B5: "What are the best preclinical models of orthopaedic infection for the evaluation of therapeutic efficacy?"

Jessica Amber Jennings, Ezzuddin Abuhussein, Louise Kruse-Jensen, T. Fintan Moriarty, Javad Parvizi, Edward M. Schwarz & Claudia Siverino

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Response/Recommendation: As with all research on living organisms, the best model is primarily determined by the hypothesis to be tested. Species studied to address questions relevant to orthopaedic infection range from worms[1] to horses[2], and general animal welfare rules apply (e.g. molecular/mechanistic and initial dose-ranging/therapeutic index studies should be tested in small species, while clinically relevant hypotheses of pharmacokinetics/biomechanics/implant designs should be tested in larger species). There has also been a revolution in research tools and outcome measures in preclinical models of orthopaedic infection such that the scientific rigor and reproducibility of the experimental design now impact the ethics of animal research and the validity of conclusions pertaining to therapeutic efficacy. While there are published reviews that provide guidance on species that should be used for questions along the preclinical spectrum [3-5], work is required to optimize an ideal experimental design based on: 1) the principles of the 3Rs (Replacement, Reduction and Refinement) for animal research, 2) currently available technologies to achieve the desired scientific rigor of the conclusions (pilot vs. definitive preclinical evidence), and 3) the feasibility of the approaches to allow reproducibility by other investigators in the field. To satisfy these current scientific standards, the best preclinical models of therapeutic efficacy must include quantification of the pathogenic inoculum, evidence of infection prior to treatment, and quantification of the pathogenic burden at the prospective endpoint. Superior studies also include statistically powered longitudinal outcomes (e.g. radiology, serology, bioluminescent imaging) and ex vivo analyses (e.g. histology, microbiology, biochemistry, molecular biology).

Level of Evidence: Strong

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

Rationale: We interpreted "best" to imply most ethical, rigorous, and reproducible. As there are no validated in silico (computational) or in vitro "preclinical models of orthopaedic infection" we only considered non-human vertebrae animal models. A comprehensive literature search was conducted using the search words ""Prosthesis-Related Infections, orthopaedic infection, osteomyelitis, joint infection, PJI, Animal Experimentation, treatment efficacy, therapeutic evaluation, biofilm eradication" within PubMed and Embase, which initially identifed 1749 potentially relevant unique studies, screened by two independent reviewers, of which 422 were selected for full-text review and 168 were included for evaluation. To focus on the question of "therapy efficacy" only primary research articles were included, and all studies that did not have an outcome measure to confirm establishment of chronic infection followed by randomization into control vs. treatment group(s) were excluded (animal modelling and prophylactic treatment studies were excluded). We also deemed that contemporary/state-of-the-art methodologies are the "best", and thus excluded paper published prior to 2010.

Mouse Models: Eleven publications that met the inclusion criteria used murine models[6-16]. All studies evaluated *S. aureus* bone infection. Inoculations ranged from 10^3 to 10^8 CFU administered via a contaminated implant (n=8), or direct injection into the blood, joint, or bone marrow. All studies enumerated CFU on implants and bone tissues. Most studies used bioluminescent strains (Xen29, Xen36, USA300) and monitored the infection longitudinally via bioluminescent imaging (BLI). Two studies used BLI to randomize the mice to treatment (n=10). Most studies used micro-CT as an outcome measure of osteolysis. Most studies performed H&E, Gram, and TRAP-stained histology to confirm the infection, quantify abscesses, and osteoclasts, respectively. Some studies used electron microscopy to assess biofilm on implants and within the osteocyte lacuno-canalicular network (OLCN) of infected bone. Few studies weighed the mice or performed serology, hematology, or molecular analyses. One study used a transgenic mouse to quantify green fluorescent protein positive myeloid cells as an outcome. Taken together, the "best" murine models to assess treatment efficacy use a standardized inoculation of bioluminescent bacteria and perform longitudinal BLI to assess in vivo growth and to randomize mice to treatment groups. They also perform ex vivo studies at prospective endpoints to quantify CFU on the implant and bone tissues, quantify osteolysis via micro-CT, and histomorphometry to assess bacterial biofilms, bone, bone cells and immune cells.

Rat Models: Fifty publications utilizing rat models met the inclusion criteria and were included in the review [17-64]. The two primary rat species used were Wistar and Sprague Dawley rats. Among the studies, 66% used male rats, 18% used female rats, and 8% did not report the sex of the rats. The most common defect sites were the femur and tibia, along with their respective intramedullary channels. Notably, only one study focused on the spine [49], while a few examined the knee joints [27; 33; 60; 61]. The studies primarily utilized pin models in the tibia or femur, alongside fracture models that were fixed with stainless steel Kirschner wires (K-wires). Only a limited number of studies employed stainless steel plates for fracture fixation [33; 46; 63]. Other types of implants included polyetheretherketone (PEEK) screws [19; 47; 57; 58] and cement-coated rods [49]. The predominant microorganism tested was *Staphylococcus aureus*, with 88% of the studies using either methicillin-sensitive *S. aureus* (MSSA) or methicillin-resistant *S. aureus* (MRSA). Ten percent of the studies involved *S. epidermidis*, and only one study utilized both [18]. *S. epidermidis* was mainly used in rat models with PEEK screws [19; 57; 58]. The initial inoculation of bacteria ranged from 10^3 to 10^8 CFU per animal. Infection was established by either inoculating the bacterial solution directly into the defect or intramedullary channel, or by inserting a pre-inoculated pin or K-wire into the defect site. The inoculation volume varied between 10 to 100 µL. As an outcome measure, all studies included bacteriological assessments of the retrieved tissue to enumerate bacterial survival. However, not all studies conducted a comprehensive bacteriology assessment, as some did not analyze all the tissues involved or failed to report the exact methodology used for quantification. Radiography and micro-CT were frequently employed to evaluate bone healing or bone resorption. Histopathological analyses were also conducted to assess the presence of bacteria and/or immune cell responses. A limited number of studies quantified antibiotic concentrations in the serum, bone, and intramedullary space. Additionally, cytokine levels, such as IL-6 or TNF-α, were measured in the serum of the infected animals.

Rabbit Models: Twelve publications used rabbit models, primarily with New Zealand White rabbits due to their docility and similarity to humans in their reaction to disease and medications. The most common defect site was the tibia, due to not requiring internal or external fixation. Less common sites included the radius[65], femur[66; 67] and the mandible[68; 69]. The most common microorganism was MRSA, followed by MSSA, with fewer studies investigating gram negative microorganisms like Klebsiella pneumoniae[70] and E. coli.[71] Implants used to initiate implant-associated infection included K-wires, Jamshidi needles, and custom made titanium implants, with inoculation amounts ranging from 10^5 to 10^9 CFU. In addition to bacteriology, radiography scoring has been established as an effective measure of bone healing, although there is some debate about the most appropriate scoring systems.[72] Histomorphometric scoring is also common to assess healing and inflammation in the defect site. Some studies measured blood markers, MicroCT, weight, mortality, and systemic concentration of antibiotics as additional outcome measures. The "best" rabbit models include at minimum bacteriology, an established radiographic scoring system, and an established histomorphometric scoring system.

Pig Models: Four publications that met the inclusion criteria used porcine models[30; 73-75]. All used immature, female pigs of ~40 kg body weight. The bone infection was established by 10^4 CFU of *S.*

aureus via direct injection or together with insertion of a small non-functional steel implant. Bone infection development was confirmed after 7 days by microbiological analyses of infected bone tissue and sonication of implants. Following the therapeutic intervention period and euthanasia the exact same analyses was conducted. This allowed CFU reduction of the established infection to be the primary outcome for assessing therapeutic efficacy. This approach was feasible as a reliable human-scale revision surgery has been included in all tested therapeutic interventions of pigs[30; 73; 74]. Due to the size of pigs, intravital imaging of the infection development is difficult. If revision surgery is not a part of the therapeutic intervention the infection development should be confirmed by other analyses like imaging techniques and euthanasia of infection controls. Like sheep, pigs allow robust preclinical testing of treatment modalities included in one-stage revision of osteomyelitis, such as surgical approaches, introduction of biomaterials, implant coatings, and plastic surgery. Due to the increased use of sheep and pigs in bone infection research, there should be even more focus on obtaining better knowledge about their bone physiology, immune response and metabolism of antimicrobials in comparison to humans.

Sheep Models: Five publications that met the inclusion criteria used sheep models. Four of these studies used female sheep, and it was not reported in the fifth. Three studies used the tibia (all with intramedullary nails, but without creating fractures or osteotomy) and 2 in the femur (one study used a prosthetic hip stem, and one study used a cylindrical stainless-steel plug 20 mm long and 8 mm in diameter). All studies evaluated *S. aureus* bone infection, either MSSA or MRSA. No bioluminescent strains were used in any study. Inocula ranged from 10^7 to 10^9 CFU, added either as a liquid suspension to the intramedullary channel or implant or deposited on a collagen fleece and inserted into the intramedullary channel adjacent to the implant. All studies performed a microbiological assessment, four of them provided quantitative results, while one study cultured and identified the bacteria without quantifying bacterial load. All studies used radiography to evaluate bone changes due to infection. Only one study used histopathology to assess inflammation (acute and chronic), bone necrosis, and new bone formation.[76] No sheep study used histopathology to identify bacteria in tissues. All studies performed a routine and regular clinical examination of observations such as weight and behavior changes, limping, and local signs of infection. Three studies used a dedicated scoring system, although it was not fully described. [77-79] The remaining two did not disclose if a scoring system was used to monitor animal welfare. Hematology was also performed. In one study, WBC, CRP, and ESR were measured but discontinued due to lack of correlation with infection status.[79] Similarly, Foster et al. did not measure hematological markers for the same reason. Alegrete et al. performed regular hematology assessments including WBC and CRP, with again WBC not yielding differential results based on infection status, however, this study did show CRP to differ between groups.[76] Boot et al and Nakahara et al did not present any hematology data [76; 80].Due to the small number of sheep studies, it is challenging to identify the best model. It is not entirely clear why histopathology is less common in sheep models compared to smaller animals; however, it may be linked to the large area across which the infection is present, and the difficulty in identifying the real nidus of the infection. In the only sheep study where the infection was localized to a preformed defect, and thus easily identifiable, histopathology was performed. Another improvement needed for the sheep models is to identify improved blood biomarkers to monitor disease progression or infection burden. Animal welfare is reliant on clinical observations such as general behavior, lameness, and wound appearance.

For all the animal models described above, to meet the 3R standards, adequate power to detect significant differences in treatment effects are essential. For murine animal models, the number of animals per group ranged from 3 - 20 with the median being 10. With larger animal models, costs of animals and care must be balanced with including enough animals to detect treatment effects. For rabbits, animal number per group ranged from 3 to 23, with the median being 12. For pigs and sheep, animal numbers per group ranged from 3 to 10, with the median being 6. An overwhelming majority of the studies only included single sex of animal, making it difficult to determine whether sex differences exist in treatment strategies for MSKI.

The “best” studies also describe measures to minimize bias in outcome evaluation, including balancing of infection status at treatment start, randomization of animals into treatment groups, and blinding of treatment groups to both surgeons at the time of intervention and outcome evaluators. Quality assessment of the extracted articles determined that 60% of studies had adequate randomization described, 48% of studies had appropriate descriptions of blinded evaluators of outcome, and only 25% described blinding of the surgeon to treatment group.

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