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Critical analysis of experimental models of periprosthetic joint infection

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ABSTRACT

Introduction: Because the extreme diversity of clinical situations makes formal clinical trials difficult to carry out, animal models of periprosthetic infection in orthopaedics are needed to understand the aetiology and pathology of these infections, and to test new treatment methods. These experimental models must reproduce the features of the infections encountered in clinical practice. One of the model variables is the method of inoculation: local (intra-articular), intravenous or intra-articular. Another is the timing of the inoculation: intra-operative or postoperative. Together, these options simulate the different contamination methods: direct, by proximity or blood-borne. However, the chosen inoculation route can also affect the infection rate and severity in the various models, and in some cases do not accurately reproduce the postoperative infections encountered clinically.

Hypothesis: The direct inoculation method is the most effective for inducing a local infection on a foreign body in a joint, and the least iatrogenic.

Methods: A critical analysis of published studies was carried out to evaluate each model against three endpoints, according to the type of inoculation. The primary endpoint was the infection rate, which should be as close as possible to 100%. The secondary endpoints were the mortality rate and rate of spontaneous healing, both of which should be as low as possible. Twenty-one articles were reviewed.

Results: Intra-articular and intra-medullary inoculations had induction rates between 70 and 100%; intra-articular inoculations had an induction rate of 100%, while intravenous inoculation had a rate of 47 to 77%. The mortality rates were lower with the intra-articular and intramedullary inoculations (5 to 23%) than for the intra-articular inoculations (37%) and intravenous inoculations (28 to 56%). The spontaneous healing rate was 0 to 30% for intra-articular and intramedullary inoculations, 30 to 53% for intravenous inoculations and 0% for intra-articular inoculations.

Conclusion: Direct inoculation methods are most effective at reproducing chronic periprosthetic joint infections, without putting the animal’s life at risk or allowing for spontaneous healing. The simulation of blood-borne infections is more random.

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1. Introduction

Many animal models have been created to study musculoskeletal infections, particularly ones that reproduce osteomyelitis. Most of the models are based on Norden’s work [1] in the late 1970s. Extrapolations have been made from this initial model to help us better understand periprosthetic joint infections (PJI) [2]. These infections are a major issue because of the increasing number of prostheses being implanted. Each year, more than 200,000 joint prostheses are implanted in France, with 1 to 1.5% becoming infected. Staphylococcus is the most prevalent bacterial species implicated [3]. However, the clinical scenarios vary greatly, making it difficult to plan comparative or even randomized clinical trials.

Animal models are good for studying the prophylactic and therapeutic effects of antibiotics on prosthesis-related infections because infections can be induced homogeneously and reproducibly under experimental conditions. They help us understand the pathophysiology of PJI and to test new treatments, such as...
systemic antibiotics, antibiotic-loaded bone cements and implant coatings. For these models to be applicable to humans, they must reproduce the infection method and progression of the human PJI as closely as possible, namely the absence of spontaneous healing and progression to chronic infection, while being reproducible and easy to carry out. In addition, they must be ethically acceptable (approved by research ethics committee) and low cost.

One of the important considerations is the method of inoculation: intra-operative intra-articular, postoperative intra-articular and intravenous (blood-borne) or by proximity (intramedullary). Each type of inoculation simulates one of the various contamination methods encountered during clinical practice. For example, local inoculation (intra-articular) is the inoculation method that best reproduces the conditions of nosocomial infection, which is the most common type of infection. It is attributed to direct contamination of the surgical wound or implant. No matter its form, inoculation should consistently produce an infection that is likely to become chronic, without leading to the animal’s death. This reproduces the features of most PJs in humans. This led us to evaluate the contamination method used in all published PJI models, which was classified using certain criteria. First, the contamination must result in a 100% or nearly 100% infection rate. Second, the rate of mortality and spontaneous healing must be as close to 0% as possible.

We hypothesized that the direct inoculation method was the most effective for inducing a local infection on a foreign body in the joint, and the least iatrogenic.

2. Material and methods

A search was performed using PubMed to identify relevant articles using the keywords experimental or model + joint + infection or periprosthetic + infection (Fig. 1).

Articles were included if they featured an orthopaedic periprosthetic joint infection model.

Articles were excluded when:

- the infection did not reproduce a PJI, in particular models of subcutaneous cage implantation that reproduce a foreign body infection that is dissimilar to PJI in humans because of subcutaneous abscess is formed that does not infect the bone or joint [3,4];
- the model induced osteomyelitis without arthritis.

Twenty-one articles were retained and analysed that encompassed nine different models of PJI [5–25]: 7 in rabbits, 1 in mice, and 1 in rats.

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**Fig. 1.** Study flow chart.
Each article was analysed to determine the method of inoculation, bacterium used, surgical technique (and more generally the methods, including ethics approval), resemblance of the PJI to the human condition (particularly in terms of function, bone appearance and absence of spontaneous healing), and the goal of the study (development of model, test of local or systemic antibiotics, etc.) (Table 1).

Four methods of inoculation were found:

- intra-operative intra-articular inoculation [5,6,10,13,14,16–25]. This consisted of injecting the inoculum (0.1 to 0.5 ml depending on the protocol) into the joint after a device had been implanted (Table 1) and the skin closed; a 1 cc syringe with a 16G needle was used in these cases;
- intra-operative intramedullary inoculation [9,11,15]. This consisted of injecting the inoculum into the bone’s medullary canal before implantation, at the time of the diaphyseal catheterization (generally using a syringe with a 16G needle, and injecting 0.002 to 0.1 ml of bacterial suspension, depending on the animal species);
- postoperative intravenous inoculation [7–9]. This consisted of injecting the inoculum (1 ml bacterial suspension) in a peripheral vein (ear vein in rabbits) after implantation using a 22–24G catheter;
- postoperative intra-arterial inoculation [12]. This consisted of injecting the inoculum into the femoral artery after implantation; this method required exposing the femoral artery 2 cm above the knee joint and then introducing a 26G catheter to inject 1 ml of bacterial suspension.

For all the models, independent of the method of inoculation, the infection diagnosis was made based on microbiological analysis (particularly, bacterial counts) of the bone harvested during the

### Table 1
Comparison of different animals models by inoculation method (NZW: New Zealand white, PJI: periprosthetic joint infection).

<table>
<thead>
<tr>
<th>Type of inoculation</th>
<th>First author</th>
<th>Year of publication</th>
<th>Microorganism used</th>
<th>Implant used</th>
<th>Type and number of animals used</th>
<th>Goal of study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>[16,17,20–22,25], evaluation of diagnostic methods [18,19], evaluation of bioactive polymers [23], evaluation of antibiotic-loaded cements [24]</td>
</tr>
<tr>
<td>Intra-articular intramedullary</td>
<td>Southwood [9]</td>
<td>1985</td>
<td>S. aureus</td>
<td>Hemiarthroplasty of hip: femoral component with ball bearings and cemented pins</td>
<td>125 short-haired rabbits</td>
<td>Demonstrate reduced resistance to infection in the presence of foreign body</td>
</tr>
<tr>
<td></td>
<td>Alt [11]</td>
<td>2006</td>
<td>S. aureus</td>
<td>Tibial intramedullary locked nail (distal end placed intra-articular)</td>
<td>30 NZW rabbits</td>
<td>Test implant coatings, some of which were gentamicin impregnated</td>
</tr>
<tr>
<td></td>
<td>Antoci [15]</td>
<td>2007</td>
<td>S. aureus</td>
<td>Titanium nail+vancomycin coating in distal femur (distal end placed intra-articular)</td>
<td>24 Wistar Rats</td>
<td>Test benefits of using vancomycin coating for preventing PJI</td>
</tr>
<tr>
<td></td>
<td>Southwood [9]</td>
<td>1985</td>
<td>S. aureus</td>
<td>Hemiarthroplasty of hip: femoral component with ball bearings and cemented pins</td>
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<td>Demonstrate reduced resistance to infection in the presence of foreign body</td>
</tr>
</tbody>
</table>

S. aureus: Staphylococcus aureus; PJI: periprosthetic joint infection.
animals' autopsy. In most studies, the diagnosis was supplemented with histological or radiographical analysis.

3. Results

Local injection of the inoculum (intra-articular or intramedullary) was the method of the inoculation that led to the highest infection rate (75–100% for intra-articular and 70–100% for intramedullary) and the lowest mortality rate (Table 2). Even though the mortality rate was not always reported [5,8,13–15,20–22,24,25], it was estimated to be 5 to 23% for intra-articular inoculation [6,10,16–19,23], and 11 to 17% for intramedullary inoculation [8,10]. In our own rabbit model of intra-articular inoculation [5,16–25], the number of deaths increased when rifampicin was given; the observed 23% rate in the last study was due to profuse diarrhoea in rabbits (non-published data).

The spontaneous healing rate was 0 to 25% for intra-articular inoculation and 0 to 30% for intramedullary inoculation.

The other inoculation methods, namely intravenous and intra-articular, produced lower infection rates (47–70% infection rate after IV inoculation with 30–53% spontaneous healing, possibly due to a lavour effect of rabbit serum) or led to excess mortality (37% for intra-articular and 28–56% for intravenous inoculation).

4. Discussion

Direct local inoculation (either intramedullary or intra-articular) is the most effective inoculation method in studies of chronic PJIs, resulting in a high infection rate and low mortality rate relative to the other methods of inoculation. The other methods (intra-articular and intravenous) led to higher mortality rate, probably due to the technical challenges associated with arterial catheterization in the lower limbs of small animals and likely bacteremia with severe secondary infection [9]. This may explain why few studies have been published with these methods of inoculation.

Although the direct inoculation model does not simulate bloodstream infections, it makes it possible to study the large majority of early PJIs. For this reason, it has been used during animal model development, study of the pathophysiology of infection and also treatments.

The implant used is an important element to consider, particularly because of biofilm formation. It would be interesting to test new materials or materials that resemble those used in humans.

Other variables affect the infection rate, mortality rate and spontaneous healing rate, such as the animal species and type of microorganism.

Most of the models reviewed use rabbits because of their reactions to infection, which mimic human joint infections (inflammatory scar, skin fistula, osteitis on radiographs, reduced joint range of motion) and the ease of performing surgical procedures on them, including joint replacement [26]. The pharmacokinetics of antibiotics in rabbits is close to that of humans, making it possible to evaluate new treatments and other pathophysiological features, such as the effect of the virulence of Staphylococcus aureus in vivo. And finally, these animals are more susceptible to infection than rats or mice, and do not cost too much, especially in comparison to large animals such as sheep and pigs [27]. However, they have poor digestive tolerance to certain antibiotics (namely rifampicin), which can induce severe diarrhoea and cause elevated mortality.

Most models use a strain of S. aureus because this is a very common pathogen found in musculoskeletal infections, particularly in PJIs in humans. There is joint and bone tropism, which is the subject of other studies. But other bacteria can cause certain PJIs, and the strains used do not necessarily represent the causative agents in humans [28]. The main limitation of this review is that none of the models used a strain of coagulase-negative Staphylococcus, which is common in humans [29]. The goal of developing models of PJIs in animals revolves around the possibility of studying the pathophysiology of such infections, and the treatment possibilities that ensue. This requires research into the microorganisms representative of the bacterial population found in musculoskeletal infections in humans. Moreover, the use of different species of animals and different types of implants can make it difficult to compare the various models; this is another important limitation of this review.

5. Conclusion

Direct inoculation is the most effective experimental contamination method used to obtain a PJ, but this procedure does not model infection disseminated through the blood or by proximity. Experimental models of blood-borne infections are trickier to implement, and they induce lower infection rates and excessive mortality.

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L.G. and A.S.M. declare that they have no competing of interest.


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