ICM 2025 Question B32: "Are there any physical non-cytotoxic methods that can be utilized to disrupt and destroy biofilm in orthopedic infections?"

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RESPONSE/RECOMMENDATION: Yes, photodynamic therapy, ultrasound treatment, and electrical treatment such as induction heating have been widely studied as effective physical methods to disrupt and destroy biofilms in orthopedic infections, and various strategies to reduce their cytotoxicity have also been investigated. However, Level 1 evidence demonstrating the efficacy and safety of the treatments in clinical trials does not exist and needs to be addressed in the future.

LEVEL OF EVIDENCE: Weak

DELEGATE VOTE: Agree: [% vote], Disagree: [%], Abstain: [%]

RATIONALE: Various physical methods have been explored as potential alternatives antibiotic drug treatments for biofilm eradication. To answer this question, we conducted a systematic review, using specific MESH terms developed by librarians, to identify all relevant publications in the Medline and Embase databases, covering studies published up to November 2024. Search Results yielded 889 publications in English language. Two of the authors went through title and abstract screening and discrepant results were adjudicated by a third person. Then 82 full articles were reviewed. Finally, 69 articles were included in this systematic review. The treatment methods included 14 articles related to photodynamic therapy, 21 articles related to ultrasound, 28 articles related to electric treatment, and 6 articles related to other methods. Below is a summary of the findings.

1. **Photodynamic therapy (PDT)** is a treatment modality that involves the systemic or local application of various photosensitizers, followed by exposure to light of specific wavelengths and the presence of oxygen and other factors, to eradicate tumors or bacteria.[1 2] This method transfers energy from the photosensitizer (PS) to oxygen through photoexcitation, generating reactive oxygen species (ROS), which dissolve bacterial cell membranes and inactivate proteins, thereby demonstrating efficacy against biofilm infections.[3] Various novel and existing reagents have been applied as PS, and it has been reported that PS combined with bactericidal dyes or detergents exhibits a potent effect on biofilms upon photoexcitation.[4; 5] Nanoparticles such as titanium dioxide (TiO_2) nanoparticles and TiO_2 nanorods have demonstrated bactericidal effects against biofilms and bacteria when exposed to UV or near-infrared light.[6-9] Additionally, it has been reported in in-vitro studies and rat models that combining photothermal therapy (PTT) and PDT using red phosphorus and near-infrared light can effectively disrupt biofilms without causing damage to normal tissues.[10] These technologies have also been applied to implant coatings, demonstrating potential for preventive effects against implant-associated infections.[11-13] The advantages of antibacterial PDT include the absence of concerns regarding antibiotic resistance, the ability to selectively target bacteria using various PS with specific properties, minimal damage to host tissues, relatively rapid bactericidal activity (within 30 minutes), effectiveness against both Gram-negative and Gram-positive bacteria as well as fungi, and efficacy in treating wound infections with compromised blood flow.[14] On the other hand, the

limitations of these technologies include the necessity for surgical intervention to apply PS to the biofilm surrounding implants and to activate them using a light source. Additionally, there are no practical examples of their application in clinical trials, and their effectiveness in real-world clinical settings has yet to be validated.

2. **Ultrasound (US) treatment** has been widely reported as a useful tool for identifying causative pathogens in the diagnosis of periprosthetic joint infections (PJI). Additionally, it is a physical technology that has shown promising utility in the treatment of biofilms, with its effectiveness being increasingly documented.[15] The effect of US on biofilms derives from its ability to deliver energy either directly from the device or through the skin, transferring it to biological tissues or metallic surfaces.[16] US is generally classified based on its frequency, with frequencies above 1 MHz referred to as high-frequency US and those below 500 kHz as low-frequency US. High-frequency US is characterized by its ability to deliver energy with high precision to a targeted area. This property enables the generation of thermal energy and the production of as nanoparticles in liquids. In the treatment of orthopedic infections, technologies have been reported that combine high-intensity focused US (HIFU)**,** which generates thermal energy, with low-temperature-sensitive liposomes (LTSL) for antibiotic delivery[17]. Additionally, bactericidal techniques utilizing nanoparticles generated by HIFU have also been documented.[18 19] On the other hand, low-frequency US, characterized by its lower frequency and ability to deliver energy over a wide area, is prone to inducing cavitation (the formation and collapse of bubbles) in liquids. Leveraging this property, it has been suggested that low-frequency US can enhance the transport rate of antimicrobial agents to bacteria, thereby increasing the efficacy of antibiotics.[20] Furthermore, several studies have reported the bactericidal effects of combining low-frequency US with vancomycin or gentamicin. [21 20 22; 23] The use of piezoelectric ultrasonic scalpels and the combination of low-intensity pulsed US (LIPUS) with povidone-iodine have also been demonstrated to be effective in bacterial eradication.[24; 25] Pulse lavage, which is frequently used in orthopedic surgeries, has been reported to be ineffective against biofilms when used alone.[26] However, studies have shown that its combination with US can effectively reduce biofilm formation. [27] Furthermore, it has been reported that cavitation induced by low-frequency US can inhibit the expression of the *icaAD* and *mecA* genes in methicillin-resistant bacterial strains, while also enhancing the activity of human β-defensin-3.[28 29] Su et al proposed a novel therapeutic strategy called spatiotemporal sono-metalloimmunotherapy utilizing MnO_2-hydrangea nanoparticles as metalloantibiotics. The combination of US with such sonosensitizers in sonodynamic therapy has shown promise for the effective disruption of implant-associated biofilms, highlighting its potential utility in this field.[30] On the other hand, several in vitro studies have reported that US itself does not possess intrinsic antibacterial effects, and bacteria may remain even after the disruption of biofilms.[31-34] Additionally, sonication has been associated with adverse effects such as damage to articular cartilage and implants. [35]Therefore, for future clinical applications, further investigation is required to evaluate not only its efficacy against biofilms but also its safety profile.

3. **Electrical treatment:** The generation of electric currents and electric fields is known to strongly influence the growth and death of both prokaryotic and eukaryotic cells.[36] These effects also extend significantly to the disruption of biofilms and the regulation of bacterial growth and death.[37] van der Borden et al. reported that the application of direct current (DC) for six hours successfully caused the detachment of biofilms from stainless steel surfaces, suggesting that this method could serve as an effective approach for the treatment of biofilm-associated infections.[38] Subsequently, Brinkman et al. reported that the bactericidal effect of direct current (DC) within

biofilms, known as the electricidal effect**,** is at least partially mediated by the production of reactive oxygen species (ROS), which induce bacterial death within the biofilm.[39] Direct current (DC) electric treatment has been shown to be effective against both Gram-positive and Gram-negative bacteria. It has also been reported that anodizing metal surfaces to form a nanotube structure and applying electrical stimulation can reduce biofilm formation.[40]Additionally, it has been confirmed to enhance the efficacy of antibiotics and disrupt biofilms effectively.[41-43] This combination of DC and antibiotics, referred to as the "bioelectric effect," has been shown to efficiently promote the disruption of biofilms.[36] On the other hand, some studies have reported limited effectiveness for specific combinations of bacteria and antibiotics (e.g., vancomycin against *Staphylococcus epidermidis* [44]or piperacillin against *Pseudomonas aeruginosa*[45]). This highlights the need for the development of protocols tailored to specific bacterial species and antimicrobial therapies.

Ehrensberger et al. reported that a technique called Cathodic Voltage-Controlled Electrical Stimulation (CVCES) is effective in treating biofilms on titanium surfaces and within bone.[39] This method differs from conventional DC in that it controls voltage on the cathodic side. Studies conducted in vitro and in rodent models have demonstrated that it does not cause damage to surrounding tissues, exhibits synergistic effects with antibiotics and povidone-iodine, and holds promise as a technology for treating implant-associated infections, including periprosthetic joint infections (PJI).[46-52] On the other hand, it has been reported that this method is ineffective against biofilms on bone cement, and its antibacterial efficacy on non-metallic materials remains a challenge for future research.[51] Electric treatment has various applications. In a study by Taira et al., it was observed that conducting multiple short-duration electrical interventions of one minute each effectively removed *S. aureus* biofilms formed on titanium rings.[53] Additionally, in a study by Tamimi et al., a device equipped with bipolar electrodes capable of generating different waveforms was developed to investigate the bioelectric effect on biofilms formed on total knee arthroplasty (TKA) implants. Their findings demonstrated the effectiveness of this approach in biofilm removal.[54] Wang et al. designed a prototype device for wireless DC treatment using electromagnetic induction generated remotely via a wireless power source. They reported effective biofilm eradication in both ex vivo and in vivo models.[55]

Electromagnetic fields are also gaining attention as a novel therapeutic approach that leverages the conductive properties of implant materials. It has been reported that bacterial biofilms exhibit reduced metabolic activity when exposed to static electromagnetic fields generated by direct current (DC) or dynamic electromagnetic fields generated by alternating current (AC). Furthermore, the combination of electromagnetic fields with magnetic nanoparticles or antibiotics has been shown to enable effective biofilm eradication.[56; 57] The application of electrical currents to metallic implants generates magnetic fields, and the utilization of these electromagnetic fields, along with the associated thermal effects, has emerged as a promising non-invasive therapeutic strategy for targeting biofilms on implant surfaces. The efficacy of this approach has been substantiated through both in vitro experiments and studies conducted on large animal models.[58-61] Pijls et al. reported that non-contact induction heating (NCIH) of metal implants using pulsed electromagnetic fields (PEMF) is an emerging and promising field that could play a significant role in the multimodal treatment of PJI when combined with other therapies.[60; 61] NCIH uses PEMFs or alternating magnetic fields (AMF) to cause thermal damage to the bacteria within the biofilm on the metal implant surface without directly heating tissue.[59-61] While there are not yet any clinical studies published, the in vitro results are very promising: multiple in vitro studies have shown a reduced bacterial load due to the NCIH on metal implants, with some even demonstrating complete eradication of mature biofilms and others showing a synergistic effect with other antimicrobial compound.[59-61] Furthermore, Gilotra reported that capacitive coupling reduced biofilms on implant surfaces in a spinal infection animal model through a non-invasive approach.[58] These heating methods have been shown to significantly reduce bacterial counts at temperatures exceeding 60°C; however, there is concern about potential tissue damage caused by the heat.[57] To address these concerns, several strategies have been proposed to enhance safety and minimize heat-related damage. These include segmental heating techniques designed to target specific regions and prevent uneven heating associated with irregular implant geometries, the incorporation of antibiotics or N-acetylcysteine (NAC) to achieve therapeutic efficacy at lower temperatures, and the development of advanced acoustic sensors for real-time monitoring of excessive heat generation at the implant-tissue interface. These approaches collectively aim to mitigate potential risks and optimize the safety profile of this therapeutic intervention.[60-63] Therapies utilizing electromagnetic fields, including induction heating combined with antibiotics, are anticipated to serve as non-invasive and effective methods for the removal of biofilms on implants. With further advancements in safety-enhancing technologies and research aimed at clinical applications, this approach holds promise for future application in the treatment of implant-related infections.

4. **Other physical methods:** Plasma sterilization techniques for orthopedic implant infections have been reported, including a dielectric-barrier discharge method that utilizes the surface of joint implants as electrodes for sterilization, and a technology known as Floating Electrode Dielectric Barrier Discharge, which employs a micro-pulse design to maintain surface temperatures below 40°C.[64; 65] In particular, non-thermal inductive discharge plasma treatment holds significant potential for the comprehensive removal of extensive biofilms attached to implants, making it a promising approach for applications in the treatment of implant-related infections.[51; 66]Additionally, the use of solid-state lasers, such as erbium: yttrium-aluminum-garnet lasers.[67], the freezing nitrogen ethanol composite, commonly used in tumor surgeries[68], and the extracorporeal shock wave therapy has been shown to be effective in disrupting biofilms around implants in both in vitro and in vivo studies.[67; 69]

In summary, various physical sterilization methods have demonstrated the ability to directly disrupt biofilms or eliminate bacteria, as well as indirectly enhance the delivery of antibiotics and other therapeutic agents to infection sites. These innovative approaches hold significant potential for application in the treatment of orthopaedic infections. However, achieving substantial bactericidal and biofilm eradicating effects typically requires surpassing specific energy thresholds, and to date, no clinical trials have validated these methods for their safety and efficacy in humans. While most physical methods discussed in this systematic review have demonstrated safety in vitro or in vivo, developing standardized protocols for clinical implementation and ensuring their safety in human applications remains a critical challenge in the field that must be addressed through future research and development.

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