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QUESTION 5: Does an animal model for periprosthetic joint infection (PJI) exist?

RECOMMENDATION: Yes, there are several animal models using different species and implant designs that have claimed to pertain to PJI. However, the majority of these models are not representative of clinical PJI.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 88%, Disagree: 4%, Abstain: 8% (Super Majority, Strong Consensus)

RATIONALE

Despite its increasing prevalence, our fundamental understanding of how bacteria enter the human prosthetic joint, establish biofilm, resist immune response and overcome clinical treatment remains limited. Establishing representative animal models of human disease has led to translational breakthroughs in medical fields such as immunology [1], toxicology [2], oncology [3] and orthopaedics specifically have led to the introduction of novel therapies such as for fracture healing [4] and for improved osseointegration surfaces [5] in joint reconstruction. With such examples, it is conceivable that a clinically representative animal model of PJI could improve our understanding of the pathogenesis of PJI and consequently lead to novel strategies for PJI prevention and treatment.

A systematic review of the literature was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to identify published animal models described to be representative of PJI. The majority were in mice (14) [6–19], with rabbit (5) [20–24], rat (2) [25,26], sheep or ovine (2) [27,28] and dog or canine (1) [29] comprising the species utilized. Utilizing large-animal models such as dogs and sheep permit more frequent serum analyses and involve bony architecture that contains osteons and Haversian systems, which are similar to human bone [30]. However, larger animals have more porous bone that turns over more rapidly compared to humans, making metrics such as osseointegration and osteolysis more difficult to interpret [31]. Smaller animal models are advantageous due to their substantially lower-running costs and, uniquely thus far in the case of mice, the possibility of genetic manipulation to reproduce human disease states [32,33]. However, rodent immune systems are mostly rich in lymphocytes, a stark difference from the largely neutrophil-based immune response found in humans [34]. There currently is no consensus on which animal species is ideal for modeling PJI.

The majority of studies failed to utilize implants that effectively recreate the periprosthetic environment, characterized by the implant separating the articular space from the intramedullary space, or that bear load. The most popular choice was a stainless steel wire inserted retrograde into the femoral canal [6–9,11–13,16–18,24–26,35,36], an implant which does not bear load, is not of the same material as arthroplasty implants, is mechanically loose and fails to recreate the periprosthetic space. The second most popular choice was a titanium screw (with or without a washer) placed across the proximal tibial cortex [14,15,23,28,37], an implant which bears load and uses a correct arthroplasty material, but does not involve the medullary canal and preserves articular cartilage. Three articles utilized implants that bore weight and separated the articular and medullary spaces [19,21,22]. However, two of these articles utilized a silicone implant [21,22] and only one utilized the correct titanium alloy used in clinical arthroplasty implants [19]. This latter example was the only model that fulfilled implant-related criteria. Troublingly, two articles made cortical bone windows and utilized no metal or plastic-based implants whatsoever [10,20].

Almost all studies (23) involved gram-positive organisms including methicillin-sensitive *Staphylococcus aureus* (MSSA) [7–9,11–21,24,25,28], methicillin-resistant *Staphylococcus aureus* (MRSA) [6,22,23,26], and *Staphylococcus epidermidis* [10]. All bacteria utilized in retrieved studies were commercially available strains. There is incomplete information pertaining to the biofilm-forming ability of these strains and, to our knowledge, no study used bacteria derived directly from clinical PJI. The most common method of bacterial inoculation involved injecting bacteria into the articular space following implant insertion and wound closure [7–9,11,12,16,17,21–23,26,28]. Alternatives that share clinical relevance included injecting bacteria into the medullary canal prior to implant insertion [10,18,20,24], pipetting bacteria onto the implant immediately after insertion [6], and administering bacteria intravenously [13,25]. Another method which is not clinically representative is to culture the implant in bacterial broth for 24 hours, permitting biofilm to form on the surface prior to insertion [14,15].

Methodology to determine bacterial viability varied across the retrieved articles, but was not restricted to model type. More comprehensive analyses were identified in mouse-based studies, with biofilm architecture, bacterial colony counting on tissues and implant surfaces and descriptions of immune responses being collectively described in several studies. To date, no non-mouse based study has included quantitative measurements of bacteria, biofilm, and host immune response.

Mouse-based models of PJI are currently the most popular and provide the most comprehensive methodology for PJI-related investigations. Unfortunately, the majority of these models fail to utilize implants that function like their clinical counterparts. This finding is disappointing considering the successful animal models available in orthopaedics for trauma [38] and sports-related conditions [39].

Although intramedullary pins remain popular in PJI-themed models, they have obvious deficiencies when trying to represent arthroplasty components and have been confused in representing osteomyelitis and septic arthritis [10,15]. Carli et al. proposed four criteria that all animal models of PJI should meet: (1) modeling should be performed in animals with comparable musculoskeletal and immunological properties to humans, (2) utilized implants should be of clinically relevant materials, (3) models should use clinically relatable bacteria that can form biofilms on implant surfaces and (4) methodology should include quantitative measurements of bacteria, biofilm and host immune response [40]. One animal model [19] currently fulfills this criteria. Unfortunately, this model has only recently been introduced and requires further validation with the testing of prophylactic or therapeutic PJI investigations.

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