QUESTION 10: Can a biomaterial surface be modified to dispel bacterial adherence and biofilms? What are the potential concerns in modifying implant surfaces to combat biofilms?

Authors: Yixin Zhou, Matthew Kheir, Valentin Antoci, Luigi Zagra

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)

Post Meeting Rationale:

The material surface used for implantation is a significant factor in bacterial colonization leading to PJI [1,2]. In 1987, Anthony Gristina [3] 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 [4]. As a result, there is a wide array of anti-infective surfaces proposed for utilization in orthopaedic implant applications.

Gallo et al. [5] summarized the available options as bactericidal, anti-adhesion surfaces, coatings, and alternative materials. Romanò et al. [6] proposed a newer classification regime that describes antibacterial coating under three distinctive groups [7]:

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 [8–10]. To achieve that, surfaces can be physically and mechanically prepared, and coated or chemically modified.

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 [11–14] and one clinical study [15] reported the side effects of surface modification. Silver 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 [11–14]. Nevertheless, such effects are hard to correlate with clinical outcomes. Glehr et al. [15] performed the only clinical study that focused on silver while examining its use in mega-prosthesis. They have documented the presence of heavy metal poisoning symptoms, even though no correlation with the blood silver 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 silver nanoparticles (AgNPs) have the potential to be toxic to many cell types in a dose- and time-dependent manner, especially when inhaled, injected, or ingested [16–18]. Interestingly, Shen et al. [19] 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 silver, and less commonly, to AgNPs [20,21]. This is because prolonged exposure to AgNPs, unlike silver ions, is less likely to result in resistance genes since AgNPs have broad-spectrum capabilities by targeting multiple sites on or within bacterial cells [22]. Nevertheless, resistance to silver seems to be a slow process and is a less of a problem compared to antibiotic resistance [23]. Concerning though, Kaweeteerawat et al. [24] 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. Silver nanoparticles 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.

References:

1. Gbejuade HO, Lovering AM, Webb JC. 2015. The role of microbial biofilms in prosthetic joint infections. Acta Orthop. 86(2):147–158.

2. Rochford ETJ, Richards RG, Moriarty TF. 2012. Influence of material on the development of device-associated infections. Clin. Microbiol. Infect. Off. Publ. Eur. Soc. Clin. Microbiol. Infect. Dis. 18(12):1162–1167.

3. Gristina AG. 1987. Biomaterial-centered infection: microbial adhesion versus tissue integration. Science 237(4822):1588–1595.

4. Antoci V, Adams CS, Parvizi J, et al. 2007. Covalently attached vancomycin provides a nanoscale antibacterial surface. Clin. Orthop. Relat. Res. 461:81–87.

5. Gallo J, Panacek A, Prucek R, et al. 2016. Silver Nanocoating Technology in the Prevention of Prosthetic Joint Infection. Mater. (Basel, Switzerland) 9(5).

6. Romanò CL, Scarponi S, Gallazzi E, et al. 2015. Antibacterial coating of implants in orthopaedics and trauma: a classification proposal in an evolving panorama. J. Orthop. Surg. Res. 10:157.

7. Antoci V, Adams CS, Hickok NJ, et al. 2007. Antibiotics for local delivery systems cause skeletal cell toxicity in vitro. Clin. Orthop. Relat. Res. 462:200–206.

8. Helmus MN, Gibbons DF, Cebon D. 2008. Biocompatibility: meeting a key functional requirement of next-generation medical devices. Toxicol. Pathol. 36(1):70–80.

9. Bernthal NM, Stavrakis AI, Billi F, et al. 2010. A mouse model of post-arthroplasty Staphylococcus aureus joint infection to evaluate in vivo the efficacy of antimicrobial implant coatings. PLoS One 5(9):e12580.

10. Secinti KD, Özalp H, Attar A, Sargon MF. 2011. Nanoparticle silver ion coatings inhibit biofilm formation on titanium implants. J. Clin. Neurosci. Off. J. Neurosurg. Soc. Australas. 18(3):391–395.

11. Zhao L, Wang H, Huo K, et al. 2011. Antibacterial nano-structured titania coating incorporated with silver nanoparticles. Biomaterials 32(24):5706–5716.

12. Unnanuntana A, Bonsignore L, Shirtliff ME, Greenfield EM. 2009. The effects of farnesol on Staphylococcus aureus biofilms and osteoblasts. An in vitro study. J. Bone Joint Surg. Am. 91(11):2683–2692.

13. Li Y, Xiong W, Zhang C, et al. 2014. Enhanced osseointegration and antibacterial action of zinc-loaded titania-nanotube-coated titanium substrates: in vitro and in vivo studies. J. Biomed. Mater. Res. A 102(11):3939–3950.

14. Xu Z, Wang X, Liu X, et al. 2017. Tannic Acid/Fe3+/Ag Nanofilm Exhibiting Superior Photodynamic and Physical Antibacterial Activity. ACS Appl. Mater. Interfaces 9(45):39657–39671.

15. Glehr M, Leithner A, Friesenbichler J, et al. 2013. Argyria following the use of silver-

coated megaprostheses: no association between the development of local argyria and elevated silver levels. Bone Joint J. 95–B(7):988–992.

16. Lee KJ, Nallathamby PD, Browning LM, et al. 2007. In vivo imaging of transport and biocompatibility of single silver nanoparticles in early development of zebrafish embryos. ACS Nano 1(2):133–143.

17. AshaRani P V., Low Kah Mun G, Hande MP, Valiyaveettil S. 2009. Cytotoxicity and genotoxicity of silver nanoparticles in human cells. ACS Nano 3(2):279–290.

18. Gandjbakhch E, Varlet E, Duthoit G, et al. 2018. Pregnancy and newborn outcomes in arrhythmogenic right ventricular cardiomyopathy/dysplasia. Int. J. Cardiol. 258:172–178.

19. Shen X-T, Zhang Y-Z, Xiao F, et al. 2017. Effects on cytotoxicity and antibacterial properties of the incorporations of silver nanoparticles into the surface coating of dental alloys. J. Zhejiang Univ. Sci. B 18(7):615–625.

20. Silver S. 2003. Bacterial silver resistance: molecular biology and uses and misuses of silver compounds. FEMS Microbiol. Rev. 27(2–3):341–353.

21. Panáček A, Kvítek L, Smékalová M, et al. 2018. Bacterial resistance to silver nanoparticles and how to overcome it. Nat. Nanotechnol. 13(1):65–71.

22. Markowska K, Grudniak AM, Wolska KI. 2013. Silver nanoparticles as an alternative strategy against bacterial biofilms. Acta Biochim. Pol. 60(4):523–530.

23. Percival SL, Bowler PG, Russell D. 2005. Bacterial resistance to silver in wound care. J. Hosp. Infect. 60(1):1–7.

24. Kaweeteerawat C, Na Ubol P, Sangmuang S, et al. 2017. Mechanisms of antibiotic resistance in bacteria mediated by silver nanoparticles. J. Toxicol. Environ. Health. A 80(23–24):1276–1289.