Experimental models in the investigation of device-related infections

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There has been an increasing concern with the problem of device-related infections, ever since foreign materials such as metal or plastic began to be used in implant surgery. The prophylaxis and treatment of such infections is difficult to evaluate in clinical studies, because placebo-controlled prophylaxis trials are thought to be unethical, and no single centre has enough patients for comparative treatment studies. For this reason different experimental models have been developed to study aspects of device-related infections. In this review, these infection models are presented. Different applications of the tissue-cage guinea pig model are summarized. This model allows the study of pathogenesis, natural course, prophylaxis, and treatment of device-related infection. In addition, by using this infection model, novel microbiological in-vitro tests could be developed, and questions of biocompatibility analysed.

Introduction

During the last four decades, metals or plastics have been increasingly used for different types of devices (Ingraham, Alexander & Matson, 1947; Pudenz *et al.*, 1957; Charnley, 1972; Szilagyi *et al.*, 1972). Of all problems associated with such implants, the most severe is infection. The commonest microorganisms involved in such infections are *Staphylococcus aureus*, *Staphylococcus epidermidis* and *Escherichia coli*. However, any microorganism may be implicated (Andrews *et al.*, 1981; Widmer *et al.*, 1990a). Without removal of the foreign material, antimicrobial therapy often fails to cure device-related infections (Dougherty, 1988).

During the last ten years, different experimental models have been used to elucidate the multiple problems encountered in device-related infections (Zimmerli *et al.*, 1982; Zimmerli, Lew & Waldvogel, 1984; Zimmerli, Zak & Vosbeck, 1985; Widmer *et al.*, 1990b, 1991). Whereas in the early eighties the main research effort was directed to the study of pathogenesis (Zimmerli *et al.*, 1982, 1985), within the last five years much has been learned about drug therapy and prophylaxis of device-related infection (Bouchenaki *et al.*, 1990; Widmer *et al.*, 1990b, 1991).

Animal models of device-related infections

Suture model

James & MacLeod (1961) developed the stitch abscess model in the mouse. In their experimental model of superficial skin infection, they could show that the presence of

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suture material decreased the abscess-forming dose from 10^7 cfu to 10^2 cfu of *S. aureus*. Despite a heavy granulocyte infiltration surrounding the suture, the infection could not be eliminated. With these experiments, the high susceptibility to infection, and the persistence of established infection, could be experimentally demonstrated for the first time.

Following these experiments, the same experimental model was used to analyse the infection potentiating properties of different suture materials (Katz, Mordechai & Mirelman, 1981).

Vascular graft model

After the introduction of vascular grafts in clinical medicine, the problem of vascular graft infection was studied in experimental models. Dogs are the experimental animals commonly used (Busuttil *et al.*, 1979). Other experimental animals that have been used are pigs, minipigs, calves and baboons (Kron *et al.*, 1980). The following aspects have been studied using the vascular graft model: healing characteristics (e.g. the influence of pseudointimal integrity on susceptibility to infection) the influence of material on development of infection, and the pathogenesis of haematogenous infections.

Catheter and prosthetic valve endocarditis model

Garrison & Freedman (1970) developed the first model of endocarditis. They used a catheter to induce and maintain endocarditis in rabbits. With a similar model in rats, aspects of endocarditis prophylaxis have been extensively studied (Glauser *et al.*, 1983). These models gave the rational background for the recommendations regarding antimicrobial prophylaxis for the prevention of bacterial endocarditis. In another, more sophisticated model, tricuspid prosthetic valve endocarditis was studied in calves (Grogan *et al.*, 1980). This model can be used to study the technical problems of prosthetic-valve replacement, the quality of different prosthetic materials and the natural history of prosthetic-valve endocarditis, and to test the efficacy of antibiotic prophylaxis and treatment.

Knee joint model

Blomgren *et al.* (1981) implanted finger endoprostheses into rabbit knees in order to study haematogenous infections in the joint implant. The same model is useful for the systematic study of antibiotic prophylaxis.

Tissue cage model

The tissue-cage model has been developed to study various aspects of prosthetic infections, including the pathogenetic mechanisms leading to the high susceptibility of implanted devices to infection and their persistence (Zimmerli *et al.*, 1982, 1984, 1985). In this model, perforated polymer cylinders are subcutaneously implanted into guinea pigs.

Table. Application of the tissue-cage model

Clinical problem	References
Local immune deficiency	Zimmerli *et al.* (1982, 1984)
Risk of haematogenous seeding on extravascular devices	Zimmerli *et al.* (1985)
Efficacy of prophylaxis	Tshefu *et al.* (1983), Zimmerli *et al.* (1984), Widmer *et al.* (1991)
Efficacy of therapy	Tshefu *et al.* (1983), Zimmerli *et al.* (1985), Widmer *et al.* (1990a,b, 1991), Bouchenaki *et al.* (1990)
Correlation between drug efficacy *in vivo* and in device-related infections	Widmer *et al.* (1990a, 1991), Vergères *et al.* (1992)
Testing of biomaterials (biocompatibility, susceptibility to infection)	Widmer *et al.* (1992)

Application of the tissue-cage model

The Table shows different aspects that have been studied with the tissue-cage model.

Study of the pathogenesis of device-related infections

Tissue cages are subcutaneously implanted into guinea pigs. This imitates the clinical situation of extravascular devices such as pacemaker batteries, subcutaneous catheters and shunts, breast implants, etc. The accumulation of interstitial fluid and leucocytes in the vicinity of the tissue cage allows study of local host defence mechanisms. We observed a locally acquired granulocyte defect which may be responsible for the high susceptibility of implants to infection (Zimmerli *et al.*, 1982, 1984). There is evidence that this defect is a consequence of the prolonged stimulation of the granulocyte by the non-phagocytosable implant.

Haematogenous implant infection

Whereas infection up to one year after surgery is mostly due to intra-operative contamination, little is known about the pathogenesis of late prosthetic infections. We employed the tissue-cage model to determine whether extravascular devices could be infected by the haematogenous route (Zimmerli *et al.*, 1985). Intracardiac inoculation of 50 million cfu *S. aureus* Wood 46, resulting in bacteraemias of 10^2–10^3 cfu/mL, led to selective infection in 42% of the tissue cages without microbiological evidence of infection elsewhere. These experiments indicate that antibiotic prophylaxis might be considered in patients with extravascular devices undergoing procedures complicated by bacteraemia.

Efficacy of prophylaxis

The tissue-cage model described can be used to analyse the conditions for adequate antimicrobial prophylaxis. By testing different time intervals between bacterial inoculation and start of treatment, the importance of timely prophylaxis and the need for multiple doses could be evaluated (Tshefu *et al.*, 1983; Zimmerli *et al.*, 1985). In tissue

cages which were directly inoculated with *S. aureus* Wood 46, prophylaxis with four doses of rifampicin was 100% efficient before and up to 3 h after, but only 57% efficient 24 h after bacterial challenge (Tshefu *et al.*, 1983). With doses of rifampicin starting either before, or up to 3 h after, experimental bacteraemia with *S. aureus*, no implant infection occurred (Zimmerli *et al.*, 1985). Similar results were obtained with *E. coli* as the test strain (Widmer *et al.*, 1991).

Efficacy of therapy

Device-related infections tend to persist despite treatment with an antibiotic with excellent in-vitro activity (Dougherty, 1988; Widmer *et al.*, 1990*a*). We therefore analysed the efficacy of different antimicrobial drugs against *S. epidermidis* (Widmer *et al.*, 1990*b*), *S. aureus* (Zimmerli *et al.*, 1991), *E. coli* Widmer *et al.*, 1991), and *Salmonella dublin* (Widmer *et al.*, 1990*a*). The main finding in these studies was that rifampicin-containing regimens were much more efficient against staphylococci than any other drug (Widmer *et al.*, 1990*b*; Zimmerli *et al.*, 1991). However, rapid emergence of resistance was observed if rifampicin was given alone (Zimmerli *et al.*, 1991). In Gram-negative infections, quinolones were the most efficient drugs (Widmer *et al.*, 1990*a*, 1991).

Development of in-vitro tests to predict drug efficacy in device-related infection

The choice of a therapeutic antimicrobial agent is usually guided by the in-vitro susceptibility (MIC) of the microorganism to the drug. In treating device-related infections, this choice is obviously often not adequate, since the infection persists, regardless of the length of the treatment (Widmer *et al.*, 1990*a*). We therefore looked for more appropriate in-vitro tests which take into account the special situation of device-related infections. In these infections bacteria are likely to be in the stationary phase of growth, against which all antibiotics show a diminished activity. Furthermore, bacterial adherence to foreign materials alters their susceptibility to antimicrobial agents.

We used the tissue-cage model to validate novel microbiological tests taking into account the above mentioned properties of the microorganisms. These studies showed that drug efficacy on stationary and adherent microorganisms, but not MICs, predicted the outcome of device-related infection (Widmer *et al.*, 1990*a*, 1991; Vergères *et al.*, 1992).

Tests of biocompatibility

Most biocompatibility tests are performed with cell culture systems and/or histology specimens from animals with bioimplants. However, these tests do not allow evaluation of the correlation between biocompatibility and infection susceptibility of foreign materials.

We used the tissue-cage model to study this correlation. By implanting two different materials (Teflon and ceramic), we tested the minimal infecting dose on the one hand, and the degree of inflammation (leucocyte counts and protein levels in tissue-cage fluid) on the other hand. In a first study we could show a direct correlation between biocompatibility and resistance to infection. Ceramic tissue cages provoked more

inflammation, but were ten times more susceptible to infection with *S. epidermidis* than Teflon cages (Widmer *et al.*, 1992).

Conclusions

The use of animal models has allowed us an insight into pathogenesis, prophylaxis, and treatment of device-related infections. As soon as a reproducible in-vitro test allows prediction of the efficacy of antimicrobial drugs in such infections, animal experiments will be redundant. However, the tissue-cage model will still be useful to test the relation between biocompatibility and infection susceptibility of different clinically important biomaterials.

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