ICM 2025 Question B22: "Are there any novel alloys that are resistant to formation of biofilm during orthopedic infections?

Authors: Christopher Spiegel, Hernando Gaitan Lee, Philippe Hernigou

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Response/Recommendation: Based on available data, nanostructured titanium alloys such as Ti-13Nb-13Zr and magnesium-based alloys doped with antimicrobial elements show potential to resist biofilm formation in orthopedic implants.

Level of Evidence: Moderate

Delegate Vote: Agree: [% vote], Disagree: [%], Abstain: [%]

Rationale: Orthopedic implants have revolutionized healthcare by restoring function and mobility to patients suffering from musculoskeletal disorders. Among the materials employed, titanium (Ti) and its alloys dominate due to their exceptional mechanical properties, corrosion resistance, and biocompatibility. However, implant-associated infections remain a critical issue, necessitating innovative strategies to impart antimicrobial properties to these materials [1]. Thus, a variety of implant alloys are present on the market, the most common implant alloys are titanium based such as Ti6Al4V, titanium grade CP4 and tiMo15, Cobalt chromium alloys and stainless steel [2]. There are also efforts to introduce a variety of new implant alloys like magnesium alloys, tantalum alloys, zirconium alloys and mostly ceramic derivatives [3]. To answer this question a comprehensive literature search was conducted using the search words "novel alloys" or "coated materials, biocompatible"or "nanotubes" or "nanostructures" and "orthopedic implant" or "prosthesis-related infections" or "Orthopedic infection" or "endoprosthetic joint infections" or "periprosthetic joint infection" or "orthopedic procedures" and "antibiofilm" or "anti-biofilm" or "resistance" or "anti-bacterial agents" within PubMed and Embase, which initially identified 95 potentially relevant unique studies, screened by two independent reviewers, of which 41 were selected for full-text review and 41 were included for evaluation.

Developments in implant alloys

Titanium based implants

Widely regarded as the standard for orthopedic implants, Ti-6Al-4V combines high strength with corrosion resistance [4]. The alloy exhibits a high strength-to-weight ratio, with a tensile strength of approximately 900 MPa and a density of about 4.4 g/cm^3, making it significantly lighter than cobalt-chromium alloys while still providing substantial mechanical strength [5]. Corrosion resistance is another critical property of this material, and the formation of a stable and adherent titanium dioxide (TiO_2) passive layer upon exposure to physiological environments greatly enhances its resistance to oxidation and corrosion. This passive layer is crucial, as it mitigates the risk of ion release and its associated cytotoxic effects [6].

It is extensively used in joint replacements, spinal implants, and dental prostheses due to its favorable mechanical properties and ability to integrate with bone. Another important characteristic of titanium alloys is their biocompatibility, which stems from their ability to induce favorable biological responses upon implantation [7]. The osseointegration process, where bone cells integrate with the implant surface, is vital for the long-term success of joint replacements. Studies have demonstrated that titanium and its alloys exhibit optimal cellular responses, facilitating the proliferation and differentiation of osteoblasts, the cells responsible for bone formation [8,9,10]. The elasticity modulus of titanium alloys is approximately 110 GPa, which is notably lower than that of traditional materials such as stainless steel (210 GPa) [11]. This lower modulus reduces stress shielding effects, wherein the bone is subjected to reduced mechanical loading, potentially leading to bone resorption around the implant. By more closely matching the mechanical properties of human bone, titanium alloys help maintain optimal bone health and loading conditions [12].

Vanadium-free alternative to Ti-6Al-4V, primarily alloyed with elements like Nb, Zr, Mo, and Ta [13]. Specifically Ti-6Al-7Nb replaces vanadium with niobium, enhancing biocompatibility while maintaining high strength and corrosion resistance [14]. Research indicates that this alloy reduces cytotoxic effects associated with vanadium, making it a safer option for long-term implantation [15]. Recent studies highlight its ability to integrate well with bone, particularly when combined with antibacterial surface treatments such as silver or zinc coatings [16]. Characterized by its low elastic modulus, Ti-13Nb-13Zr minimizes stress shielding, a phenomenon where high stiffness of the implant results in bone resorption [17]. This alloy's compatibility with bone tissue has been extensively documented, with evidence supporting its use in load-bearing applications. However, while its biocompatibility is exceptional, antibacterial properties are limited [18]. After equal channel angular swaging of Ti13Nb13Zr a nanostructured material was gained which led to an further reduction of bacterial cell counts [19]. Commercially pure titanium (CP-Ti) is widely used in dental and orthopedic implants due to its high corrosion resistance and moderate strength. CP-Ti (Grade 2) is particularly noted for its ductility, while CP-Ti (Grade 4) provides greater strength, making it suitable for more demanding applications [4]. Both grades promote osseointegration, with treatments such as plasma spraying and hydroxyapatite coatings further enhancing their integration with bone tissue [20]. Despite these advantages, their lack of inherent antibacterial activity necessitates the application of antimicrobial coatings or drug-loaded systems [1]. Emerging alloys such as Ti-15Mo-5Zr-3Al and Ti-12Mo-6Zr-2Fe demonstrate strong potential for orthopedic applications due to their superior mechanical properties and corrosion resistance. Ti-15Mo, for instance, has excellent biocompatibility and osseointegration capabilities when surface-modified with nanoscale roughness [21]. However, comprehensive studies evaluating their antibacterial properties are still needed to confirm their efficacy in reducing bacterial colonization.

Magnesium based implants

Magnesium (Mg) alloys have gained attention for their biodegradability and biocompatibility, while recent research has focused on enhancing their antimicrobial properties. Magnesium exhibited antimicrobial properties due to the increasing pH in the surrounding environment [22]. While magnesium only reduces the bacterial count, incorporation of antimicrobial elements or agents like Cu, Ag, and tannic acids can introduce greater efficiency in inhibiting biofilm formation [23]. In addition, Mishra et al. (2024) explored alloying and coating strategies to improve the mechanical and corrosion resistance of magnesium implants, further enhancing their antimicrobial and osteoconductive properties [24].

Hydrogels containing magnesium phosphates also have potential in surgical decontamination of dental implants, effectively reducing peri-implantitis-associated infections [25]. Furthermore, the use of magnesium implants combined with alternating magnetic fields to enhance hydrogen release and proton depletion offers a novel approach for combating osteomyelitis by promoting bacterial eradication and tissue repair [26]. Lastly, composite materials like magnesium/poly lactic acid (Mg/PLA) blends have demonstrated improved antibacterial and anti-inflammatory properties during biodegradation, addressing infection-related complications in bone healing applications [27].

Zinc based implants

Zinc (Zn) is an essential element in the human body, and its alloys have been investigated for biomedical applications. Zinc possesses antimicrobial properties depending on the concentration present to the bacteria [28]. However, Zinc is able to reduce bacterial counts, by destroying the outer cell membrane [29]. Recently approaches have been made by doping Zn based implants with antimicrobial elements like Cu and Ag [30].

Cobalt-Chromium based implants

CoCrMo alloys are widely used in orthopedic implants due to their mechanical strength and corrosion resistance. Surface modifications and alloy doping with Cu and Ag have been employed to enhance their biocompatibility and antimicrobial properties [31,32]. Different surface modifications on CoCrMo alloys affect cell viability and adhesion, highlighting the importance of surface engineering in improving implant performance [33].

Conclusion:

Titanium and its alloys are indispensable in orthopedic applications due to their superior mechanical properties and biocompatibility. However, their lack of inherent antimicrobial properties necessitates innovative solutions to prevent infections. Strategies such as surface modifications, antimicrobial coatings, elemental doping, and drug-loaded coatings have the potential to enhance the antibacterial performance of these materials while supporting osseointegration. The most difficult aspect of in fighting PJI with novel alloys is to find a balance between biocompatibility and antimicrobial efficiency. The use of copper and silver has important influence on body health. The risk of developing cancer, Alzheimer's, and other immune deficiencies are dependent on ion release to the human body [34, 35]. With implants, ion release occurs and can be difficult to control [36]. A promising approach to reduce bacterial counts is the use of nanostructured surfaces [37,38]. As nanoparticles can be used as coatings [39], nanostructured alloys produced using innovative manufacturing processes can ensure a sustained antimicrobial effect [40,41]. Continued research and development in this field is crucial for improving implant success rates and enhancing patient outcomes.

References:

1. Souza JGS, Bertolini MM, Costa RC, Nagay BE, Dongari-Bagtzoglou A, Barão VAR. Targeting implant-associated infections: titanium surface loaded with antimicrobial. iScience. 2020 Dec 29;24(1):102008. doi: 10.1016/j.isci.2020.102008. PMID: 33490916; PMCID: PMC7811145.

2. Jiao J, Zhang S, Qu X, Yue B. Recent Advances in Research on Antibacterial Metals and Alloys as Implant Materials. Front Cell Infect Microbiol. 2021 Jul 2;11:693939. doi: 10.3389/fcimb.2021.693939. PMID: 34277473; PMCID: PMC8283567.

3. Wang N, Ma Y, Shi H, Song Y, Guo S, Yang S. Mg-, Zn-, and Fe-Based Alloys With Antibacterial Properties as Orthopedic Implant Materials. Front Bioeng Biotechnol. 2022 May 23;10:888084. doi: 10.3389/fbioe.2022.888084. PMID: 35677296; PMCID: PMC9168471.

4. Abdel-Hady Gepreel M, Niinomi M. Biocompatibility of Ti-alloys for long-term implantation. J Mech Behav Biomed Mater. 2013 Apr;20:407-15. doi: 10.1016/j.jmbbm.2012.11.014. Epub 2012 Dec 6. PMID: 23507261.

5. Ashby, M. F., & Jones, D. R. H. (2012). *Engineering Materials 1: An Introduction to Properties, Applications

6. Vera, M. & Linardi, Evelina & Lanzani, Liliana & Méndez, Claudia & Schvezov, Carlos & Ares, Alicia. (2014). Corrosion resistance of titanium dioxide anodic coatings on Ti–6Al–4V. Materials and Corrosion. 66. 10.1002/maco.201407988.

7. Marin, Elia & Lanzutti, Alex. (2023). Biomedical Applications of Titanium Alloys: A Comprehensive Review. Materials (Basel, Switzerland). 17. 10.3390/ma17010114.

8. Brånemark, P I et al. "Osseointegrated titanium fixtures in the treatment of edentulousness." Biomaterials vol. 4,1 (1983): 25-8. doi:10.1016/0142-9612(83)90065-0

9. Albrektsson, T et al. "Osseointegrated titanium implants. Requirements for ensuring a long-lasting, direct bone-to-implant anchorage in man." Acta orthopaedica Scandinavica vol. 52,2 (1981): 155-70. doi:10.3109/17453678108991776

10. Asti A, Gastaldi G, Dorati R, et al. Stem Cells Grown in Osteogenic Medium on PLGA, PLGA/HA, and Titanium Scaffolds for Surgical Applications. Bioinorg Chem Appl. 2010;2010:831031.

11. Marin E, Fusi S, Pressacco M, Paussa L, Fedrizzi L. Characterization of cellular solids in Ti6Al4V for orthopaedic implant applications: Trabecular TitaniumTM. J Mech Behav Biomed Mater. 2010;3(5):373–81.

12. Guillemot, Fabien. "Recent advances in the design of titanium alloys for orthopedic applications." Expert review of medical devices vol. 2,6 (2005): 741-8. doi:10.1586/17434440.2.6.741

13. Abd-Elaziem, Walaa & Darwish, Mostafa & Hamada, Atef & Daoush, Walid. (2024). Titanium-Based alloys and composites for orthopedic implants Applications: A comprehensive review. Materials & Design. 241. 10.1016/j.matdes.2024.112850.

14. Niinomi M. Mechanical biocompatibilities of titanium alloys for biomedical applications. J Mech Behav Biomed Mater. 2008 Jan;1(1):30-42. doi: 10.1016/j.jmbbm.2007.07.001. Epub 2007 Aug 27. PMID: 19627769.

15. Li, Jingling et al. "Surface-modified titanium and titanium-based alloys for improved osteogenesis: A critical review." Heliyon vol. 10,1 e23779. 18 Dec. 2023, doi:10.1016/j.heliyon.2023.e23779

16. Jia B, Zhang Z, Zhuang Y, Yang H, Han Y, Wu Q, Jia X, Yin Y, Qu X, Zheng Y, Dai K. High-strength biodegradable zinc alloy implants with antibacterial and osteogenic properties for the treatment of MRSA-induced rat osteomyelitis. Biomaterials. 2022 Aug;287:121663. doi: 10.1016/j.biomaterials.2022.121663. Epub 2022 Jul 5. PMID: 35810539.

17. Niinomi, M. (2002). Recent research and development in titanium alloys for biomedical applications and healthcare goods. Science and Technology of Advanced Materials, 4(5), 445-454.

18. Aguilera-Correa, J. J., Conde, A., Arenas, M. A., de-Damborenea, J. J., Marin, M., Doadrio, A. L., et al. (2017). Bactericidal activity of the Ti-13Nb-13Zr alloy against different species of bacteria related with implant infection. Biomed. Mat. 12 (4), 045022. doi:10.1088/1748-605X/aa770c

19. Klinge L, Kluy L, Spiegel C, Siemers C, Groche P, Coraça-Huber D. Nanostructured Ti-13Nb-13Zr alloy for implant application-material scientific, technological, and biological aspects. Front Bioeng Biotechnol. 2023 Aug 24;11:1255947. doi: 10.3389/fbioe.2023.1255947. PMID: 37691899; PMCID: PMC10484403.

20. Le Guéhennec, L et al. "Surface treatments of titanium dental implants for rapid osseointegration." Dental materials : official publication of the Academy of Dental Materials vol. 23,7 (2007): 844-54. doi:10.1016/j.dental.2006.06.025

21. Bandyopadhyay A, Mitra I, Goodman SB, Kumar M, Bose S. Improving Biocompatibility for Next Generation of Metallic Implants. Prog Mater Sci. 2023 Mar;133:101053. doi:

22. Robinson, D.A.; Griffith, R.W.; Shechtman, D.; Evans, R.B.; Conzemius, M.G. In vitro antibacterial properties of magnesium metal against Escherichia coli, Pseudomonas aeruginosa and Staphylococcus aureus. Acta Biomater. 2010, 6, 1869–1877. [CrossRef]

23. Song Q, Yang L, Yi F, Chen C, Guo J, Qi Z, Song Y. Antibacterial Pure Magnesium and Magnesium Alloys for Biomedical Materials—A Review. Crystals. 2024; 14(11):939. https://doi.org/10.3390/cryst14110939

24. Mishra, T. N., Kumar, A., & Prasad, S. B. (2024). Magnesium based implants: Alloying and coating strategies for improvement in its biomechanical and biocorrosion properties. Proceedings of the Institution of Mechanical Engineers, Part L: Journal of Materials: Design and Applications. https://doi.org/10.1177/14644207241269609

25. Behmanesh, S., Chow, K., Dondani, J., Al-Hashedi, A. A., & Tamimi, F. (2024). Effectiveness of 2D magnesium phosphate hydrogel for surgical decontamination of dental implants: A case series. Journal of Prosthodontics. https://doi.org/10.1111/jopr.13961

26. Yang, X.-Y., Sun, S., Huang, X., Ge, J., Han, Z., Huang, C., Wang, Y., & Cheng, L. (2024). Magnesium implants with alternating magnetic field-enhanced hydrogen release and proton depletion for anti-infection treatment and tissue repair. Bioactive Materials. https://doi.org/10.1016/j.bioactmat.2024.05.010

27. Qian, Y., Wang, X., Wang, P., Jin, W., Shen, Y., Cai, K., Bai, J., Lu, M., & Tang, C. (2024). Biodegradable implant of magnesium/polylactic acid composite with enhanced antibacterial and anti-inflammatory properties. Journal of Biomaterials Applications. https://doi.org/10.1177/08853282241257183

28. Ning C, Wang X, Li L, Zhu Y, Li M, Yu P, Zhou L, Zhou Z, Chen J, Tan G, Zhang Y, Wang Y, Mao C. Concentration ranges of antibacterial cations for showing the highest antibacterial efficacy but the least cytotoxicity against mammalian cells: implications for a

new antibacterial mechanism. Chem Res Toxicol. 2015 Sep 21;28(9):1815-22. doi: 10.1021/acs.chemrestox.5b00258. Epub 2015 Aug 10. PMID: 26258952; PMCID: PMC4925100.

29. Ye, Q., Chen, W., Huang, H., Tang, Y., Wang, W., Meng, F., et al. (2020). Iron and Zinc Ions, Potent Weapons Against Multidrug-Resistant Bacteria. Appl. Microbiol. Biotechnol. 104 (12), 5213–5227. doi: 10.1007/s00253-020-10600-4

30. Jia B, Zhang Z, Zhuang Y, Yang H, Han Y, Wu Q, Jia X, Yin Y, Qu X, Zheng Y, Dai K. High-strength biodegradable zinc alloy implants with antibacterial and osteogenic properties for the treatment of MRSA-induced rat osteomyelitis. Biomaterials. 2022 Aug;287:121663. doi: 10.1016/j.biomaterials.2022.121663. Epub 2022 Jul 5. PMID: 35810539.

31. Zhang, E., and Liu, C. (2016). A New Antibacterial Co-Cr-Mo-Cu Alloy: Preparation, Biocorrosion, Mechanical and Antibacterial Property. Mater Sci.Eng. C Mater Biol. Appl. 69, 134–143. doi: 10.1016/j.msec.2016.05.02

32. Jiang, F., Zhu, W., Zhao, C., Li, Y., Wei, P., Wan, T., et al. (2019). A Strong, Wear- and Corrosion-Resistant, and Antibacterial Co–30 at.% Cr–5 at.% Ag Ternary Alloy for Medical Implants. Materials Design 184, 108190. doi: 10.1016/j.matdes.2019.108190

33. Lohberger B, Stuendl N, Glaenzer D, Rinner B, Donohue N, Lichtenegger HC, Ploszczanski L, Leithner A. CoCrMo surface modifications affect biocompatibility, adhesion, and inflammation in human osteoblasts. Sci Rep. 2020 Feb 3;10(1):1682. doi: 10.1038/s41598-020-58742-9. PMID: 32015475; PMCID: PMC6997456.

34. Cheng F, Peng G, Lu Y, Wang K, Ju Q, Ju Y, Ouyang M. Relationship between copper and immunity: The potential role of copper in tumor immunity. Front Oncol. 2022 Nov 7;12:1019153. doi: 10.3389/fonc.2022.1019153. PMID: 36419894; PMCID: PMC9676660.

35. Squitti R, Ventriglia M, Simonelli I, Bonvicini C, Costa A, Perini G, Binetti G, Benussi L, Ghidoni R, Koch G, Borroni B, Albanese A, Sensi SL, Rongioletti M. Copper Imbalance in Alzheimer's Disease: Meta-Analysis of Serum, Plasma, and Brain Specimens, and Replication Study Evaluating ATP7B Gene Variants. Biomolecules. 2021 Jun 29;11(7):960. doi: 10.3390/biom11070960. PMID: 34209820; PMCID: PMC8301962.

36. Arregui, M.; Latour, F.; Gil, F.J.; Pérez, R.A.; Giner-Tarrida, L.; Delgado, L.M. Ion Release from Dental Implants, Prosthetic Abutments and Crowns under Physiological and Acidic Conditions. Coatings 2021, 11, 98. https://doi.org/10.3390/coatings11010098

37. Park CH, Lee CS, Kim YJ, Jang JH, Suh JY, Park JW. Improved pre-osteoblast response and mechanical compatibility of ultrafine-grained Ti-13Nb-13Zr alloy. Clin Oral Implants Res. 2011 Jul;22(7):735-742. doi: 10.1111/j.1600-0501.2010.02053.x. Epub 2010 Dec 2. PMID: 21121961.

38. Cao Y, Su B, Chinnaraj S, Jana S, Bowen L, Charlton S, Duan P, Jakubovics NS, Chen J. Nanostructured titanium surfaces exhibit recalcitrance towards Staphylococcus epidermidis biofilm formation. Sci Rep. 2018 Jan 18;8(1):1071. doi: 10.1038/s41598-018-19484-x. PMID: 29348582; PMCID: PMC5773551.

39. Ahmed OB, Alamro T. Evaluation of the antibacterial activities of face masks coated with titanium dioxide nanoparticles. Sci Rep. 2022 Nov 4;12(1):18739. doi: 10.1038/s41598-022-23615-w. PMID: 36333396; PMCID: PMC9636400.

40. Klinge, L., Siemers, C., Kluy, L. et al. Nanostructured Ti–13Nb–13Zr for dental implant applications produced by severe plastic deformation. Journal of Materials Research 37, 2581–2588 (2022). https://doi.org/10.1557/s43578-022-00587-1

41. Kluy, L., Klinge, L., Spiegel, C., Siemers, C., & Groche, P. (2024). Design of thermomechanical processes for tailored microstructures: Methodology and application to nanocrystalline titanium alloy Ti-13Nb-13Zr (NanoTNZ). Manufacturing Letters, 41(Supplement), 421–428. https://doi.org/10.1016/j.mfglet.2024.09.050