B8: "What critical pathogens should be routinely evaluated in preclinical models to study important questions in orthopaedic infection research?

Ahmad Abbaszadeh, Mohammad Soleimani, Saeed Kordo, Edward M. Schwarz, Javad Parvizi.

Response/Recommendation: The literature indicates that, in addition to prevalent pathogens, other gram-negative bacilli and Entrobacteriales should be evaluated in orthopaedic infections, especially in preclinical models.

Level of Evidence: Moderate

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

Rationale: Orthopaedic infections can cause devastating complications, including long hospital stays and prolonged antibiotic treatment, and pose high morbidity and mortality in patients (1). A limited assortment of common microorganisms is recognized as the principal etiological pathogens responsible for the majority of orthopaedic infections, including *Staphylococcus aureus*, coagulase-negative Staphylococcus (*S. epidermidis*), *Escherichia coli*, and *Enterobacter cloacae* (2–4). However, they are not the only microorganisms that cause such a devastating condition. Hence, Preclinical models are crucial in evaluating the pathophysiology of the infection and the development of antimicrobial agents (5).

A systematic review was conducted to determine what organisms should be routinely evaluated in orthopaedic research. A total of six studies were included (four human studies (6–9), one on sheep (10), and one on dogs (11)). All studies (n = 6, 100%) were case series. Due to the nature of the studies, we were not able to perform a meta-analysis. The human studies found 284 microorganisms, and the other two found 42 and 71 microorganisms. The studies evaluated infections of biofilm (6), surgical site (8,11), fracture-related (7), septic arthritis (9), and osseointegration (10).

One study with 42 microorganisms did not report the exact number of each microorganism, and data extraction was not feasible (10). In the remaining studies (705 microorganisms), the most reported isolates were *S. aureus* (methicillin-susceptible and methicillin-resistant) (n = 168, 23.8%), Enterobacteriaceae (n = 158, 22.4%), CoNS (n = 156, 22.1%), other gram-negative bacilli (n = 69, 9.7%), other Enterobacteriales (n = 52, 7.3%), *S. pseudointermedius* (n = 31, 4.3%), Streptococcus (n = 31, 4.3%), Enterococcaceae (n = 22, 3.1%), gram-positive cocci (n = 11, 1.5%), gram-positive bacilli (n = 10, 1.4%), and Pasturella spp. (n = 2, 0.2%). The *S. pseudointermedius* isolates were only observed in one study with dog subjects, as it is primarily a pathogen for domestic animals (10).

Bone and joint infections caused by the Staphylococcus genus, including *S. aureus* and *S. epidermidis*, and the Enterobacteriaceae family, including *E. coli*, *K. pneumoniae*, and *E. cloacae*, have been reported and evaluated. However, what is more important is that the pathogenesis of other Enterobacteriales and gram-negative bacilli should not be overlooked. Moreover, *S. pseudointermedius* was the isolate in more than half (52.5%) of the surgical site infection cultures in an animal study, indicating it is a potential pathogen for orthopaedic infections. Furthermore, we suggest considering the Food and Drug Administration (FDA) suggestion of microorganisms to be tested against, including *Acinetobacter baumanii*, *Bacterioides fragilis*, *Candida albicans*, *Candida tropicalis*, *Enterococcus faecalis*,

Enterococcus faecium, *Escherichia coli*, *Haemophilus influenzae*, *Klebsiella aerogenes*, *Klebsiella oxytoca*, *Klebsiella pneumoniae*, *Micrococcus yunnanensis*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Serratia marcescens*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Staphylococcus haemolvticus*, *Staphylococcus hominis*, *Staphylococcus saprophyticus*, *Streptococcus pneumoniae*, and *Streptococcus pyogenes*.

In conclusion, the evidence demonstrates that, in addition to prevalent pathogens, other gram-negative bacilli and Entrobacteriales should also be evaluated in preclinical models. Furthermore, evaluation of any technology against fungi can be important. Preclinical studies mostly focus on common pathogens, e.g., *S. aureus*, *S. epidermidis*, *E. coli*. Nonetheless, more preclinical studies on less common microorganisms are warranted for a comprehensive systematic review and meta-analysis. Publication of these novel studies needs to quantitatively document the pathology in the bone and soft tissue, and the strains need to be sequenced and deposited into a broadly accessible reference microorganism bank (i.e. the American Type Culture Collection, ATCC).

References:

1. Parvizi J. Orthopedic infections: no one is denying anymore that we have a problem! Vol. 31, Knee Surgery & Related Research. Springer; 2019. p. 1–2.
2. Arciola CR, Campoccia D, Ehrlich GD, Montanaro L. Biofilm-based implant infections in orthopaedics. Biofilm-based Healthcare-associated Infections: Volume I. 2014;29–46.
3. Lovati AB, Bottagisio M, de Vecchi E, Gallazzi E, Drago L. Animal models of implant-related low-grade infections. A twenty-year review. A modern approach to biofilm-related orthopaedic implant infections: advances in microbiology, infectious diseases and public health volume 5. 2016;29–50.
4. Phillips JE, Crane TP, Noy M, Elliott TSJ, Grimer RJ. The incidence of deep prosthetic infections in a specialist orthopaedic hospital: a 15-year prospective survey. J Bone Joint Surg Br. 2006;88(7):943–8.
5. Beagan MLC, Dreyer CH, Jensen LK, Jensen HE, Andersen TE, Overgaard S, et al. The potential of sheep in preclinical models for bone infection research–A systematic review. J Orthop Translat. 2024;45:120–31.
6. Coraça-Huber DC, Kreidl L, Steixner S, Hinz M, Dammerer D, Fille M. Identification and morphological characterization of biofilms formed by strains causing infection in orthopedic implants. Pathogens. 2020;9(8):649.
7. Fonkoue L, Tissingh EK, Ngouateu MT, Muluem KO, Ngongang O, Mbouyap P, et al. The microbiological profile and antibiotic susceptibility of fracture related infections in a low resource setting differ from high resource settings: a cohort study from Cameroon. Antibiotics. 2024;13(3):236.
8. Liu S, Qi Q, Chen Z, Liu N, Guo Z, Sun C, et al. Polymicrobial and monomicrobial infections after spinal surgery: a retrospective study to determine which infection is more severe. Asian Spine J. 2017;11(3):427.
9. Nasim O, Khalil A, Khan S, Kohli S, Pantelias C, Banoori F, et al. Microbiological profile and clinical features of septic arthritis of the Shoulder: A 10-year cohort single-centre study. Cureus. 2023;15(12).
10. Williams DL, Bloebaum RD, Beck JP, Petti CA. Characterization of bacterial isolates collected from a sheep model of osseointegration. Curr Microbiol. 2010;61:574–83.
11. Hagen CRM, Singh A, Weese JS, Marshall Q, Linden A zur, Gibson TWG. Contributing factors to surgical site infection after tibial plateau leveling osteotomy: a follow-up retrospective study. Veterinary Surgery. 2020;49(5):930–9.