ICM 2025 Question B19: "Does delivery of local antibiotics have any influence in removal of biofilm in orthopedic infections?"

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RESPONSE/RECOMMENDATION: Unknown. Although the potential role of local delivery of antibiotics in combatting biofilm has been explored in some studies, due to lack of high-level evidence, we cannot provide either a supportive or oppositional recommendation on this topic.

LEVEL OF EVIDENCE: Weak

DELEGATE VOTE: Agree: [37/94% vote], Disagree: [1/3%], Abstain: [1/3%]

RATIONALE: Implant-associated infection is one of the most devastating complications following orthopedic surgeries [1]. In such infections, biofilm formation on the implant surface plays a critical role by providing bacteria with a protective environment that allows them to evade host immunity and antibiotic treatment [2]. Once a biofilm formation is completed, it is widely accepted among orthopedic surgeons that the infection becomes highly intractable, often necessitating additional surgical interventions such as debridement, irrigation and drainage, or implant removal [3].

After biofilm formation, the antibiotic concentration required to address the infection increases dramatically compared to the minimum inhibitory concentration (MIC), the minimum concentration necessary to eradicate a biofilm is termed the minimum biofilm eradication concentration (MBEC) [4,5]. Since MBEC values are extraordinarily higher than MIC values, achieving such concentrations through systemic administration is nearly impossible.

In this manuscript, we examine whether biofilms on implant surfaces can be effectively removed through local antibiotic administration, with evidence drawn from 1) *in vitro* studies, 2) *in vivo* animal studies, and 3) *in vivo* human studies. To address this, a comprehensive literature search of the PubMed, Scopus and CINAHL databases, was conducted using MeSH terms developed by librarians. The search initially identifying 252 potentially relevant unique studies. These publications were, screened by two independent reviewers, and of which 83 final publications were selected for in-depth review and 28 included for final evaluation. It should be noted that, this manuscript focuses on whether antimicrobial agents can remove biofilms that have formed, and therefore excludes papers on whether antimicrobial agents can prevent or inhibit biofilm formation. Even in the absence of direct evidence of biofilm removal, the eradication of bacteria from biofilms or clinical cures achieved with implant retention were considered indirect indications of biofilm removal.

Among the eight extracted in vitro studies, four focused solely on the inhibition of biofilm formation [6–9]. Additionally, one study focused on biofilm removal but investigated the effects of antiseptic solutions, such as Povidone-iodine, instead of antibiotics [10]. Three studies evaluated the effect of antibiotics on biofilm removal [11–13]. In all three studies evaluating biofilm removal, biofilms were formed in vitro, while one study also included an in vivo biofilm model formed on a rat femur. All three studies utilized gentamicin in their experiments, and two studies also evaluated vancomycin. Regarding the bacteria responsible for biofilm formation,

Staphylococcus aureus (*S. aureus*) was used in all studies. Dall et al. investigated the recovery of *S. aureus* from biofilms formed over 24 hours using the dissolvable bead biofilm assay [11]. The MBEC was determined for commonly used antimicrobial agents and combination regimens, including gentamicin, daptomycin, ciprofloxacin, vancomycin, rifampicin, clindamycin, and linezolid. Among these, only gentamicin and daptomycin were found to be effective. The study also reported on effective and ineffective combinations of antibiotics in enhancing or diminishing the activity of gentamicin or daptomycin. Okae et al. examined the effects of locally administered doses of gentamicin, vancomycin, and cefazolin, with or without systemic doses of vancomycin and rifampicin, against *S. aureus* in both *in vitro* and *in vivo* biofilms formed on stainless steel implants [13]. In the in vivo biofilm model, biofilms were formed on implant surfaces using a rat femoral osteomyelitis model over 3 and 14 days. In a CFU recovery assay, MBEC values for in vivo biofilms were higher than those for in vitro biofilms. Moreover, MBEC values for 14-day biofilms were higher than those for 3-day biofilms, indicating that the complexity and maturation of biofilms increase the concentration of antibiotics required to eliminate bacteria within the biofilm. Sekar et al. described the synergistic antibacterial effects of gentamicin and ketorolac in reducing *S. aureus* and *S. epidermidis* in in vitro biofilms formed over 6 and 24 hours [12]. The effects of these drugs were assessed using CFU assays, live-dead staining, and SEM. Notably, the study highlighted that the longer a biofilm matures, the more challenging its removal becomes. Conversely, prolonged exposure of biofilms to antibiotics resulted in greater efficacy. This aspect is supported by the work of Castaneda et al. who reported that MBEC is lower when local antimicrobial exposure time is longer [14]. In addition, Moore et al. found that antibiotic-loaded calcium sulfate beads containing vancomycin and tobramycin may be more effective in treating multispecies biofilms than single antibiotic alone [15].

Nine *in vivo* animal studies were reviewed. Five studies were outside the scope of this review [16–20] . One study established an implant-related infection model and performed revision surgery with local antibiotics treatment, where the biofilm on the implant was surgically removed [21]. Another study evaluated biofilm removal with implant retain, but specifically focused on the effects of protease treatment [22]. Two studies initiated local antimicrobial treatment after biofilm formation while retaining the implant [23,24]. Regarding experimental animals, both studies used rats as their models. For bacterial selection to induce infection, both studies employed *S. aureus.* Penn-Barwell described an implant-stabilized segmental defect rat model contaminated with *S. aureus* [24]. They used local administration of Bismuth thiol in hydrogel with systemic cefazolin, and showed decreased bacterial recovery at 14 days. However, although a 6-hour interval was allowed for bacterial biofilm establishment prior to initiating local treatment, this duration may have been insufficient for robust biofilm formation. Ashar et al. initiated treatment 10 days post-infection in a femoral canal implant model inoculated with methicillin-resistant *S. aureus* [23] . They employed a combination of ciprofloxacin-laden low-temperature-sensitive liposomes and local high-intensity focused ultrasound. Although complete eradication was not achieved, the treatment significantly reduced CFUs. Notably, they presented SEM images showing a reduction in bacterial burden and biofilm formation compared to other treatment groups.

Eleven human *in vivo* studies were reviewed, five studies were either prevention studies, involved no residual implant, did not address implant-related infections, or were methodological

papers without presenting results [25–29] . Six of which focused on the treatment of established biofilm-related implant infections using local antibiotic therapy while retaining the implant [30–35]. All six studies were case series, with the number of patients ranging from 2 to 10. Surgical interventions commonly included debridement, irrigation, continuous local antibiotic perfusion (CLAP) or local antibiotic delivery, replacement of modular components, and negative pressure wound therapy (NPWT), with a primary emphasis on infection control and implant preservation. The studies targeted a wide range of pathogens, including methicillin-resistant *S. aureus*, methicillin-sensitive *S. aureus*, *Cutibacterium acnes*, *Pseudomonas aeruginosa*, and other resistant bacterial strains. Local antibiotic perfusion therapies predominantly utilized gentamicin. The outcomes demonstrated effective infection control. Implant preservation was mostly achieved. Although direct evidence of biofilm removal was not provided, the successful retention of implants may indirectly indicate the potential of local antibiotic therapies to eradicate bacteria within biofilms, a critical requirement for curing implant-associated infections. Beyond the studies included in the review, numerous other reports/ case series have demonstrated the successful local administration of antibiotics, highlighting the potential efficacy of local antibiotic therapies [36]. Indelli et al. also reported the successful outcomes of a multimodal strategy for the salvage of acutely infected arthroplasty in 62 patients, incorporating local antibiotic administration by calcium sulfate beads [37]. The use of local antibiotics may play a role if applied as part of a multimodal approach rather than on its own.

In conclusion, although numerous *in vitro,* animal studies, and human studies have focused on infection prevention and inhibition of biofilm formation in implant-associated orthopedic infections, only a small number of basic studies have addressed the removal of established biofilms using local antibiotic administration. While some studies have suggested the potential of local antibiotics, there is a lack of clarity regarding the types and doses of antibiotics required for effective biofilm removal through local treatment. Most research has focused on *S. aureus*, with limited investigations into gram-negative bacteria and mixed infections, highlighting a significant gap in the literature. Furthermore, the scope of antibiotics studied is narrow, with insufficient exploration of novel therapeutic agents. In human studies, although several case reports have described the effectiveness of local antibiotic treatments, no research with a high level of evidence was identified. We believe that the current evidence is insufficient to reach either a supportive or oppositional consensus on this research question. However,

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