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Review

Animal models for percutaneous-device-related infections: a review

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ABSTRACT

This review focuses on the construction of animal models for percutaneous-device-related infections, and specifically the role of inoculation of bacteria in such models. Infections around percutaneous devices, such as catheters, dental implants and limb prostheses, are a recurrent and persistent clinical problem. To promote the research on this clinical problem, the establishment of a reliable and validated animal model would be of keen interest. In this review, literature related to percutaneous devices was evaluated, and particular attention was paid to studies involving the use of bacteria. The design of percutaneous devices, susceptibility of various animal species, bacterial strains, amounts of bacteria, method of inoculation and methods for subsequent evaluation of the infection are discussed in detail. Given that an ideal animal model for study of percutaneous-device-related infection is still not existent, this article presents the basis for the construction of such a standardized animal model for percutaneous-device-related infection studies. The inoculation of bacteria is critical to obtain an animal model for standardized studies for percutaneous-device-related infections.

1. Introduction

A percutaneous device is an object made from a synthetic material that penetrates the skin through a surgically created defect [1]. At present, percutaneous devices are widely used in clinical treatment, and applications include indwelling catheters, external fixators, electrical connection of sensors, vascular access devices, dental implants, auditory prostheses and orthopaedic prostheses, among others [2]. Although the application of percutaneous devices greatly improves the quality of life of patients, there are still considerable drawbacks. Specific problems, as reviewed previously [3], include marsupialization (i.e. the process of epidermal migration along a percutaneous implant resulting in the formation of an epidermis-lined pouch in which the implant rests), per-migration (the process by which epidermal cells migrate through the pores of a percutaneous implant, eventually filling the pores with epidermal maturation products), bacterial infection or abscess formation, avulsion (mechanical disruption of the tissue/implant interface) and extrusion (destruction of tissue–implant continuity with loss of the implant function). In particular, the occurrence of an infection with bacteria colonizing the percutaneous device is a prelude to marsupialization, per-migration and avulsion. Thus, infection is the most common reason for the ultimate failure of a percutaneous device. Infection rates around percutaneous devices are rather high in comparison with other categories of permanently implanted devices, such as prosthetic joint infections (<2%) [4], with reported rates ranging from 5% to 30% in bone-anchored prostheses [5,6] to >50% for external fixators [7,8].

Researchers have explored various strategies to prevent infection of percutaneous devices. First, proper surgical procedures (e.g. hand hygiene and aseptic techniques) and systemic antimicrobial prophylaxis have been applied as standard in clinics over recent decades. Furthermore, studies have been concentrating on the development of a dynamic interface between the skin tissue and the percutaneous device, such as by using biomaterials, by modifying the implant shape, or by applying specific micro- and nano-conformations on the surface [9–14]. Animal models without bacterial inoculation were usually employed for the evaluation of these strategies. However, more recently, the local application of antibacterial materials or antibacterial drugs has attracted increasing attention in the field of percutaneous devices to prevent the occurrence of infections [15–17]. The efficacy of this new generation of antibacterial-containing devices can only be verified when a reliable percutaneous-device-related infection model exists. Previous attempts have been made to construct a reliable infection model [15,17–20], but at present, the animal species, strain of bacteria, amount and method of inoculation, and methods for subsequent evaluation of the infection remain variable. Therefore, this review aimed to evaluate the existing animal models for percutaneous-device-related infection, with a specific focus on the inoculation of bacteria.

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Table 1
Spontaneous infection rates around percutaneous devices in various animal models, not employing bacterial inoculation.

Species	Position	Study duration	Infection rate [reference]
Mice	Dorsum	3 days to 6 months	0% [21–25]
Rats	Dorsum	3 days to 9 weeks	0% [26–29], 3% [12]
	Scalp	1–3 weeks	0% [9,30], 8% [31]
Rabbits	Dorsum	3 weeks to 8 months	0% [32–35], 12.5% [36], 50% [37]
	Tibia	3–8 months	0% [35,38,39], 7% [36]
	Proximal tibia metaphysis	4 weeks	58% [40],75% [41], 90% [42]
	Scalp	3 weeks to 8 months	0% [35,38,39]
Guinea pigs	Tibia	3–7 weeks	0% [35,38]
	Dorsum	3–7 weeks	0% [35,38]
Micropigs or pigs	Limbs	14 days	44% [43]
	Dorsum	1–15 months	0% [44], 13% [45], 17% [46]
	Dorsum	90 days	25% [47]
Dogs	Dorsum	4–32 weeks	33% [48]
Goats or sheep	Abdominal wall	4 months	8% [49]
	Dorsum	14 weeks	0% [50]
	Tibia	3–9 weeks	0% [51,52], 20% [53]
	Proximal tibia metaphysis	24 weeks	85% [54]

2. Animal models with spontaneous infection

Various animals have been used in studies related to percutaneous devices. First, it can be questioned whether a spontaneously occurring infection can be constructed reliably (i.e. without the intentional inoculation of bacteria). Table 1 shows spontaneous infection rates; these are the results from control groups or groups that did not receive any treatment.

In general, it can be concluded that spontaneous infection rates are relatively low (<25%), and the authors describe a significant variability. Despite this variability, it seems that the highest natural infection rate might be achieved in investigations regarding the proximal tibia metaphysis in rabbits and sheep. Further analysis showed that the reason behind this higher infection rate was likely due to biomechanical factors (i.e. a relatively high mobility of the skin/soft tissues at the proximal tibia metaphysis area) [54]. Therefore, the infection rate would largely depend on chance, and this would increase the variability of the experiment substantially, resulting in the need to use many more animals to evaluate treatment efficacy. Overall, it was concluded that achieving reliable natural infection around percutaneous devices is not yet obtainable in an animal model.

3. Animal models with bacterial inoculation

3.1. Infection rates of animal models with bacterial inoculation

A common alternative method to obtain a more reliable infection rate is to inoculate bacteria into the surgical wound. Microorganisms, primarily bacteria, are responsible for most device-related infections. Indeed, ample explorations have been conducted to study the performance of percutaneous devices after deliberate infection (Table 2).

For most studies, the infection rate in the control groups was fairly reliable and (close to) 100%, despite the fact that the animal models varied in many aspects (e.g. animal species, implant position, inoculated bacteria and time points). In contrast to the natural infection process, where infection occurs when the increasing bacterial load is too high to be combated by the immune system, controlled infection from bacterial inoculation can standardize some important variables precisely, such as host, type of implant, inoculated bacterium, inoculated load, wound size and duration of infection. Therefore, the inoculation of bacteria is a very effective way to construct and investigate an infection around a percutaneous device.

3.2. Function of inoculated bacteria

To achieve a reliable infection at the exit site of a percutaneous device, researchers need to identify the exact effects of different bacteria on the formation of such an infection. In 1999, Clasper et al inoculated *Staphylococcus aureus* in a sheep external fixator model, and detected the microbes present in the contaminated area on days 7 and 14. They reported that, in addition to the applied *S. aureus*, nine other species of microbes were detectable in the superficial implant tract or medulla [67]. Oka et al [57] and Gimeno et al [17] confirmed this finding in rabbit and sheep models, respectively. Later, Williams et al provided more evidence to corroborate these results in a rabbit model [59]. In their experiment, a certain strain of *S. aureus* was inoculated repeatedly from week 2 and weekly thereafter. Finally, the collected samples were analysed to ascertain the bacteria strains existing in the infection. Other bacteria strains were found as well as *S. aureus*; however, the ratio of different bacteria was not described. More interestingly, the substrain of *S. aureus* detected at the end of the experiment was representative of the normal skin flora, rather than the applied substrain of bacteria [59].

In contrast, Koseki et al constructed an infection model on the femur of rats by bacterial contamination, and found that the bacteria isolated from the purulence or drainage were of the same strain as was inoculated [56]. However, this discrepancy might be explained by the fact that the latter study used specific-pathogen-free animals.

Based on the overall consensus, the mechanism of percutaneous infection after bacterial inoculation may be as follows (Fig. 1). First, a local infection is initialized by the inoculation of bacteria. Thereafter, the properties of the percutaneous device, the host immune response and the bacteria present in the micro-environment determine the final formation of an infection. If the infection is constructed successfully, the final composition of the pathogens present after a prolonged period of time depends on the interaction of the inoculated bacteria and the commensal bacteria.

4. Construction of an animal model with bacterial inoculation

As mentioned, the initial infection can be achieved by bacterial inoculation; however, the final formation of infection can be influenced by various factors, such as the host immune response, bacterial inoculation load, properties of the percutaneous device and environment around the percutaneous devices. A successful infection model can only result from a balance between these factors. In this