have been used in Europe for tumor orthopedic reconstruction due to their inherently high risk of postoperative SSIs (up to 47%).[3] The MUTARS system was first introduced in 1992. It is now used in Europe, Australia, and various Asian countries. Other companies producing megaprostheses and approved in the European Union include Agluna (Accentus Medical) and PorAg (Waldemar Link). In a recent meta-analysis by Fiore et al, there were 8 cases of argyria and no detectable cases of systemic toxicity.[35] Long-term studies are warranted since systemic symptoms could arise later in life.

Iodine

As iodine-coated implants have been gaining attention due to their potential to reduce the incidence of IRI,[36,37] it is imperative to investigate their effects in the context of spine surgery.

An iodine coating was proven to be effective in the treatment of postoperative infections in various orthopedic procedures that used titanium implants.[38] In fact, studies as early as 2011 have reported that iodine-supported titanium implants showed significantly lower bacterial adhesion in vitro compared to uncoated titanium implants. [36] While they were not placed in the spine, an in vivo study of iodine-coated implants proved

effective in their prevention of drug-resistant bacteria such as MRSA up to 8 weeks postoperatively in rats. Ueoka et al found that the use of an iodine coating on titanium implants was effective in preventing bacterial growth and reducing the risk of infection after implant surgery. [39] Iodine coatings helped prevent the attachment of MRSA, for which there is particular concern, in addition to *Pseudomonas aeruginosa*, methicillin-sensitive *Staphylococcus aureus*, and *Candida albicans*, showing promise as a preventive measure for early onset periprosthetic joint infection and in preventing IRIs in compromised hosts. [40,41] Particularly in the cases of IRI treatments in the setting of spine implants, there was a reinfection rate of 0% with the use of iodine-coated implants. [41] One drawback is the relatively lower bacterial reduction typically seen in these animal models.[36]

Out of the 6 studies conducted by the group Shirai and Tsuchiya centered in Japan that displayed the effectiveness of iodine-coated implants against microbial infections, there were no allergic reactions or thyroid malfunctions reported in the patients who underwent spinal surgery.[41] Considering that thyroid dysfunction is thought to occur with excessive iodine exposure[42] and that postoperative infections are a major complication of implants, such findings are encouraging. Overall, iodine-coated implants have the potential to reduce the need for further surgeries that result in increased health care costs. More extensive research is required specifically in spine implants to determine variables such as optimal iodine coating parameters. Overall, the literature suggests that iodine-coated spine surgery implants may potentially be an effective measure for reducing the risk of IRIs in surgical patients.

Chitosan

Chitosan is a biocompatible polysaccharide with antimicrobial properties conferred by quaternary ammonium groups at its surface. The mechanism of action is bacterial membrane perforation. It is primarily sourced from crustacean shell waste in the food processing industry (crab, prawns, and shrimp exoskeletons). As chitosan-derived polymers are biodegradable and hydrophilic, there have been numerous in vitro trials on titanium demonstrating its antibacterial activity. Across multiple studies, these coatings have reduced bacterial viability by over 60%.[43]

Chitosan can be used as a drug-eluting coating or covalently grafted on surfaces based on its degree of chemical modification. A recent in vivo model in spine surgery was used by Kodama et al to demonstrate the antibacterial efficacy of quaternized chitosan against bioluminescent *S aureus* using coated spine interbody mesh cages in rat tails. Treated cages demonstrated the inhibition of bacterial growth both during the observation period and in ex vivo quantification when measured with fluorescence intensity. Chitosan-based coatings also displayed improved postoperative healing through wound scoring and less bone destruction on microcomputed tomography analysis.[44] Other studies have proven that chitosan coatings combined with tobramycin are able to display long-term elution in acidic microenvironments, such as those triggered by infection.[45] Chitosan was also demonstrated to be nontoxic in bone-relevant models with greater osteointegration capacity.[46]

Quaternary Ammonium Polymers

Quaternary ammonium polymers (QAPs) are positively charged polymers containing polyatomic ions of the structure $[NR_4]^+$ with intrinsic broad-spectrum antimicrobial properties.[47] The positively charged quaternary ammonium groups trigger electrostatic interactions with negatively charged bacterial cell membranes, which cause their disruption and subsequent lysis and bacterial death.[48] In quaternary ammonium groups, the density of cationic charges is the primary driver of the biocidal effect of QAP-treated surfaces.[49] The advantage of high-density QAPs is that they are not known to generate any bacterial resistance as there are no published data to our knowledge on that specific topic.[50] The Massachusetts Institute of Technology team led by Dr. Klibanov published numerous studies during the past 2 decades on quaternized *N*,*N*-hexyl,methyl-polyethylenimine and *N*,*N*-dodecyl,methyl-polyethylenimine coated or painted on various substrates.[51,52] In vitro studies demonstrated their relative nontoxicity to human cells.[53,54]

Due to difficulties with covalent binding of *N*,*N*-hexyl,methyl-polyethylenimine on titanium, they devised a strategy to coat hydrophobic *N*,*N*-dodecyl,methyl-polyethylenimine on metals. In a sheep fracture model, Schaer et al demonstrated excellent osteoconductivity and antibacterial activity of coated locking compression titanium and stainless steel plates.[51]

Chlorhexidine-Based Coatings

Chlorhexidine is a cationic biguanide antimicrobial that has been used to mitigate infection on wound dressings and catheters.[55,56] The coatings may additionally include associated strategies to achieve slow release in order to claim extended durability (from days to

potentially weeks). Activ Point is a slow-release chlorhexidine device that has been used to prevent dental implant infections.[57] Wound dressings have also been devised that allow for subtoxic burst release of chlorhexidine over the span of a week. In a murine model, these chlorhexidine-functionalized dressings resulted in a 3 $\log_{10}$ reduction in the bacterial burden of the wound when compared to unmodified dressings.[58] Riool et al designed a chlorhexidine-releasing epoxy coating designed primarily for noncemented titanium implants under high mechanical stress. The coating functioned through burst release, with 80% occurring within the first 24 hours and the remaining taking place over the course of the following 4 days. In a subcutaneous infection murine model, it succeeded in preventing implant colonization with *S aureus*. In fact, the coating killed the inoculum in its entirety.[59]

Chlorhexidine is limited given its demonstrated dose- and time-dependent toxicity.[60] The compound has been shown to decrease protein synthesis in eukaryotic cells.[61] Additionally, it is reported that chlorhexidine inhibits DNA synthesis and cell proliferation and can exhibit cytotoxicity at concentrations 5 to 2400 times below what is used in clinical practice.[62]

Antiadhesive Coatings

Numerous parameters impact bacterial adhesion on surfaces. Surface charge, wettability, roughness, topography, and stiffness play important roles.[63]

Poly(ethylene glycol) (PEG)-based polymer coatings have long been the standard to confer antiadhesive properties to surfaces. Saldarriaga et al have demonstrated both in vitro and in vivo decreased biofilm formation on a cross-linked PEG-based polymer coating applied to silicone rubber samples in a subcutaneous infection mouse model.[64] Surfaces covered with PEG have been known to be biocompatible for more than 2 decades.[65]

Surface Modifications

Antibacterial Physical Surface Modification

Antibacterial physical surface modification can be achieved through roughening/polishing/texturing implant materials. Indeed, surface topography and roughness directly impact the ability of bacteria to adhere to surfaces. Increased surface roughness provides more surface area and thus substrate for bacteria to adhere to and proliferate on.[66] Furthermore, excessively smooth biomaterials can inhibit osteogenic differentiation.[67] Therefore, there are optimal surface patterns that improve the osteogenicity of materials while preventing bacterial adhesion.

Nanostructuring

Nanostructuring has gained significant traction due to its ease of deployment across the industry. In this approach, the bulk material is not modified, but its surface architecture is irreversibly changed. Machine processing significantly reduces the surface grain size, which confers enhanced mechanical and biomedical properties to titanium.[68] In vitro, nanostructured implants display some antimicrobial activity mainly by preventing bacterial adhesion.[69] Additionally, nanostructuring's improved osteointegration benefits were demonstrated in vivo using porous titanium.[70]

Nanotopographical designs have been carefully studied in order to be optimized for osteoconductivity and antiadhesive effect against bacteria. These parameters have been known since Puckett et al demonstrated that nanorough surfaces created by electron beam evaporation decreased the adhesion of *S aureus*, *Staphylococcus epidermidis*, and *P aeruginosa*, while nanotubular and nanorough surfaces produced by anodization increased it.[71] Such surfaces were proven to reduce bacterial counts on surfaces by typically <1 $\log_{10}$ (50%–90%) in vitro. Given the expectation that these technologies would underperform in vivo, most trials combined antimicrobial nanoparticles or eluting chemical compounds with nanostructuring in order to achieve significant bacterial reductions in vivo.[72]

Nanovis (Columbia City, IN, USA) has US Food and Drug Administration-approved nanostructuring for titanium and commercializes pedicle screws in the US market. No human data on potential infection reduction using such implants are available at this time.[71,73]

Chemical Surface Modification

Oxidation

Micro-arc oxidation confers antimicrobial properties to orthopedic implants, often through the incorporation of metallic particles or nanoparticles (silver, copper, and zinc) onto the material surface.[74 75]In this process, surfaces are exposed to an electrolyte and an increasing voltage is applied. A passivating, anodic film forms that leads to the growth of an oxide layer. As the applied voltage increases, parts of the oxide layer begin to break down. In these locations, the desired electrolyte is incorporated into the surface until the oxide layer is completely replaced. Calcium acetate and glycerophosphate disodium are often the base electrolytes used to confer antimicrobial properties to implant materials. These elements are associated with a

dose-dependent response; however, they are reported to be cytotoxic at high levels.[76]

Covalent Bonding of QAPs

QAPs can be covalently grafted to implant surfaces on the backbone of polymers. While antimicrobial resistance is not a major concern with QAPs,[50] a covalently bonded mechanism improves durability while reducing unnecessary leaching.

Recently, DeBogy Molecular (Battle Creek, MI, USA) produced a QAP named DBG-21 that was covalently grafted on titanium alloy discs. Treated discs achieved a 3.6 $\log_{10}$ reduction against adherent MRSA (biofilm) vs controls in a murine subcutaneous infection model at 7 days and 1.92 $\log_{10}$ reduction at 14 days.[77] The authors found no electrolyte disturbance or organ failure. Local peri-implant histopathology did not reveal differences between treated and control surfaces, which supports the biocompatibility of the treatment process.

Covalent Bonding of Antibiotics

Antibiotics such as vancomycin were successfully covalent bound to titanium and demonstrated an antimicrobial effect in vivo.[17] One of the limitations of grafting antibiotics on surfaces is steric hindrance. These molecules were designed to be active in solution and not grafted with a constrained orientation on surfaces. This may limit the efficacy of such compounds as their density is slow and the active sites are not necessarily available for bacterial contact.

Surface Treatment Processes for Surface Modification

While the majority of the literature on this topic describes processes that are lengthy (at least 24 hours), we briefly describe different possible methods of achieving surface technologies aimed at modifying either the surface topography or the chemistry of implants.

Surface Topography Processes

Acid etching is a process through which the metal surface is oxidized and selectively dissolved. This is commonly done with sulfuric acid; however, the process can involve other alternatives.[78] The artificially roughened surface enhances the biomechanical properties of implants by increasing the potential for interfacing and interlocking capability, which can also lead to improved bone formation.[79,80]

One of the most promising recent emerging methods to obtain nanometer-scale surfaces is discussed, namely, electrochemical anodizing leading to nanotubular structures with a controlled diameter in the range of 15 to 250 nm.[81]

Surface Coating or Surface Grafting Processes

Surface activation is required prior to covalent bonding of antimicrobial compounds. Activation is highly dependent on the combination of the chosen target material and its antimicrobial compound. It may consist of plasma treatment, electrolysis, immersion in acid, or even ultraviolet treatment.[14]

Deposition of antimicrobial compounds can be done through spraying, dip-coating, spin-coating, or drop-casting processes. Given the technology employed (coating vs grafting), the number of deposition steps may greatly vary and therefore impact treatment complexity. Generally speaking, uniform coatings will require a single-step deposition while more complex composite coatings will require several steps. Single-step covalent grafting requires the use of bifunctional compounds able to both graft on activated surfaces and display antimicrobial efficacy. Standard antimicrobial compounds grafted on surfaces most likely require multiple steps as a chemical linker needs to be attached to activated surfaces before linking the antimicrobial compound to the linker next.

Once deposited, antimicrobial compounds can be cured by heat (baking), ultraviolet treatment, or spontaneously through incorporation in a self-curing matrix. The required curing time varies based on the specific technology from minutes to several days, which evidently impacts scaling and further commercialization.

Thus, researchers are putting great emphasis on the development of materials with nanostructured surfaces that inhibit bacterial adhesion, biofilm formation, and, ultimately, bacterial infection, without local or systemic toxicity. Concerning chemical surface modifications, excellent antiadhesion properties have also been reported. Further study is needed to determine the adverse side effects of these technologies, such as problems with mechanical properties, toxicity, and interference with osseointegration. Furthermore, only a few physical/chemical surface modifications appear suitable for clinical use. These new technologies' in vivo efficacy and long-term effects on host cells and resistant bacteria are poorly understood. They need to be further investigated before clinical application and market introduction.

DISCUSSION

In the absence of mitigation measures aimed at controlling the formation of biofilm on medical devices, the unabated rise of IRIs may trigger policy changes from payers aimed at restricting implantations of medical devices to selected patients only. This shift has already started in multiple single-payer countries with socialized health care.[82] Also, the emergence of antibiotic-resistant bacterial strains has pushed for the development of nonselective antibacterial surface technologies and next-generation innovative solutions.[16] Most of these technologies, though interesting at the academic level, have not become mainstream in the industry due to concerns over safety (silver agents), transient efficacy (antibiotic-leaching compounds), or scalability (multistep processes or in situ polymerization, meaning that surface coatings or surface modifications are produced by a chemical reaction in contact with the implant surface, which is suboptimal for the industry).[31,83] An ideal antimicrobial surface protection should be able to support the following claims: prevention of IRIs, long-lasting protection of implant surfaces from late onset bacterial hematogenous spread, indirect decrease of surrounding tissue bacterial load by drastic implant biofilm inhibition, excellent local and systemic biocompatibility profile and stability (no release of potentially toxic compounds), sterilizability, scalability, and cost-effectiveness. We speculate that a permanent surface modification that would be both antibacterial and biocompatible would dramatically reduce the incidence of IRIs and make implant removals unnecessary in most cases.

Infection Is the Last Great Obstacle to Quality of Life Improvement in Spine Surgery

Historically, infection control in health care settings, especially when using implants, has been ensured by adhering to strict standards of collective hand hygiene, the frequent use of sterile personal protective equipment, prophylactic antibiotics, aseptic protocols, skin decontamination protocols, irrigation of surgical sites with saline and antiseptics, and clean wound care. However, these preventive measures do little to control the growth of bacterial biofilm on the surface of the implant itself (most often medical-grade titanium or composites).[4] Despite best efforts using such multimodal strategies, infection rates across numerous medical disciplines have failed to show any significant decrease for decades. With the popularization of medical implants, it rapidly appeared that IRIs presented a very complex treatment challenge compared to other non-IRIs. Indeed, further supporting the uniqueness of IRIs, there is ample evidence demonstrating the key role of biofilm formation on implants in infection control failure and infection recurrence. Biofilm provides shelter, nutrients, and resistance to eluting antimicrobials. With that in mind, it became obvious that the challenge laid at the surface of implants. As Nobel Prize Winer Wolfgang Pauli stated, "God made the bulk; surfaces were invented by the devil." [84] Also, most surface technologies that demonstrated high efficacy in vitro never achieved acceptable bacterial reductions in vivo. Of course, biological interactions that occur within live bodies are infinitely more complex than those that occur in test tubes. In addition to these shortcomings in terms of efficacy, the progressive elution or leaching of those coatings has always raised much concern from regulatory bodies due to their unknown effects in humans (eg, systemic acute and chronic toxicity, cancer, immune response).

The Unacceptable Lifelong Burden of Implant-Related Infections

In patients with multiple comorbidities, implants can turn infective at any time. Even years after implantation, surgeries and simple dental procedures can turn into life-threatening events such as bacterial endocarditis.[85]

The Challenge Lies at the Surface of the Implants

Many attempts have been made to minimize bacterial adhesion, inhibit biofilm formation, and provide effective bacterial killing. Biofilm formation has been shown to commence within a few hours after bacterial contamination of the implants.[11] In fact, the presence of an implant, and therefore bacterial biofilm, decreases the bacterial load threshold to produce a persistent infection by a factor of 1000 to 10,000. [86]

Regulatory Considerations

There is no unique regulatory pathway to have an antimicrobial treatment commercialized in spine surgery. In fact, the FDA does not have a predefined pathway for all antimicrobial surface technologies in orthopedics or spine surgery due to the absence of an existing approved antimicrobial product. Depending on the technical characteristics of the surface technology, the desired claims, and the existence of a predicate device or not, there will be a large scope of suitable pathways, ranging from device-specific pathways (de novo, 510 k, premarket approval or PMA), HDE

Table. Surface modification (grafting) and coating technologies for implants.

Technology	Development	Coatable	Graftable
Silver	In-market outside of the United States (Resitage, Kyocera, Kyoto Japan)[32]	x	
Other metal oxides	In-market (eg, Bactiguard, Tullinge Sweden)[22]	x	
Chlorhexidine	In-market for dental implants (eg, Activ Point, Altstatten Switzerland)[57]	x	x
Nanostructuring	In-market (eg, Nanovis, Columbia City, USA)[71]	NA	NA
Acid etching	In-market for dental implants (eg, Steri-Oss Etched, Zurich, Switzerland)[88]	NA	NA
Antibiotics	In-market outside of the United States (eg, The EXPERT Tibial Nail PROtect, Raynham, USA)[19]	x	x
Iodine	Clinical trials outside of the United States[41]	x	
Chitosan	In vivo[43]	x	x
Antiadhesive coatings	In vivo[64]	x	
Quaternary ammonium compounds	In vivo[77]	x	x
Oxidation	In vivo[75]	NA	NA

Abbreviation: NA, not applicable.

(humanitarian device exemption), and combination devices ("drug-device"). Naturally, as more experience is gained from the introduction of the first antimicrobial technologies in spine surgery, it is to be expected that a starting framework would be available to all applicants, thus facilitating commercialization. Implant-related HAI reduction claims before commercialization most likely will require a randomized controlled trial demonstrating a statistically significant reduction of IRIs in patients with antimicrobial implants vs those with nonantimicrobial implants. Because infections are relatively infrequent in degenerative spine surgery in healthy patients (1%), executing a well-powered study always proves to require an extremely high number of subjects in both arms, which represents a tremendous financial obstacle for most medical device companies. However, depending on the desired claims, a trial in high-risk patient populations such as complex spine reconstructions in cancer patients will certainly require lower numbers of included subjects. Naturally, as their immune system can be expected to be weakened, the treatment arm will most likely be at a significant disadvantage. According to Parvizi et al, there may be a need for a specific pathway for anti-infective devices, combining simpler preclinical data and strong postmarket real-world evidence obtained through strict surveillance.[87]

CONCLUSION

Numerous antimicrobial surface technologies for spine surgery materials, some of which are in the midst of regulatory review or already in-market outside the United States, have proven some level of in vivo safety and efficacy (Table). While spine surgeons are traditionally accustomed to biomechanics and biology concepts, some familiarity with upcoming surface technologies is helpful to understand the anti-infective strategies designed to address the rapidly worsening challenge of implanted-related HAIs.

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