# Prevention of infection with tobramycin-containing bone cement or systemic cefazolin in an animal model

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**Abstract:** We investigated in an animal model the efficacy of tobramycin-containing bone cement and systemic cefazolin for infection prophylaxis. In 18 female rabbits, the femoral cavity was inoculated with *Staphylococcus aureus* before injection of bone cement. The first group of six rabbits received tobramycin-containing Simplex-P bone cement. Two other groups of six rabbits received plain Simplex-P bone cement. Preoperatively, in one of the two latter groups cefazolin was administered intravenously. The other group served as untreated controls. The rabbits were monitored for clinical signs of infection. At 7 days' follow-up, the femora were harvested and cultures from the bone adjacent to the cement plug were quantified. Cultures from the rabbits which received antibiotic prophylaxis (either cefazolin systemically or tobramycin-containing bone cement) were all negative. In contrast, all rabbits in the untreated control group had positive cultures. These rabbits also had other signs of infection such as an elevated erythrocyte sedimentation rate and loss of body weight. Culture results were confirmed by the absence of bacterial DNA in the polymerase chain reaction hybridization assay. In conclusion, we found that both tobramycin-containing bone cement and systemic cefazolin are effective in preventing implant bed infection in rabbits up to 7 days after contamination with *S. aureus*. © 2000 John Wiley & Sons, Inc. J Biomed Mater Res, 52, 709–715, 2000.

**Key words:** tobramycin; bone cement; prophylaxis of infection; animal model; cefazolin

## INTRODUCTION

Adequate infection prophylaxis is mandatory in arthroplasty surgery. Methods to reduce the sources of bacterial contamination in the operating theater (such as ultraclean air, waterproof gowns, gloves, and adhesive plastic drapes) are useful but not perfect.[1] Contamination can still occur and antibiotics may be indicated to prevent infections. In the literature, the optimal mode of administration of prophylactic antibiotics is still subject of discussion. Dutch guidelines state that there is no indication for the use of antibiotic-containing bone cement in primary arthroplasty, if operated under prophylaxis of systemic antibiotics and an ultraclean air system.[2] Data from the Swedish hip arthroplasty registry show an increased use of antibiotic-containing bone cement in primary hip arthroplasty from approximately 10% of all primary hip arthroplasties performed in 1978 to 80% in 1996.[3] The different modes of administration of antibiotics have been compared for efficacy by only a few experimental and clinical studies. Petty et al. showed in a study in dogs that systemic antibiotic treatment as well as local treatment with antibiotic-containing bone cement reduced infections of the implant bed, but only the latter was found to be significantly different from controls.[4] Josefsson et al. compared prophylaxis with systemic antibiotics versus gentamicin bone cement in total hip arthroplasty in a prospective randomized clinical trial.[5,6] At 5 years' follow-up, significantly more infections occurred in the group receiving systemic antibiotics. However, at 10 years' follow-up of 1688 hips, infection rates in the systemic antibiotics group and in the antibiotic-containing bone cement group were no longer significantly different. In a simi-

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lar study, McQueen et al. found no difference in these two modes of infection prophylaxis in 401 patients at 2 years' follow-up.[7]

It is obvious from the few available studies that there is still a lack of scientific proof regarding the efficacy of systemic (intravenous) versus local (bone cement) administration of antibiotics to prevent implant bed infection. In the present study, we investigated the efficacy of prophylaxis either with intravenously administered cefazolin or by use of tobramycin-containing bone cement in an experimentally infected implant bed. We chose these two types of antibiotic with different routes of administration (systemic and local) because of their clinical relevance. Cefazolin is a first-generation cephalosporin and is used widely by orthopedic surgeons for treatment of staphylococcal infections. It has a longer half-life and provides for higher serum concentrations than the other first-generation cephalosporins. Tobramycin-containing bone cement has previously been shown to be efficacious in prevention of infections both *in vitro* and *in vivo* in rabbits.[8,9] For this type of cement, no data are available on its efficacy as a prophylactic treatment in comparison with systemic antibiotics. Therefore, the aim of the present study was to investigate the efficacy of tobramycin-containing bone cement and systemic cefazolin in preventing infection in a rabbit model.

## MATERIALS AND METHODS

### Design

In a total of 18 rabbits, the femoral cavity was inoculated with $10^6$ colony-forming units (CFUs) of *Staphylococcus aureus.* Six rabbits (group A—systemic antibiotic) received an intravenous injection of cefazolin before inoculation. Subsequently, plain Simplex-P bone cement (Stryker Howmedica Osteonics) was injected into the femoral cavity. Six rabbits (group B—tobramycin cement) received only tobramycin-containing Simplex-P bone cement after local inoculation of the femoral canal. Six rabbits (group C—control) received no antibiotic treatment, and plain Simplex-P bone cement was injected in the femur after local inoculation. Seven days after surgery, the animals were killed and the femoral cortex adjacent to the cement was cultured. The efficacy of the three treatments was assessed based on the number of CFUs of the bacteria and on the detection of *S. aureus* DNA by a polymerase chain reaction (PCR) hybridization assay. The guidelines according to the Dutch act on animal experiments (1985) were observed.

### Bacterial strain

*Staphylococcus aureus,* strain Wood-46 (ATCC 10832) was used to inoculate the rabbit's femur. After culture in Mueller–Hinton broth, a stock of aliquots was frozen. The concentration of bacteria was determined by serial dilution and plating on blood agar. Preoperatively, samples containing $10^7$ CFU/mL were prepared. A volume of 0.1 mL ($10^6$ CFU) was injected into the rabbit femoral cavity. Previous studies have shown this dosage to result in a 100% infection rate of cement bodies.[10]

### Surgery

Healthy adult female New Zealand white rabbits (Ico: NZW) weighing 3000–3500 g were obtained 1 week before surgery to acclimatize them to the housing in the Central Animal Laboratory. They were fed daily with 80–100 g antibiotics-free rabbit diet and water *ad libitum.*

Preoperatively the rabbits were weighed. The systemic antibiotic (cefazolin, 30 mg/kg) was injected 30 min before surgery, into the left auricular vein of the rabbits in group A. The anesthesia was prepared by an intramuscular injection of 4 mg methadone, 4 mg acepromazinemaleate, and 0.5 mg atropine. A preoperative blood sample was taken from the left auricular vein 5 min before surgery. A pressure line was introduced into the auricular artery for measuring blood pressure. Subsequently the anesthesia was induced by an intravenous injection of etomidate (8–12 mg). An endotracheal tube was introduced through which the anesthesia was maintained by a 1:1 mixture of nitrous oxide, oxygen, and halothane 1%. The skin of the outer right thigh was clipped and the rabbit was placed with its left side on the table.

The operative area was disinfected with povidone-iodine and isolated by sterile drapes. Subsequently, a skin incision (approximately 3 cm) was made parallel to the femur shaft, over the trochanter tertius of the right femur. The trochanter tertius was exposed by splitting the fascia, retracting the femoral biceps and coccygeofemoral muscles posteriormedial, and scraping the periost. The cortex was penetrated with a small drill (diameter 1.2 mm), using an air-pressured AO mini-drill. Subsequently, the femoral canal was reamed up to 4.0 mm in width. The content of the medullary canal was suctioned. Cooled (4°C) sterile bone cement was vacuum-mixed on the surgical table. The rabbits received either plain Simplex-P bone cement (groups A and C) or tobramycin-containing Simplex-P bone cement (group B). After injection of 0.1 mL of the bacteria suspension into the femoral canal, approximately 1.2 mL of cement was inserted. The exact amount of inserted cement was determined by weighing the syringe containing the cement. The fascia, subcutis, and cutis were closed with Vicryl 3–0 after polymerization of the cement and wound drainage with saline. Pain relief was provided by intramuscular injection of 3.0 mg nalbufine immediately postoperatively and subsequently 0.1 mg buprenorfine. Buprenorfine injection was repeated when necessary.

### Follow-up

#### General

Postoperatively, routine AP and lateral X-rays were made of the right femur. The rabbits recovered in a temperature-

controlled recovery cage. The rabbits were monitored by a daily clinical examination, with special attention for wound healing, the presence of a fracture, eating, activity level, and body temperature. The erythrocyte sedimentation rate (ESR) and white blood cell counts (WBCs) were measured before surgery and 1 and 7 days after. After 7 days, the rabbits were killed with an intravenously administered overdose of pentobarbital N2.

### Autopsy and sample acquisition

After the animals were killed, the skin of the left and right thighs was clipped, disinfected with povidone-iodine, and isolated with sterile drapes. The right and left (control) femora from all animals were excised and cleaned from tissue debris. Using a high-speed dental drill with a circular diamond saw, the external surface of the right femur was notched circumferentially at each end of the shaft and longitudinally on two sides. A mallet and an osteotome were used to break off each metaphysis and then to free the lateral half of cortex adjacent to the cement. Care was taken not to damage the cement. The bone samples from the left femur were taken from the site corresponding to the right femur operation site.

### Bacteriological examination

The lateral half of cortex adjacent to the cement plug (in the right femoral canal) and bone from the corresponding site of the left femur were submitted for quantification of bacteria. For this purpose, the bone samples of approximately 1 g were cut into small pieces and homogenized in 10 mL phosphate-buffered saline (pH 7.4) using a Polytron tissue grinder. Subsequently, the number of bacteria (CFU) per gram of bone was determined by dilution and plating on blood-agar plates.

### Histology

The medial half of the bone was used for histological evaluation and fixed in 4% buffered formalin. After decalcification and dehydration the cortex was embedded in paraffin and sectioned on a microtome (Reichert-Jung 2030; Biocut, Leica, Rijswijk, The Netherlands). The sections were mounted on slides and stained with hematoxylin and eosin.

### PCR hybridization assay

A part of the lateral half of the right femoral cortex (mean weight 0.24 g) adjacent to the cement plug was collected for molecular biological analysis for the presence of bacterial DNA. Samples were incubated for 18 h at 60°C in digestion buffer [500 m*M* Tris (pH 9), 20 m*M* ethylenediamine tetraacetic acid (EDTA), 10 m*M* NaCl, 1% sodium dodecyl sulfate (SDS), 0.5 mg/mL proteinase K] to release total DNA. DNA was isolated using a PCR purification kit (Qiagen, Hilden, Germany). DNA was amplified by the technique described by Wilbrink et al.[11] Broad-range biotin-labeled primers, targeting conserved regions of the 16S-rRNA gene, were used to set up an eubacteria-specific PCR. An internal spike was added to screen for possible inhibition of PCR and to reduce the amplification of contaminating DNA. The presence of *S. aureus* DNA was determined by reverse line blot hybridization (RLB). We used the RLB technique as described by Kaufhold et al.[12] For this purpose, we used a genus-specific staphylococcal oligonucleotide probe (5′-AACCTACCTATAAGACTGG-3′) and a species-specific *S. aureus* oligonucleotide probe (5′-TCAAAAGTGAAAGACGGTC-3′) which were covalently linked to a membrane (Biodyne C; Pall Biosupport, Portsmouth, UK). Using a miniblotter system (MN45; Immunetics, Cambridge, MA), PCR products were hybridized to the oligonucleotide probes on the membrane for 1 h at 42°C. After hybridization, nonspecific DNA was washed of the membrane at 55°C and the membrane was incubated at 42°C with Streptavidin-peroxidase (Boehringer Mannheim Biochemica, Mannheim, Germany). Finally, the presence of *S. aureus* DNA was visualized on a film (Hyperfilm ECL) using an enhanced chemoluminescent detection system (ECL; Amersham International, Little Chalfont, England).

## RESULTS

All rabbits recovered well from surgery. The inserted cement [mean ± standard deviation (SD)] weighed 1.46 ± 0.09 g in group A (tobramycin cement), 1.28 ± 0.18 g in group B (systemic antibiotic), and 1.29 ± 0.17 g in group C (control).

The loss of body weight (mean ± SD) of the rabbits at 7 days was 106 ± 101 g (3.7% as a percentage of their initial body weight) in group A, 65 ± 52 g (2.1%) in group B, and 246 ± 109 g (8.5%) in group C.

The ESR was elevated at 7 days' follow-up, especially in the control group (Fig. 1). The elevation of ESR was less in both antibiotic groups. Leukocyte counts were not different among the three groups (Fig. 2).

Cultures from the rabbits that received antibiotic prophylaxis (either cefazolin systemically or tobramycin-containing bone cement) were all negative. In contrast, all six rabbits in the control group (plain bone cement, no antibiotics) had positive cultures (Table I). In all rabbits, cultures from the left femur (not operated on) were negative.

Histology of sections of the right femur showed no marked differences among the three groups with regard to signs of infection. In sections of the control group only minimal elevation of the periost and enlargement of Haversian canals was seen, with no destruction of the cortex or increase in leukocytes [Fig. 3(a–c)].

Using the PCR-hybridization assay, the presence of *S. aureus* DNA was identified in the right femur of all the rabbits in the control group (Fig. 4). In contrast, the femur samples from groups that received antibiotic

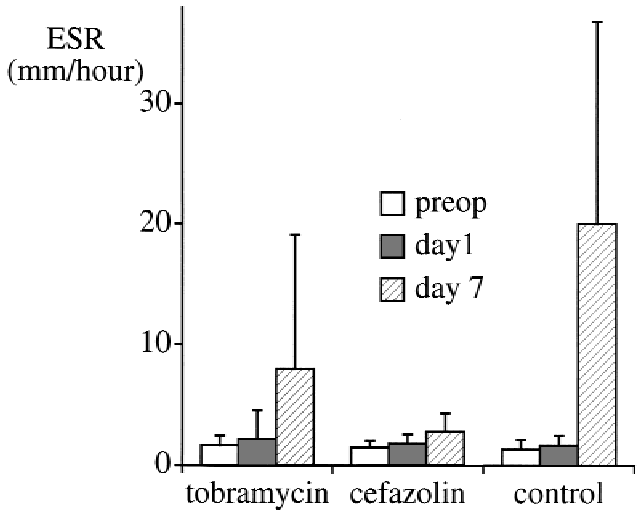


**Figure 1.** Erythrocyte sedimentation rates (mean) in the antibiotic-treated groups and the untreated control group, at three different time points (preoperatively and 1 and 7 days' follow-up). Error bars represent standard deviation.

prophylaxis, either cefazolin systemically or tobramycin-containing bone cement, *S. aureus* DNA was not detectable.

## DISCUSSION

In the present study, we demonstrated that both tobramycin-containing bone cement and systemically administered antibiotic can prevent infection of the rabbit's femur after inoculation with *S. aureus.* Nielsen et al. obtained similar results comparing the use of gentamicin-impregnated bone cement with systemic administration of dicloxacillin in a rabbit model.[13] In a canine model, Petty et al.[4] compared the prophylactic efficacy of adding gentamicin to bone cement with other antibiotic treatment modalities, including the use of intravenous cefazolin. The prophylactic effect of the use of gentamicin-impregnated bone cement was absolute; that of the use of intravenous cefazolin was not. In contrast to their results, we did not see any infection in rabbits that received cefazolin systemically to prevent local infection. Because details of their infection model regarding the inoculum size, volume of inserted cement, and type of bacterial strain used were not provided, it is difficult to explain the different results obtained in their model. The prophylactic effect of systemic antibiotics may depend on the animal species used, because in another rabbit model, a single preoperative dose of cefazolin prevented *S. aureus* infection during spinal instrumentation.[14] Another factor that influences the outcome of an infection model is the timing and mode of administration of the inoculum. Blomgren and Elson et al. studied the effect of gentamicin-impregnated bone cement on hematogenous infection in experimental models.[15,16] When the inoculum was administered intravenously, 6 weeks after the initial operation, both authors found no significant difference in the incidence of infection whether or not gentamicin was used in the bone cement. The antibacterial effect of gentamicin was shown only when the hematogenous inoculation occurred immediately after wound closure.[15] Even when a knee arthroplasty in rabbit is inoculated via an intra-articular injection 7 days after implantation, an infection is difficult to initiate.[17] As a consequence of this, Schurman et al. could not show a persistent prophylactic effect up to 1 week of bone cement containing gentamicin.

The infection rate after joint replacement surgery can be influenced by many prophylactic methods. Guidelines for prevention of infection differ between hospitals, mainly because it is hard to prove the effect of an individual factor contributing to the reduction of infection rate after surgery. Clinically, randomized prospective studies evaluating such factors need to include many patients, and as a consequence, it is difficult to control the contribution of one factor when studying the other.[18–21] In addition, the generalizability of the results of randomized trials is often low

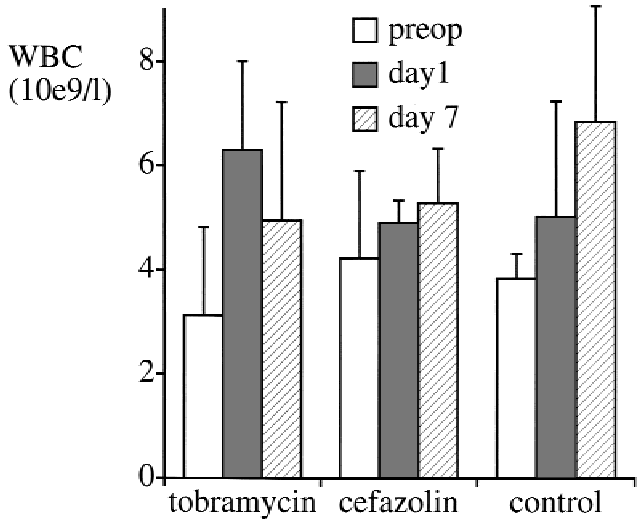


**Figure 2.** White blood cell counts (mean) in the antibiotic-treated groups and the untreated control group, at three different time points (preoperatively and 1 and 7 days' follow-up). Error bars represent standard deviation.

**TABLE I**
**Results of Culture of Right Femoral Cortex**

| Group of Rabbits | Incidence of Infection | Culture ($^{10}$log CFU/g, mean ± SD) |
|---|---|---|
| Tobramycin cement | 0/6 | 0 |
| Cefazolin systemically | 0/6 | 0 |
| Controls | 6/6 | 5.39 ± 0.79 |

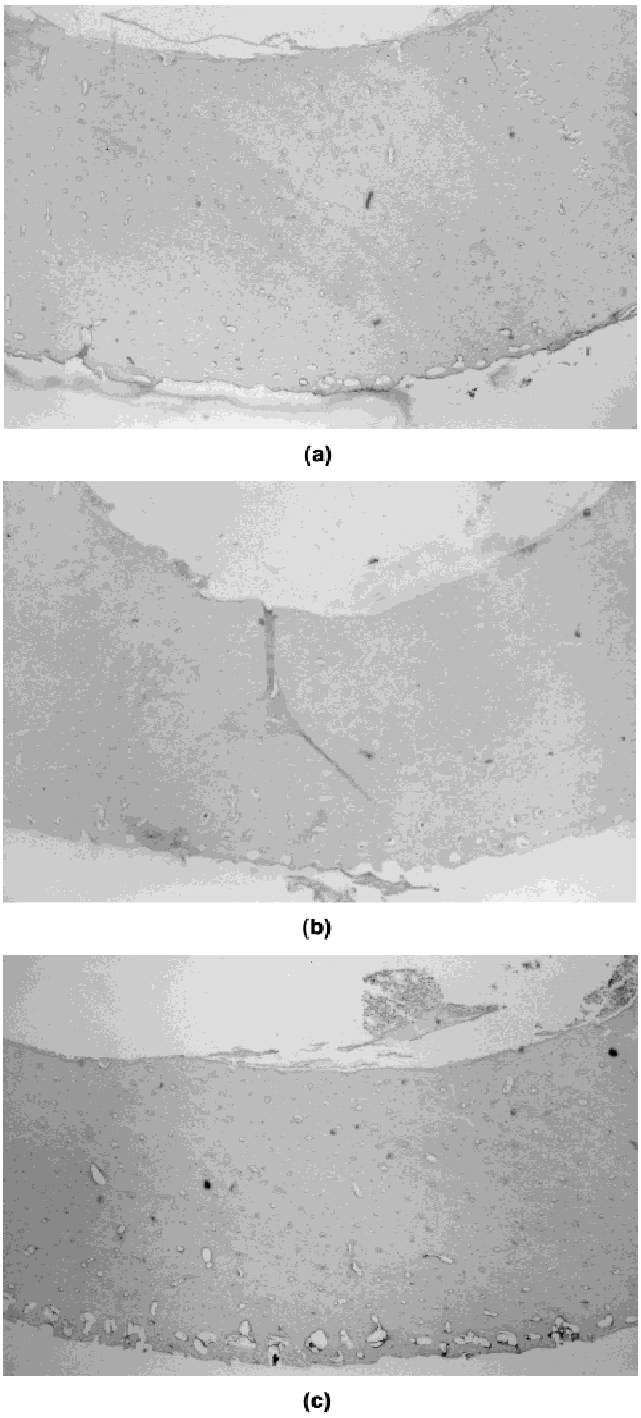


**Figure 3.** Photomicrographs (hematoxylin and eosin, original magnification ×30) of tissue sections of the femoral cortex of rabbit. Histological changes are nearly absent in rabbits in which tobramycin-containing bone cement (a) or systemic cefazolin (b) was used to prevent staphylococcal infection. Controls (c) showed minimal periosteal reaction and enlargement of Haversian canals.

owing to restrictive patient selection in these trials or to the fact that results obtained in centers of excellence are often not representative of results in the community.[22]

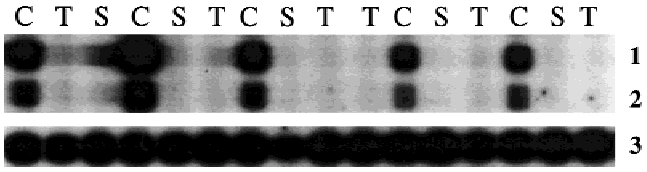


**Figure 4.** Details of the film with the results of the reverse line blot hybridization assay. PCR products of the right tibiae of the rabbits in the three different treatment groups are oriented in vertical lanes (T = tobramycin group; C = control group; S = systemic cefazolin group). The oligonucleotides are oriented in horizontal lanes (1 = staphylococci probe; 2 = *S. aureus* probe; 3 = internal spike probe). An internal spike was added to all samples to exclude possible inhibition: The lower lane shows no inhibition in samples that were negative for staphylococci or *S. aureus.*

In the literature, the debate as to whether to use antibiotic-containing bone cement or systemic antibiotics for prophylaxis of arthroplasty infection is not yet concluded.[4,6,7] The difficulties in correctly diagnosing deep infection have prompted authors to reclassify their results at longer follow-up periods.[6] The long-term follow-up studies of Josefsson et al. illustrated nicely that for some patients it took years for the infection to manifest itself, whereas others' signs and symptoms of infection had to be reinterpreted.[5,6,23] It might well be that the combination of the two strategies, both antibiotic-containing bone cement and systemic antibiotics, is the optimal choice. Espehaug et al. evaluated infection incidence after 10,905 primary cemented hip replacements in Norway, with a follow-up of 8 years.[24] The effect of prophylaxis of antibiotics administered systemically, in bone cement, or both was studied. The best results were obtained with the combination therapy. Nowadays, economic arguments could also influence the choice between different strategies in medicine. Persson et al. calculated that although the use of antibiotic-containing bone cement as a prophylactic option next to systemic antibiotics can reduce the risk of costly revision, this might not always be the most cost-effective strategy.[25]

In the present study, the minimal detectable level for *S. aureus* was 1000 CFUs per gram of bone. For reasons of reproducibility, we did not choose to concentrate the bacteria in smaller sample volumes after milling of the bone. However, in addition to our dilution and plating method, we also used a PCR-hybridization assay. PCR-based methods for detection of bacterial DNA can improve sensitivity of diagnosis of orthopedic implant infections.[26] Using a PCR-hybridization assay, we confirmed both the presence of *S. aureus* DNA in the untreated controls as well as its absence in the two antibiotic-treated groups. These findings convincingly demonstrate the efficacy of both types of antibiotic prophylaxis.

It can be disputed that although our study provided enough power to reveal differences between the cefa-

zolin or tobramycin and the control group, respectively, the power of actual comparison between the cefazolin and tobramycin groups was low, and therefore we could not arrive at a conclusion regarding differences between the two antibiotic groups. This power is low because both treatments were efficacious, as none of the animals in each group had positive cultures. Thus, such a comparison of two apparently efficacious treatments would require a large number of animals (>100). The question of clinical relevance of data would then arise. In addition, the subsequent PCR-hybridization assay supported our findings that both systemic antibiotic and local tobramycin bone cement are effective for infection prevention.

We used *S. aureus* (strain Wood 46), susceptible to both tobramycin and cefazolin, as the infectious agent. Recently, Scott et al. showed in an *in vitro* study that some bacterial strains resistant to the usual systemic concentrations displayed some degree of susceptibility to tobramycin-containing bone cement.[8] This phenomenon has been addressed by other authors who compared systemic administration of cefazolin with topical cefazolin administration using microspheres.[27] Similarly, the high local release of antibiotic from antibiotic-containing bone cement might be an advantage compared to systemic antibiotics in preventing infections with resistant strains of bacteria.

This animal model was used to study the development of an infection in the rabbit after initial contamination with a pathogen. This aspect differs from the situation of treating an already existing infection. Thus, this model does not allow for the evaluation of the efficacy of different treatment options for an infected prosthesis, such as treatment with a one- or two-stage revision, or by retaining the prosthesis and systemic antibiotics.[28–36] Study of the efficacy of tobramycin-containing bone cement as a treatment modality is the goal of a future animal study.

In conclusion, we have demonstrated the efficacy of tobramycin-containing bone cement and systemically administered cefazolin in preventing infection in the rabbit by both culture and detection of bacterial DNA. Possibly, both antibiotic regimes applied together will provide optimal prophylaxis of orthopedic prosthesis infection.

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