B25: What Are the Best Strategies to Prevent Biofilm Formation and Maturation?

German A Norambuena, Farideh Najafi, Ahmed Ghaithi, Alison Klika, Imre Sallai, Alberto V Carli, Goran Bicanic, Bartolome L Allende.

Response/Recommendation:

The best strategies to prevent biofilm formation and maturation involve reducing bacterial burden around implants and using surface modifications to limit bacterial attachment.

Strength of recommendation: Weak

Delegate Vote:

Rationale:

Biofilms are defined as complex communities of microorganisms residing within an exopolysaccharide matrix that adheres to a surface. Biofilm formation is typically classified into three stages; (a) initial attachment (reversible and irreversible), (b) maturation of microcolonies, and (c) dispersion/detachment [1]. Three key factors required for its formation are bacteria load, favorable surface characteristics, and sufficient time for bacterial adhesion and maturation [2, 3].

Preventing biofilm formation and maturation remains a critical challenge in orthopedic surgery, as biofilms frequently lead to implant failure, chronic infection, and need for revision surgeries. Direct prevention strategies involve implant surface modifications designed to inhibit bacterial attachment, while indirect strategies focus on reducing the microbial burden near the implant surface. This systematic review summarizes preclinical evidence from animal studies as well as clinical results, with an emphasis on direct prevention strategies currently available on the market.

Direct prevention strategies

Surfaces can resist bacterial colonization through intrinsic physical or chemical properties, or by incorporating antibacterial molecules that are firmly attached to the surface. These surfaces are known as passive surfaces. The deposition of nanospikes or making surfaces 'super' hydrophobic or hydrophilic are examples of passive efforts to limit bacterial attachment, which are currently in preclinical development [4, 5]. Another example includes covalently bonded antibacterial coatings, which maintain a localized antibacterial effect while minimizing the risk of antimicrobial resistance and cytotoxicity. *In-vivo* evidence of the efficacy of passive coatings was demonstrated by Stewart et al. [6], who reported significant biofilm inhibition using a vancomycin-modified titanium surface in a sheep model of fracture-related infection.

Surfaces that lack intrinsic antibacterial properties but instead release antimicrobial agents to prevent biofilm formation and eliminate planktonic organisms are known as active surfaces. Silver-coated implants have an active surface that releases silver ions and have been available on the European market for over a decade. Qin et al. [7] reported that silver nanoparticles immobilized on titanium surfaces significantly reduce the risk of implant-associated infections by inhibiting biofilm formation and bacterial adhesion. Despite this, clinical results have been inconsistent. Wafa et al. [8] found that silver-coated megaprostheses achieved an 85% (17/20) infection control success rate compared to 57.1% (12/21) for untreated implants ($p=0.05$). In contrast, Parry et al. [9] reported no significant difference in infection-free survival between silver-coated (n=89) and

non-silver-coated (n=305) prostheses in high-risk patients with primary extremity bone tumors (86.8% and 91.8% at 5 years, respectively, p=0.193). Additionally, 30 patients with silver ion doped calcium phosphate implants exhibited significantly lower infection rate compared to similar patients groups in the literature (p = 0.001) [10]. A meta-analysis by Fiore et al. [11] highlighted mixed results, reporting infection rates of 9.2% (44/445) and 13.7% (25/183) for primary and revision surgeries using silver-coated implants, compared to 11.2% (57/507) and 29.2% (47/161) for untreated implants, respectively. Interestingly, the effectiveness varied among the three types of silver coatings studied, suggesting that not all silver-coated implants perform equally. Alternative metals such as copper and zinc have shown promise as antibacterial coatings, though their clinical application remains limited due to concerns about potential cytotoxicity [12-14].

Iodine-coated implants have demonstrated efficacy to reduce bacterial viability compared to untreated implants *in vivo* [15]. Clinically, Shirai et al. [16] reported a reinfection rate of 4.2% and a survival rate of 91% for iodine-coated implants after 5.6 years of follow-up, with no thyroid abnormalities or allergies detected. A more recent study from the same group investigated iodine-coated implants in 477 compromised patients, reporting an overall infection rate of 3.7% after a mean follow-up of 41 months [17].

Numerous antibiotic-releasing coatings have been developed, such as hydrogels loaded with vancomycin, gentamicin, or amikacin, which provide prolonged, high local antibiotic concentrations at the implant interface to reduce biofilm formation [18-20]. Sol-gel films, glyceryl monostearate-based implants, fibrin gels, and high specialized steel implants have demonstrated the ability to release antimicrobials within peri-implant spaces for sufficient durations to clear polymicrobial biofilms [21-26].

Recent advances, although not yet in clinical use, include enzyme-responsive hydrogels that release antibiotics upon bacterial detection and temperature-responsive polymer brushes [27, 28]. Additionally, coatings based on antimicrobials such as peptides, amino acids, and plant-derived natural products have gained attention due to their strong action against biofilm formation in animal models [24, 29-31]. Clinically, gentamycin coatings have been evaluated in high-risk infection setting. Franz et al. [32] demonstrated that gentamicin-coated tibial nails in patients with open fractures significantly reduced fracture site infections. A systematic review by De Meo et al. [33] further supported these findings, concluding that gentamicin-coated tibial nails are the preferred choice for reducing infection risks in open fractures or high-risk patients.

Indirect prevention strategies

Indirect strategies focus on reducing bacterial load near the implant surface through meticulous surgical techniques, antiseptic irrigation solutions, antibacterial powders and beads, antibiotic hydrogel carriers, antibiotic-loaded cements, and intravenous prophylaxis. For example, vancomycin powder completely prevented biofilm formation in a rabbit model [34]. Antibiotic-loaded PMMA cement has been shown to reduce revision rates following total knee arthroplasty [35]. However, Carli et al. [36] found that while vancomycin-loaded PMMA did not significantly reduce bacterial burden, it effectively prevented biofilm formation on implants in an animal periprosthetic joint infection (PJI) revision model.

Various antiseptic solution show significant promise in preventing biofilm-related complications [37]. Additionally, antibiotic solution such as allicin in combination with vancomycin significantly reduced *Staphylococcus epidermidis* biofilms in a rabbit model [38].

Hydrogel carriers for antibiotic represent another effective strategy. In a multicenter, randomized prospective study involving 380 primary and revision arthroplasty patients found that

antibiotic-loaded hydrogel (ALH) coatings reduced early surgical site infections to 0.6% in the treatment group compared to 6% in the control group ($p = 0.003$) [39]. Similarly, a retrospective observational study comparing 17 patients undergoing aseptic revision hip surgery treated with ALH against matched controls found no PJIs in the ALH group versus six cases in the control group ($p < 0.0001$), with a minimum follow-up of six months [40]. Another clinical trial involving 256 patients randomized to receive fast-resorbable ALH coatings after internal osteosynthesis reported no surgical site infections in the treated group compared to 4.6% in the control group ($p < 0.03$) [41].

Innovative molecular approaches, though still in the preclinical phase, continue to evolve. Endolysins and advanced peptides targeting bacterial virulence factors have shown potential in dismantling established biofilms [42, 43]. Quorum-sensing inhibitors delivered via beads or solutions can disrupt *Staphylococcus* biofilm assembly [44]. Additionally, monoclonal antibodies targeting *Staphylococcal* toxins or surface proteins also represent a promising avenue for future research [45].

Conclusion:

Minimizing microbial burden during surgery and the immediate postoperative period is arguably the most critical strategy to prevent biofilm formation and maturation. If microorganisms reach the implant surface, active preventions strategies such as silver-coated implants have demonstrated some success in reducing periprosthetic joint infections in oncological applications. Similarly, iodine-based coatings, hydrogel carriers, and gentamicin-coated titanium rods -already available on the market- offer promising approaches for biofilm and PJI prevention.

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