G54: Does the use of povidone-iodine-coated orthopaedic implants reduce the incidence of surgical site infection (SSI)/periprosthetic joint infection (PJI)?

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Response/Recommendation:
Yes. Based on the limited studies available, iodine-coated orthopaedic implants appear to be effective in reducing the risk of surgical site infection (SSI)/periprosthetic joint infection (PJI) after arthroplasty.

Level of Evidence: Limited

Delegate Vote:

Rationale:

Periprosthetic joint infection (PJI) most commonly occurs via the development of a biofilm and bacterial adherence to implant surfaces. A biofilm is the formation of pathogens and microbial cells that form strong interactions with an extracellular matrix, replete with polysaccharides, biopolymers, proteins, teichoic acids, lipids, and extracellular DNA, to survive and propagate. In order to attach to arthroplasty components, biofilm undergoes a four-stage process: cellular adhesion, cellular aggregation, biofilm maturation, and cellular detachment.

In the first stage of biofilm formation, bacteria attaches to the biomaterial surface in a reversible manner.[1–3] It is reversible due to the characteristics of the external environment, including pH, composition, and temperature, among others.[4,5] If successful, these adhesions can propagate to form microcolonies.[6,7] Once microcolonies have been established, the bacterial colony unit attracts more nutrients and spreads toward the periphery of the biomaterial device.[8–11] As the colony gains more nutrients and spreads further, the infection naturally worsens until it experiences environmental stresses that prevent further growth and propagation.

Several decades ago, Anthony Gristina developed the ‘race for the surface’ hypothesis which describes how the colonization on the surface of a prosthetic device or implant within the human body is a ‘race’ between microbes and host cells.[12] Whichever group of cells inhabits the implant surface first is likely to remain there in perpetuity. This theory helps us understand not only which environments and characteristics are likely to allow for biofilm formation, but also helps us to understand ways in which to thwart the colonization of pathogens on the surface of prosthetic components.

The type of implant surface can substantially impact the rate and severity with which a PJI can occur. The type of implant surface is divided into two broad categories – antibacterial coatings and modification of the surface itself. Within antibacterial coatings, there are both active and passive coatings. Active coatings release antibacterial agents to destroy bacteria whereas passive coatings prevent bacteria from attaching or propagating on the biomaterial surface. Modification

of the surface itself is rarely used as it can impact the ability of the prosthesis to integrate within host tissues.

Active coatings on arthroplasty components are geared toward killing bacteria and other microorganisms that can form biofilms.[13] Active coatings can further be subdivided into contact-based and release-based mechanisms.[14] Contact-based active coatings create adhesions to surfaces of specific antibacterial agents which aids in the killing of those microorganisms. These materials are often synthetic such as quaternary ammonium compounds which exert their bactericidal capabilities via a charge imbalance.[15] Specifically, this means that the positively charged calcium and magnesium compounds preferentially bind to the negatively charged phospholipid membrane of the bacteria on the outer surface of the biofilm. This covalent bond disrupts the cellular membrane of the microorganism and leads to bacterial cell death. Natural quaternary ammonium compounds are also available such as antimicrobial peptides (AMP) and AME bactericidal agents.[16–20] The AMP and AMEs are groups of peptides that can initiate a series of chemical reactions leading to bacterial cell death. Onaizi et al. evaluated the use of AMPs for antibacterial coatings of medical implants and demonstrated that the use of AMPs has a broad range of antimicrobial killing potential.[21]

Release-based mechanisms are described as systems with carriers for bactericidal agents that can be eluted over time in a controlled manner. These coatings can be created with hydrogels, ceramics, or polyelectrolyte multilayers. A new technology has incorporated silver cations and anions with highly oxidized iodine.[22] Another new technology incorporates low molecular weight therapeutic agents composed of a polymeric matrix that can store multiple antimicrobial drugs.[23] Furthermore, antimicrobial agents, such as antibiotics, can be ‘wrapped’ in release-based mechanisms for scheduled elution and delivery to a biofilm. For example, an antibacterial device, TYRX, is an absorbable antibacterial wrap that can deliver antibiotics to a site of biofilm formation. In a study of 500 high-risk cardiac patients, this wrap was able to deliver minocycline and rifampin and reduce infection by up to 90% compared to a control group.[24]

Passive coatings do not release bactericidal agents to the biofilm, but rather prevent bacterial adhesion to prosthetic devices and components. An example of passive coating can be found in ultraviolet irradiation of titanium dioxide which decreases bacterial adhesion without impacting any effect on osseointegration.[25] Polymer coatings can also be applied as a coating to orthopaedic implants to inhibit bacterial adhesion. For example, hydrophilic polymethacrylic acid, polyethylene oxide, and protein-resistant polyethylene glycol all have shown the ability to reduce bacterial adhesion in biofilm formation.[26,27] Other organic compounds, such as albumin[28], hydrogels[29–31], and silicone-nitride ceramics[32,33], have shown efficacy in the literature in reducing rates of postoperative infection in orthopaedic procedures.

Iodine-coated implants have recently gained popularity as a way to reduce the rates of PJI and reoperation following arthroplasty procedures. Iodine is abundant in the thyroid and one of the heaviest elements. It is also commonly paired with povidone to form povidone-iodine which is a widely used antiseptic in operating rooms worldwide. Iodine generally does not incur any antibacterial resistance, which makes it an appealing antiseptic and coating option for implants. Iodine-coated prostheses generally consist of a povidone-iodine electrolyte as the coating combined with an anodic oxide film.

Iodine is generally treated with Ti-6Al-4 V titanium implants with success in reducing rates of infection. For example, Inoue et al. demonstrated in an *in vivo* analysis that the mean viable bacterial activity was significantly lower on iodine-coated titanium surfaces versus control surfaces.[34] Another study validated the use of iodine-coated external fixation pins in rabbit models which found that pins coated with iodine were more effective at reducing signs of infection and inflammation of the pins[35]. Additionally, this study found that the osteoconductivity of the pins was enhanced in the presence of an iodine coat. Miwa et al. also evaluated the incidence of infection following the use of iodine coated knee arthroplasty implants for malignant bone tumor resection.[36] Among 302 patients, they found that 33 (10.9%) patients developed a SSI. They also concluded that the use of an iodine coated implant was associated with a reduced risk of PJI compared to non-coated implants (odds ratio: 0.29; $p = 0.039$).

There are several prospective cohort studies that have analyzed the rate of infection following the use of iodine coated prostheses compared to non-coated implants. A prospective clinical study on the use of iodine-coated implants found that the infection rate for these implants was low, even for immunocompromised hosts, which made the postoperative infection less severe and more manageable.[37] Another study analyzed the impact iodine coated mega-prostheses may have in the prevention and treatment of PJI.[37] Between July 2008 and May 2013, 47 patients with malignant bone tumors or septic arthritis with osteomyelitis were treated with iodine coated mega-prostheses. The authors found that, after 30.1 months follow-up on average, only one patient out of 47 had a SSI which was treated with antibiotics alone. Moreover, thyroid tests concluded that there were no abnormalities associated with thyroid function in any patient. Finally, Kabata et al. performed a clinical trial assessing how the use of iodine-supported implants impact the infection rates following complex primary, revision, or infected arthroplasties.[38] After 33 months, none of the 30 joints among the 28 patients were found to have clinical evidence of an infection and thyroid function remained stable. Moreover, no evidence of loosening or hardware complications were detected within the follow-up period. These data may suggest that iodine-coated implants are a reasonable option to prevent and treat cases of infected arthroplasty.

As previously mentioned, cytotoxicity is generally a concern with the use of these coated prosthetic components – if they are harmful to the adhesion and propagation of bacteria and biofilm, they may also be harmful to host cells and osseointegration. Studies like Ueoka et al., in which they evaluated the antibacterial activity of iodine-coated titanium implants in a rat model and demonstrated the reduction in bacterial cell viability and survival, still leave unanswered questions regarding the toxicity and osseointegration of such implants.[39,40] Copper and zinc coatings have substantial potential in the reduction of bacterial adhesion and biofilm formation but are not devoid of cytotoxicity to host cells and osseointegration.[41–43]

In conclusion, there are several options for prosthetic coating to reduce the risk of biofilm formation and PJI. Especially with the advent and popularization of silver nanoparticles and iodine-coated agents, the appropriate concentration can have excellent results in the reduction of postoperative infection. Nevertheless, these antibacterial coatings do not come without their limitations. The risk of cytotoxicity and poor osseointegration, not to mention antibacterial resistance, loom large as recognizable limitations from their widespread use. As we continue to

search for ways to mitigate and prevent PJI and postoperative infection following arthroplasty, biomaterials and antibacterial coatings on prosthetic devices should continue to be studied and optimized for regular clinical use.

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