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Original article

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

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 helps 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

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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-arterial 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 PJIs 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.

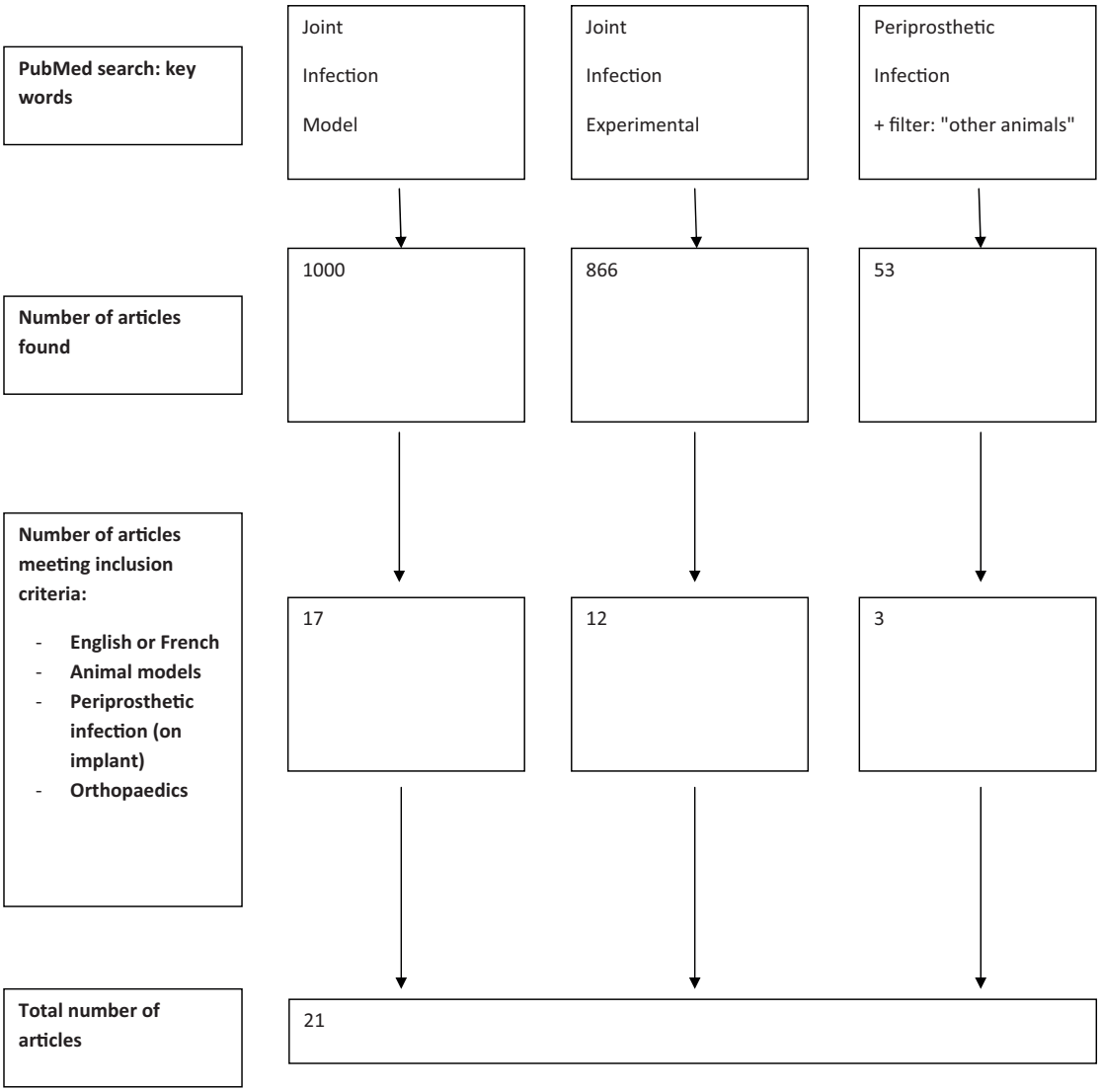

Fig. 1. Study flow chart.