

# On the Horizon From the ORS

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## Evolving Strategies To Prevent Implant-associated Infections

The consequences of implant-associated infection are significant and usually require revision surgery, with removal of the implant and prolonged antibiotic treatment. Various approaches to reduce the rate of infection have been investigated. Two recent strategies are (1) coating implants with antibiotics and (2) covalently attaching antimicrobial molecules onto the implant surface. The purpose of these bioactive surfaces is to disrupt the metabolic machinery of the microbes or to prevent bacterial adhesion to the implant and, consequently, the development of biofilm.

### Coating Implants

Finishing the surface of the implant with antimicrobial molecules or a repellent coating creates an implant surface inhospitable to bacterial attachment. The simplest example of this technology is the application of antibiotic coatings (without the use of a carrier) by spraying the metal implant with a methanol solution containing antibiotics, which is then allowed to air dry, leaving a coat of pure antibiotic powder on the device surface.<sup>1</sup> Another technique is adsorption of different antimicrobial molecules, such as chlorhexidine and polyhexamethylene biguanide, onto either unmodified electrically charged or gel-coated surfaces.<sup>2</sup> Biologic molecules, such as heparin or albumin, have also been used in a similar fashion and have been shown to interfere with the bacterial adhesive mechanisms.<sup>3</sup> Hydroxyapatite (HA) can be plasma-sprayed on metal implants and has demonstrated effectiveness

as an infection-resistant material.<sup>4</sup> Similarly, chitosan, a biopolymer derived from the shells of crustaceans or fungi, is a biodegradable, biocompatible material that has received much attention because of its bacteriostatic and osteoconductive properties; some success has been reported when chitosan is used as a coating on metal implants.<sup>5-7</sup>

An extensive list of bioactive molecules is currently being studied for the purpose of reducing bacterial attachment; many of these evolving strategies were discussed at the 2012 Orthopaedic Research Society annual meeting. Qu et al<sup>8</sup> reported that antibacterial sol-gel coatings containing 20% triclosan by weight, applied to grit-blasted surfaces of stainless steel cylindrical implants by dipping the implants in a sol solution, were effective in preventing infection surrounding external fixation pins for up to 4 weeks. Sinclair et al<sup>9</sup> used a polymer-released antimicrobial device coating: different concentrations of cationic steroidal antimicrobial-13 were combined with silicone polymer; implants were dip-coated and permitted to cure for 7 days. Following exposure to methicillin-resistant *Staphylococcus aureus*, there was a seven-log reduction in bacterial colonies within 2 hours for all treated groups. Using an osteomyelitis rat model, Lee et al<sup>10</sup> employed a double layer of poly(lactic-co-glycolic acid) encapsulation on antibiotic (cefuroxime)-coated titanium disks that extended antibiotic releasing time without burst release for up to 10 days. This coating technique

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was found to be effective against infection and was associated with less bone damage.

Silver nanoparticles have been shown to have antimicrobial properties in several applications. Lee and Murphy<sup>11</sup> evaluated the capability of achieving sustained release of silver nanoparticles that had been incorporated into HA,  $\beta$ -tricalcium phosphate, and bone-like mineral coatings. They were able to create silver particles on calcium phosphate surfaces and demonstrated release of these silver particles for up to 30 days, depending on the preparation conditions.

Jennings et al<sup>12</sup> attempted to optimize the release kinetics for a bone graft substitute, but their research may have ramifications regarding implant surfaces. They used *cis*-2-decenoic acid to prevent biofilm formation. *Cis*-2-decenoic acid is an unsaturated fatty acid messenger that is capable of inducing dispersion and inhibiting growth of biofilm colonies.<sup>13</sup>

Nelson et al<sup>14</sup> used erythromycin-impregnated strontium-doped calcium polyphosphate (SCPP) to completely inhibit bacterial growth for up to 14 days—even if the erythromycin was completely released from the scaffold within 2 days. The investigators noted that their results demonstrate that sufficient inhibition of bacterial growth at the initial stage is critical. Additionally, they found that coating this construct with additional poly(vinyl alcohol) coating actually resulted in increased infection

rates similar to that of control subjects. Thus, although SCPP may be effective in slowing down the release of antibiotic, it actually may introduce a new surface that supports infection.

### Covalent Binding

The purpose of another generation of bioactive implants is the design of surfaces that are permanently rendered antimicrobial by covalent attachment of antibiotics or custom-designed bactericidal peptides. As such, the active molecules are not allowed to elude off the surface of the implant, thus decreasing possible local and systemic toxicity and circumventing the problem of inconsistent elution characteristics while providing long-lasting protection. Parvizi et al<sup>15</sup> described a method that allows for the chemical modification of titanium alloys for the covalent attachment of vancomycin and other bioactive molecules. Once the antibiotic is tethered on the surface, via peptide linkers, it is rendered antimicrobial<sup>16-18</sup> and remains active for long periods of time.<sup>19</sup> Also, its biocompatibility is not affected.<sup>20</sup> This technology is very versatile, and we<sup>21</sup> later demonstrated that it can also be very effectively applied to biologic materials, such as bone allografts.<sup>22,23</sup> Similarly, Petzold et al<sup>24</sup> described a covalent coating of titanium surfaces with eicosapentaenoic acid by ultraviolet radiation and demonstrated some efficacy in de-

creasing the survival of bacteria. Others have used similar methods to chemically immobilize bioactive peptides on other nonmetal surfaces, such as glass and silicon.<sup>25-27</sup>

### Challenges

It is clear that significant strides are being made in our understanding of implant-associated infections and in the technologic approaches to prevent or treat them, such as advances in implant coating and the development of new, more complex bioactive molecules. Nevertheless, several major challenges remain to be overcome before these approaches reach mainstream clinical acceptance. These challenges include, but are not limited to, improving our diagnostic capabilities, overcoming resistance to chronic antibiotic therapies, and introducing these new technologies in a cost-effective manner.

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