and quorum quenching studies presented at scientific meetings utilizing multiple in vivo models [8].

The experimental strategy varies. In vitro data are relied upon to identify the molecular mechanism leading to interference with quorum sensing that causes decreased biofilm formation, whether it be blocking the signaling peptide production, blocking receptors or active initiation an antagonist signals by the agent. The in vivo data confirm that the agent decreases biofilm formation.

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QUESTION 2: Can a biomaterial surface be modified to dispel bacterial adherence and biofilms? What are the potential concerns in modifying implant surfaces to combat biofilms?

RESPONSE: The purpose of the surface modification is to decrease perioperative bacterial adherence and thus prevent biofilm formation. This has been shown in in vitro studies and in vivo animal models. There have been numerous strategies devised to alter surfaces. Such modified surfaces may interfere with the expected osseointegration, mechanical stability and long-term implant survivability. The duration of long-term anti-infective effects are unknown. To date, no positive in vitro effect has been translated into a clinical setting.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

PRE-MEETING RATIONALE

Periprosthetic joint infections (PJI) represent 1-20% of the failure mechanisms in total joint arthroplasty leading to significant morbidity and mortality [1–3]. The material surface used for implantation is a significant factor in bacterial colonization leading to PJI [4,5]. Some surfaces are more prone to bacterial adherence and formation of biofilms. A biofilm is an aggregate of microbial cells that are irreversibly associated with a surface and encapsulated in a complex polysaccharide "slime" extracellular matrix that may include enzymes, crystals and glycoproteins - together forming a living tissue [6,7]. The most common microorganisms residing in biofilms are *Staphylococcus S.* species [8,9]. The bacteria in biofilms take either sessile forms on metal, bone fragments and cement; or planktonic forms that can disperse as clumps within the joint fluid [10,11]. Due to such complexity of form, material and function, the question remains whether modified implant surfaces can play an anti-infective role and what are the main concerns with modifying biomedical devices.

Can a Biomaterial Surface Be Modified to Dispel Bacterial Adherence and Biofilm?

In 1987, Anthony Gristina [12] was the first to propose the concept of a race for the surface, wherein the fate of the biomaterial implant is dependent on a balance between tissue integration and microbial adhesion with biofilm formation. This concept sets the hypothesis that material modifications that improve osseointegraion while inhibiting bacterial adhesion would provide a theoretical advantage and eliminate the risk of infection [13]. As a result, there is a wide array of anti-infective surfaces proposed for utilization in orthopaedic implant applications.

Gallo et al. [14] summarized the available options as bactericidal, anti-adhesion surfaces, multifunctional/smart coatings and alternative materials.

Romanò et al. [15] propose a newer classification regime that describes antibacterial coating under three distinctive groups [1]:

1. *Passive surface finishing/modification* Surfaces that prevent adhesion without releasing anti-bacterial substances.
2. *Active surface finishing/modification* Surfaces that release anti-bacterial substances.
3. *Perioperative antibacterial carriers or coatings* Carriers or coatings applied during surgery that are antibacterial and either biodegradable or non-biodegradable.

Active surfaces and perioperative coatings provide only temporary solutions while they exhaust their antimicrobials in time. Passive surfaces may not provide the necessary bactericidal properties needed to eliminate the infection while their action is limited to the immediate peri-implant area. The ideal implant surface should have: (1) a strong anti-infective potential, (2) long duration of effect, (3) biocompatibility with mechanical construct and stability and (4) minimal host response and harm [16–18]. To achieve that, surfaces

TABLE 1. Proposed anti-infective surfaces for utilization in orthopaedic implant applications

Method	Type	Examples
Bactericidal	Inorganic	Ag, AgNP, AuNP, TiO2, Se, CuNP
	Organic	Coated or covalently linked antibiotics, chitosan derivatives
	Combined	Multilayer coating, positively charged polymers
	Other	Non-antibiotic (peptides, enzymes, oils)
Anti-adhesion		Anti-adhesive polymers
Multifunctional/smart coating	Passive	Nanostructured "smart" materials
	Active	Sensors conjoined to nanocontainers
Alternatives		Lytic bacteriophages

Ag, silver; NP, nanoparticles; TiO2, titanium oxide; Se, selenium; Cu, copper

can be physically and mechanically prepared and coated or chemically modified.

The early reversible adhesion stage of bacteria to titanium is largely influenced by the topographical features on the surface [19]. Several anti-adherent coatings on titanium have been created by surface modification with polymers, copolymers or proteins. Del Curto et al. [20] has shown that the crystalline phase of titanium oxide on the surface of biomaterials reduced bacterial attachment without adverse effects on the biocompatibility. Ferraris et al. [21] showed that mechanically produced nanogrooves (0.1-0.2 um) and keratin nanofibers can increase biocompatibility without increasing bacterial adhesion. Lorenzetti et al. [19] has applied hydrothermic treatment methods to similarly achieve decreased bacterial adhesion. This data is very encouraging and supports the concept that biomaterial surfaces can be modified to dispel bacterial adherence.

Silver (Ag) has been known throughout history not only for its jewelry applications but for its antimicrobial effects [22,23]. The mechanism of action is thought to be the formation of reactive oxygen species and biologically active ions that damage bacterial walls and bind to nucleic acids and interrupt bacterial replication [24]. An added advantage of Ag usage is the effect against surface-adhered bacteria without significant drug-resistance [25,26]. Harrasser et al. [27] studied the antimicrobial effects of Ag and has observed significant antimicrobial activity that was positively correlated with Ag concentrations. A recent study by Aurore et al. [28] indicated that Ag nanoparticles (AgNPs) enhanced the bactericidal activity in osteoclasts.

As such, AgNPs have gained attention for their application on implant surfaces due to their anti-biofilm potential, wide-spectrum antimicrobial properties and low cytotoxicity to human cells [18,22,29–33]. There is an abundance of literature that examine the anti-biofilm effect of AgNPs [18,25,34]. Kalishwaralal et al. [35] demonstrated that AgNPs at a concentration of 100 nM almost entirely inhibited biofilm formation (> 95%) from *S. epidermidis* and *Pseudomonas aeruginosa*. Slane et al. [33] found that bone cements impregnated with AgNPs significantly reduced biofilm formation compared to standard cement. Some studies have also mentioned the synergistic effect of AgNPs with antibiotics [36–38]. The most notable advantage of AgNP-coated surfaces is the ability to exhibit a continuously controlled-release of active agents to the periprosthetic region for a substantial period of time, thus working at both the surface layer but also in the immediate environment.

Recently, iodine has been shown to be a successful adjuvant for irrigation and debridement in cases of PJI [39]. Adapting this idea to implant surfacers, Tsuchiya et al. [40] report on a clinical study of more than 222 patients in whom iodine surface treated implants were very effective for preventing and treating infections after orthopaedic surgery. No clear cytotoxicity or adverse effects were observed. Shirai et al. [41] similarly demonstrated a significant reduction in pin tract infection rate by using iodine surface-treated insertion pins and external fixators. Kabata et al. [42] also show that iodine treated hip implants remained free of infection in 14 revision cases for infection and in 16 immunosuppressed primary total hip arthroplasties. No issues related to local and systemic toxicity or impaired osteoconductivity and bone bonding have been reported in any of these studies.

Similar to Ag and iodine, multiple studies have targeted incorporation of antibiotics into surface coatings directly deposited onto the implant [43–45]. Most of these applications build on the information learned from antibiotic-laden bone cements and provide an initial protective barrier for infection [46–48]. Current protocols include hydrogels, poly-D, L-lactide, calcium phosphate or carbonated hydroxyapatite antibiotic coatings. Other direct techniques attempt to physically modify the surface for antibiotic adsorption, or simply dip the implant in antibiotics producing a transient coating [48–50]. Recent scientific progress in biomolecular interactions and nanoscale engineering provides new inspiration for medical implant designs that may have the potential to deal with infection [51,52]. Antibiotics covalently linked to metallic surfaces have been shown to inhibit bacterial colonization both in vitro and in vivo [13,53,54]. Despite all progress, most systems are rudimentary and difficult to scale up to industry standards; further research and a smarter implant technology is necessary. Such technology should directly integrate biological defenses in the implant design, making protection feasible for the life of the replacement prosthesis.

What Are the Main Problems in Modifying Implant Surfaces in the Fight Against Biofilms?

One of the main concerns of antimicrobial biomaterials is the possible cytotoxic effect of the surface modification as related to osseointegration and implant survival in vivo. Based on a preliminary literature review, only four laboratory studies [55–58] and one clinical study [59] reported the side effects of surface modification. Ag surface modifications have shown higher lactate dehydrogenase (LDH) activity as a marker of cell death, as well as lower cell count and alkaline phosphatase (ALP) activity [55–58]. Nevertheless, such

effects are hard to correlate with clinical outcomes. Glehr et al. [59] performed the only clinical study that focused on Ag while examining its use in mega-prosthesis. They have documented the presence of heavy metal poisoning symptoms, even though no correlation with the blood Ag concentration was observed. Another two in vitro studies used zinc and farnesol (anti-fungi medicine) surface modifications respectively. The results showed lower ALP activity as well as pre-osteoblastic cell damage. Multiple studies thus agree that AgNPs have the potential to be toxic to many cell types in a dose- and time-dependent manner, especially when inhaled, injected or ingested [60–62]. Interestingly, Shen et al. [63] conducted a study which revealed that both cobalt chrome alloys and pure titanium had cytotoxic effects to osteogenic precursor cells and mesenchymal stem cells, while the incorporation of AgNPs reduced this cytotoxicity.

When working with modified surfaces, bacteria can ultimately adapt and develop resistance to the agent used. Antibiotic resistance is an everyday occurrence in clinical practice. Bacteria have also been shown to surmount resistance to the ionic form of Ag, and less commonly, to AgNPs [64,65]. This is because prolonged exposure to AgNPs, unlike Ag ions, is less likely to result in resistance genes, since AgNPs have broad-spectrum capabilities by targeting multiple sites on or within bacterial cells [66]. Nevertheless, resistance to silver seems to be a slow process and is a less of a problem compared to antibiotic resistance [67]. Concerning though, Kaweeteerawat et al. [68] suggest that AgNPs could potentially enhance bacterial resistance to antibiotics through promoting stress tolerance by induction of intracellular reactive oxygen species causing DNA mutations.

In conclusion, bacterial biofilms are difficult for antimicrobial agents to penetrate. Preventing biofilms and bacterial adherence is probably the only effective way to address the problem of PJI. AgNPs and iodine are gaining increasing popularity especially for their anti-adhesion, anti-infective, and minimal bacterial resistance properties. Nevertheless, further investigation of the long-term outcomes of patients with modified surfaced implants is warranted.

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QUESTION 3: What is the relevance of minimum inhibitory concentration (MIC) of infecting organisms in biofilm-mediated chronic infection?

RESPONSE: The use of MIC is limited to (1) defining antibiotics that the microorganism is susceptible to in its planktonic state but cannot be used to guide treatment of biofilm-based bacteria and (2) selecting long-term suppressive antibiotic regimens where eradication of infection is not anticipated. Alternative measures of antibiotic efficacy specifically in the context of biofilm-associated infection should be developed and validated.

LEVEL OF EVIDENCE: Strong

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

PRE-MEETING RATIONALE

MICs are used to define an individual microorganism's (hereafter limited to bacteria) susceptibility to a distinct array of antibiotics. Established methodologies for determining MICs relate to the planktonic state of the bacteria but not to biofilm-indwelling bacteria [1].

The majority of information relating to susceptibility testing and biofilm-indwelling bacteria originates from research in Cystic Fibrosis [2]. In relation to implant-associated biofilm infections, central venous catheters and urinary tract catheters are often investigated, but little clinical research has been performed in orthopaedic implant-associated biofilm infections [2,3].

As early as 1990, Anwar and Costerton identified the need for an extreme increase in in vitro concentrations of antibiotics, to which the planktonic bacteria were fully susceptible, when treating biofilm-indwelling bacteria [4,5]. In a review by key-opinion leaders on the topic of antimicrobial susceptibility testing in biofilm-indwelling