G59: **Is there a Role for Antimicrobial Peptides as a Treatment Modality on Patients with Orthopedic Infections?**

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Response/Recommendation:

Antimicrobial peptides (AMPs) offer a promising adjunct or alternative therapy for treating orthopedic infections, particularly in cases of infection with antibiotic resistance or failure after conventional therapy. Early-phase human trials suggest favorable safety, but further clinical research is needed to confirm their optimal use.

Level of Evidence: Moderate

Delegate Vote: Agree: X%, Disagree: X%, Abstain: X% (XX)

Rationale

Implant-associated infections remain a major complication in orthopedic surgery, leading to implant failure, prolonged hospital stay, and increased healthcare costs[1]. The causative agents often form biofilms on implant surfaces, rendering infections highly resistant to antibiotics and increasing the prevalence of multidrug-resistant pathogens[2]. Antimicrobial peptides (AMPs) offer a promising treatment alternative due to their ability to disrupt bacterial membranes, inhibit biofilm formation, and function when immobilized on implant materials[3]. Although the efficacy of AMPs in treating infection in other areas of medicine has been established[4], the role of AMPs in treating orthopedic infections is relatively new and being explored currently.

To answer the posed question above, we conducted a comprehensive systematic review of PubMed, Embase, and Cochrane Library from inception to August 2024 to identify studies examining the role of AMPs in treating orthopedic related infections. Inclusion criteria were all studies, including *in vitro*, *in vivo*, and clinical studies, examining the potential role of AMPs in treating orthopedic related infections. Exclusion criteria were studies investigating AMPs as a diagnostic modality, *in vitro* studies not examining AMPs utilization on implant materials (titanium, magnesium), and review articles. A total of 632 studies were screened for eligibility. Of which, the full texts of 46 studies were reviewed, leaving 32 studies for final inclusion. Two independent authors reviewed the abstracts and full-texts, and disagreements were resolved by a third independent author.

Studies Examining AMPs in Vitro

Various AMP coatings for implants materials, mostly titanium, have demonstrated significant bacterial load reduction, biofilm inhibition, and high biocompatibility. AMP-loaded surfaces achieved >95% bacterial inhibition, with some eliminating colonies entirely[5–10]. Studies show that AMPs exhibit a significant bactericidal effect, reducing *S. aureus* and *P. aeruginosa* by up to 10^6-fold in 30 minutes and decreasing bacterial adhesion by 45-fold compared to titanium surfaces without AMPs[11–16]. Furthermore, AMPs have been shown to completely inhibit the growth of common pathogens such as *S. aureus*, *S. epidermidis*, and *E. coli*[17–19]. These effects likely stem from their ability to disrupt bacterial membranes and heighten the immune response by increasing cytokine release[20,21]. Several studies have shown that AMPs may have a dose-dependent effect against biofilms, demonstrating up to 90% biofilm reduction against *S. epidermidis*, *E. coli*, and *P. aeruginosa*, when coating titanium surfaces with AMPs[22–25].

Additionally, AMPs may outperform conventional antibiotics. Kang et al[26], observed >4-log reduction in *S. aureus* with AMPs compared to <1-log reduction using conventional antibiotics (gentamicin, vancomycin, rifampin). Against clinically isolated bacteria and multi-resistant bacteria, such as *Methicillin Resistant Staphylococcus aureus* (MRSA), AMPs can still be effective, achieving >90% bacterial inhibition and biofilm reduction[27–30]. In a study of 17 explanted total knee arthroplasty (TKA) prostheses from patients with chronic PJI, using PLG0206 at 1 mg/mL for 15 minutes demonstrated a 10^4 reduction in bacterial colonies. Moreover, 59% of explants became culture negative following treatment[31].

Studies Examining AMPs in Vivo

In vivo studies have demonstrated the potent antibacterial, biofilm-inhibiting, and osseointegration effects of AMPs in treating orthopedic infections. Raeder et al[32] studied 36 Wistar rats with *S. epidermidis* bone graft infections and found that APIM-peptide combined with gentamicin eliminated bacteria in 77% of cases, compared to 38% in single-treatment groups, and led to 30% more bacterial eradication than gentamicin alone. Chen et al[33] tested 55 New Zealand rabbits with *S. aureus* infected implants, showing >99% bacterial killing at 7 days with Fusion Peptide (HHC36 + QK)-coated titanium (Ti-125FP), in addition to minimal bacterial adhesion, biofilm formation, and 1.6 times higher osseointegration than uncoated titanium at 60 days. Mandell et al[34] used WLBU2 irrigation in 6 mice PJI models and found significant biofilm reduction, with the highest efficacy at alkaline to physiological pH. Yan et al[35] studied 67 rabbits with femoral fractures infected with *S. aureus* and found that LL-37 significantly reduced bacterial counts at 2 and 7 days, while also lowering inflammatory markers by day 7 in comparison to cefalexin or saline.

Human-Based Studies

A series of clinical studies have been conducted on PLG0206/zaloganan, a novel AMP with independent biofilm activity[36]. A Phase 1 single ascending dose study evaluated the safety, tolerability and pharmacokinetics of PLG0206 when administered intravenously (IV) in 35 healthy volunteers, compared to 12 patients who received an IV placebo[37]. No serious adverse events occurred, and treatment-emergent adverse events were infrequent, with most events being mild in severity[37]. A Phase 1b open-label clinical trial is currently underway to assess PLG0206 in conjunction with traditional debridement, antibiotics, and implant retention (DAIR) procedures for PJI treatment of the knee[38]. Preliminary data suggest that PLG0206 continues to be well tolerated and indicates a lower PJI failure rate as compared to reported literature rates[39,40], supporting continued development of PLG0206 for PJI treatment.

References

1. Jevnikar BE, Khan ST, Huffman N, Pasqualini I, Surace PA, Deren ME, et al. Advancements in treatment strategies for periprosthetic joint infections: A comprehensive review. J Clin Orthop Trauma. 2024 Aug;55:102496.

2. Taha M, Abdelbary H, Ross FP, Carli AV. New Innovations in the Treatment of PJI and Biofilms-Clinical and Preclinical Topics. Curr Rev Musculoskelet Med. 2018 Sep;11(3):380–8.

3. Costa B, Martínez-de-Tejada G, Gomes PAC, L Martins MC, Costa F. Antimicrobial Peptides in the Battle against Orthopedic Implant-Related Infections: A Review. Pharmaceutics. 2021 Nov 12;13(11):1918.

4. Yang S, Wang H, Zhao D, Zhang S, Hu C. Polymyxins: recent advances and challenges. Front Pharmacol. 2024 Jun 21;15:1424765.

5. Wang B, Lan J, Qiao H, Xie L, Yang H, Lin H, et al. Porous surface with fusion peptides embedded in strontium titanate nanotubes elevates osteogenic and antibacterial activity of additively manufactured titanium alloy. Colloids Surf B Biointerfaces. 2023 Apr 1;224:113188.

6. Wang Y, Zhang J, Gao T, Zhang N, He J, Wu F. Covalent immobilization of DJK-5 peptide on porous titanium for enhanced antibacterial effects and restrained inflammatory osteoclastogenesis. Colloids Surf B Biointerfaces. 2021 Jun 1;202:111697.

7. Cheng H, Yue K, Kazemzadeh-Narbat M, Liu Y, Khalilpour A, Li B, et al. Mussel-Inspired Multifunctional Hydrogel Coating for Prevention of Infections and Enhanced Osteogenesis. ACS Appl Mater Interfaces. 2017 Apr 5;9(13):11428–39.

8. Pfeufer NY, Hofmann-Peiker K, Mühle M, Warnke PH, Weigel MC, Kleine M. Bioactive coating of titanium surfaces with recombinant human β-defensin-2 (rHuβD2) may prevent bacterial colonization in orthopaedic surgery. J Bone Joint Surg Am. 2011 May 4;93(9):840–6.

9. Fischer NG, Chen X, Astleford-Hopper K, He J, Mullikin AF, Mansky KC, et al. Antimicrobial and enzyme-responsive multi-peptide surfaces for bone-anchored devices. Mater Sci Eng C Mater Biol Appl. 2021 Jun;125:112108.

10. Boix-Lemonche G, Guillem-Marti J, D'Este F, Manero JM, Skerlavaj B. Covalent grafting of titanium with a cathelicidin peptide produces an osteoblast compatible surface with antistaphylococcal activity. Colloids Surf B Biointerfaces. 2020 Jan 1;185:110586.

11. Yazici H, O'Neill MB, Kacar T, Wilson BR, Oren EE, Sarikaya M, et al. Engineered Chimeric Peptides as Antimicrobial Surface Coating Agents toward Infection-Free Implants. ACS Appl Mater Interfaces. 2016 Mar 2;8(8):5070–81.

12. Scheper H, Wubbolts JM, Verhagen JAM, de Visser AW, van der Wal RJP, Visser LG, et al. SAAP-148 Eradicates MRSA Persisters Within Mature Biofilm Models Simulating Prosthetic Joint Infection. Front Microbiol. 2021;12:625952.

13. Kazemzadeh-Narbat M, Kindrachuk J, Duan K, Jenssen H, Hancock REW, Wang R. Antimicrobial peptides on calcium phosphate-coated titanium for the prevention of implant-associated infections. Biomaterials. 2010 Dec;31(36):9519–26.

14. Kazemzadeh-Narbat M, Lai BFL, Ding C, Kizhakkedathu JN, Hancock REW, Wang R. Multilayered coating on titanium for controlled release of antimicrobial peptides for the prevention of implant-associated infections. Biomaterials. 2013 Aug 1;34(24):5969–77.

15. Tian J, Shen S, Zhou C, Dang X, Jiao Y, Li L, et al. Investigation of the antimicrobial activity and biocompatibility of magnesium alloy coated with HA and antimicrobial peptide. J Mater Sci Mater Med. 2015 Feb;26(2):66.

16. Lallukka M, Gamna F, Gobbo VA, Prato M, Najmi Z, Cochis A, et al. Surface Functionalization of Ti6Al4V-ELI Alloy with Antimicrobial Peptide Nisin. Nanomater Basel Switz. 2022 Dec 6;12(23):4332.

17. Liu HW, Wei DX, Deng JZ, Zhu JJ, Xu K, Hu WH, et al. Combined antibacterial and osteogenic in situ effects of a bifunctional titanium alloy with nanoscale hydroxyapatite coating. Artif Cells Nanomedicine Biotechnol. 2018;46(sup3):S460–70.

18. Liu D, Xi Y, Yu S, Yang K, Zhang F, Yang Y, et al. A polypeptide coating for preventing biofilm on implants by inhibiting antibiotic resistance genes. Biomaterials. 2023 Feb;293:121957.

19. Ma M, Kazemzadeh-Narbat M, Hui Y, Lu S, Ding C, Chen DDY, et al. Local delivery of antimicrobial peptides using self-organized TiO2 nanotube arrays for peri-implant infections. J Biomed Mater Res A. 2012 Feb;100(2):278–85.

20. Zhou L, Xing Y, Ou Y, Ding J, Han Y, Lin D, et al. Prolonged release of an antimicrobial peptide GL13K-loaded thermosensitive hydrogel on a titanium surface improves its antibacterial and anti-inflammatory properties. RSC Adv. 13(33):23308–19.

21. Kruse HV, Chakraborty S, Chen R, Kumar N, Yasir M, Lewin WT, et al. Protecting Orthopaedic Implants from Infection: Antimicrobial Peptide Mel4 Is Non-Toxic to Bone Cells and Reduces Bacterial Colonisation When Bound to Plasma Ion-Implanted 3D-Printed PAEK Polymers. Cells. 2024 Apr 9;13(8):656.

22. Verheul M, Drijfhout JW, Pijls BG, Nibbering PH. Non-contact induction heating and SAAP-148 eliminate persisters within MRSA biofilms mimicking a metal implant infection. Eur Cell Mater. 2021 Jul 14;43:34–42.

23. Subh L, Correa W, Pinkvos T -J., Behrens P, Brandenburg K, Gutsmann T, et al. Synthetic anti-endotoxin peptides interfere with Gram-positive and Gram-negative bacteria, their adhesion and biofilm formation on titanium. J Appl Microbiol. 2020 Nov 1;129(5):1272–86.

24. Gamna F, Cochis A, Mojsoska B, Kumar A, Rimondini L, Spriano S. Nano-topography and functionalization with the synthetic peptoid GN2-Npm9 as a strategy for antibacterial and biocompatible titanium implants. Heliyon. 2024 Jan 30;10(2):e24246.

25. Wei J, Cao X, Qian J, Liu Z, Wang X, Su Q, et al. Evaluation of antimicrobial peptide LL-37 for treatment of Staphylococcus aureus biofilm on titanium plate. Medicine (Baltimore). 2021 Nov 5;100(44):e27426.

26. Kang J, Dietz MJ, Li B. Antimicrobial peptide LL-37 is bactericidal against Staphylococcus aureus biofilms. PLoS ONE. 2019 Jun 6;14(6):e0216676.

27. Zhao G, Zhong H, Zhang M, Hong Y. Effects of antimicrobial peptides on Staphylococcus aureus growth and biofilm formation in vitro following isolation from implant-associated infections. Int J Clin Exp Med. 2015 Jan 15;8(1):1546–51.

28. Nowicka J, Janczura A, Pajączkowska M, Chodaczek G, Szymczyk-Ziółkowska P, Walczuk U, et al. Effect of Camel Peptide on the Biofilm of Staphylococcus epidermidis and Staphylococcus haemolyticus Formed on Orthopedic Implants. Antibiot Basel Switz. 2023 Nov 28;12(12):1671.

29. Campoccia D, Montanaro L, Ravaioli S, Mariani V, Bottau G, De Donno A, et al. Antibacterial Activity on Orthopedic Clinical Isolates and Cytotoxicity of the Antimicrobial Peptide Dadapin-1. Int J Mol Sci. 2023 Jan 2;24(1):779.

30. D'Este F, Oro D, Boix-Lemonche G, Tossi A, Skerlavaj B. Evaluation of free or anchored antimicrobial peptides as candidates for the prevention of orthopaedic device-related infections. J Pept Sci Off Publ Eur Pept Soc. 2017 Oct;23(10):777–89.

31. Huang D, Parker DM, Mandell JB, Brothers KM, Gish CG, Koch JA, et al. Prospective Activity of PLG0206, an Engineered Antimicrobial Peptide, on Chronic Periprosthetic Joint Infection Total Knee Arthroplasty Components Ex Vivo: The Knee Explant Analysis (KnEA) Study. Microbiol Spectr. 2021 Dec 22;9(3):e0187921.

32. Raeder SB, Sandbakken ET, Nepal A, Løseth K, Bergh K, Witsø E, et al. Novel Peptides Targeting the β-Clamp Rapidly Kill Planktonic and Biofilm Staphylococcus epidermidis Both in vitro and in vivo. Front Microbiol. 2021;12:631557.

33. Chen J, Hu G, Li T, Chen Y, Gao M, Li Q, et al. Fusion peptide engineered "statically-versatile" titanium implant simultaneously enhancing anti-infection, vascularization and osseointegration. Biomaterials. 2021 Jan 1;264:120446.

34. Mandell JB, A Koch J, Deslouches B, Urish KL. Direct antimicrobial activity of cationic amphipathic peptide WLBU2 against Staphylococcus aureus biofilms is enhanced in physiologic buffered saline. J Orthop Res Off Publ Orthop Res Soc. 2020 Dec;38(12):2657–63.

35. Yan C, Liu Y, Xu Z, Yang H, Li J. Comparison of Antibacterial Effect of Cationic Peptide LL-37 and Cefalexin on Clinical Staphylococcus aureus-induced Infection after Femur Fracture Fixation. Orthop Surg. 2020 Jul 28;12(4):1313–8.

36. Huang DB, Brothers KM, Mandell JB, Taguchi M, Alexander PG, Parker DM, et al. Engineered peptide PLG0206 overcomes limitations of a challenging antimicrobial drug class. PLoS ONE. 2022 Sep 16;17(9):e0274815.

37. Huang D, Dobbins D, Ghahramani P, Friedland I, Steckbeck J. A Phase 1 Study of the Safety, Tolerability, and Pharmacokinetics of Single Ascending Doses of a First-in-Human Engineered Cationic Peptide, PLG0206, Intravenously Administered in Healthy Subjects. Antimicrob Agents Chemother. 2022 Jan 18;66(1):e0144121.

38. Peptilogics. A Phase 1b Open-Label, Dose-Escalating Study to Evaluate the Safety and Tolerability of PLG0206 in Patients Undergoing Debridement, Antibiotics, and Implant Retention (DAIR) for Treatment of a Periprosthetic Joint Infection (PJI) Occurring After Total Knee Arthroplasty (TKA) [Internet]. clinicaltrials.gov; 2022 Dec [cited 2025 Feb 4]. Report No.: NCT05137314. Available from: https://clinicaltrials.gov/study/NCT05137314

39. Urish KL, Bullock AG, Kreger AM, Shah NB, Jeong K, Rothenberger SD, et al. A Multicenter Study of Irrigation and Debridement in Total Knee Arthroplasty Periprosthetic Joint Infection: Treatment Failure Is High. J Arthroplasty. 2018 Apr;33(4):1154–9.

40. Rosas S, Hegde V, Plate FJ, Dennis D, Jennings J, Bracey DN. Bacteremia in Patients Undergoing Debridement, Antibiotics, and Implant Retention Leads to Increased Reinfections and Costs. Arthroplasty Today. 2022 Aug;16:259-263.e1.