Tobramycin-containing bone cement and systemic cefazolin in a one-stage revision
Treatment of infection in a rabbit model
Introduction

Infections of total joint prostheses are frequently associated with the presence of necrotic bone, devascularization and bacteria with specific growth characteristics. Especially the latter, that is the ability of pathogens to adapt to the presence of a foreign body and sustain capability to withstand antibiotics and host defenses, complicates treatment. Therefore, rigorous treatment modalities are necessary to eliminate the infection, but the best choice for treatment of an infected total joint prosthesis still remains to be clarified. Consensus exists among most orthopaedic surgeons to remove the infected prosthesis if possible, because the infection is difficult to treat in presence of foreign material covered with bacteria [Brandt, 1997]. Usually antibiotic-loaded bone cement is used for fixation of a new prosthesis to provide a high local tissue concentration of antibiotics. Such a revision operation can be performed either as a one-stage procedure or as a two-stage procedure. In the one-stage revision the infected implant is removed and, after debridement and lavage of the implant bed, during the same session replaced by a new prosthesis. In a two-stage revision, the insertion of the new implant is postponed until after removal of the infected implant in a time period whereby the infection is treated with systemic antibiotics and/or local antibiotic-loaded beads. The new prosthesis is inserted not until the infection parameters have regained normal levels. The use of antibiotic-loaded bone cement for fixation of the revision prosthesis is preferred given the higher incidence of infection after revision in comparison with primary joint prostheses. Where most surgeons choose the two-stage procedure for exchange of an infected prosthesis, also large series have been reported using only the one-stage procedure, especially in Europe [Buchholz, 1981, Raut, 1995]. So far, reviews of literature on infected arthroplasties reported success rates of 82-83% of one-stage revisions, and 91-93% of two-stage revisions [Garvin, 1995, Pagnano, 1997].

In a previous study, it has been shown that Simplex P tobramycin-containing bone cement can prevent Staphylococcus aureus and Staphylococcus epidermidis infections in the rabbit's femur [Nijhof, 2000a]. In that model we evaluated the development of an infection after inoculation of the medullary canal with bacteria, immediately followed by insertion of the antibiotic-containing bone cement. However, in order to treat a pre-existent implant infection, one that has developed after introduction of bacteria at an earlier time point, the antibiotic-containing bone cement should also be effective against pathogens that may have become phenotypically adapted to their new habitat. In a one-stage
revision procedure, when no previous surgical attempts have been undertaken to treat such an infection, this may be even more demanding. The purpose of the present study was to compare the efficacy of tobramycin-containing bone cement with that of systemic cefazolin for treatment of infection in a one-stage revision model. In addition to conventional culture techniques a PCR hybridization assay was used in the detection of bacteria as bacterial DNA.

I Materials and methods

Design
To establish an infection, a pre-formed non antibiotic-containing cement plug was introduced in the right tibial medullary canal of 30 rabbits, after local inoculation with S. aureus. Four weeks after insertion of the implant, the rabbits were divided into three groups (10 rabbits each), and a one-stage revision of the implant was performed in all rabbits. After removal of the infected implant and lavage of the implant bed (without formal debridement), bone cement was injected into the medullary canal. Group 1 received tobramycin-containing bone cement, Group 2 received plain bone cement (no antibiotics) as control, and Group 3 received plain bone cement and additional systemic antibiotics. Fourteen days after the revision procedures the tibiae were excised and the cortex adjacent to the cement was cultured. The efficacy of the different treatments was compared based upon the number colony-forming units of bacteria following culture.

Bacterial strain
Staphylococcus aureus, strain Wood-46 (ATCC 10832) was used. After culture in Mueller-Hinton broth, a stock of aliquots was frozen. The concentration of bacteria (colony-forming units per millilitre, CFU/ml) was determined by serial dilution and plating on blood agar. In a volume of 0.1 ml, a dose of either $10^5$ CFU or $10^6$ CFU was injected in the medullary canal of the rabbit’s tibia. The first 4 rabbits in each group received an inoculum dose of $10^6$ CFU. This dose was the same as was used in a previous study on the prevention of implant bed infection in the tibia of rabbits [Nijhof, 2000b]. In an attempt to reduce loss of rabbits due to sepsis the dose was changed to $10^5$ CFU in the subsequent rabbits. The latter inoculum dose has proved to establish an infection in another animal model of tibial implant infection [Vogely, 2000b].
Animals
Healthy adult female New Zealand white rabbits (Ico:NZW, Broekman Instituut BV, Someren, The Netherlands) weighing 3000-3500 gram were obtained one week prior to surgery to acclimatize to the housing in the Central Animal Laboratory. The animals were caged in individual cages, fed with 80-100 gram antibiotics free Hope Farms rabbit diet LKK-20 and water ad libitum. Postoperatively, the animals were kept in the barrier housing facility of the Central Animal Laboratory until they were killed.

Surgery
The anesthesia protocol was the same for both operations (induction of infection and revision of implant). Surgery was performed under strict aseptic conditions and under general inhalation anesthesia. Preoperatively the rabbits were weighed. The anesthesia was prepared by an intramuscular injection of 4 mg methadone, 4 mg acepromazine maleate and 0.5 mg atropine. 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 (#3) was introduced through which the anesthesia is maintained by a 1:1 mixture of nitrous oxide, oxygen and halothane 1%. The skin of the right leg 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. Postoperatively, pain relief was provided by 3 mg nalbufine i.m. immediately postoperative and subsequently 0.3 mg buprenorfine i.m. If necessary, buprenorfine injection was repeated postoperatively.

Infection of primary implant
At the first operation (establishment of infection), the right knee joint was opened via a parapatellar incision. Anterior to the insertion of the anterior cruciate ligament on the tibia, the medullary canal was opened. Using an air pressured AO minidrill the cortex was penetrated by a small drill (diameter 1.2 mm) and the medullary canal was reamed with drills and fraises up to a length of at least 25 mm and 3.9 mm in width. The content of the medullary canal was suctioned and flushed with saline. Prior to insertion of the implant, the bacterial suspension was introduced in the tibial canal. Subsequently, the implant (pre-formed cement on a central metal wire, 25 mm in length, 3.9 mm in diameter, Figure 1) was press-fit inserted in the medullary canal. The joint capsule and skin were closed in layers with Vicryl 3-0.
Revision of implant
The implant was exchanged 28 days after the first operation. Through the parapatellar scar the knee joint was opened. The present implant was removed from the right tibial canal, inoculated on blood agar plates and incubated for 24 hours at 37°C. In addition, medullary tissue samples were obtained for culture. Subsequently, the canal was debrided and washed with sterile antibiotic free physiologic saline. In Group 1, tobramycin-containing bone cement (Simplex P bone cement, premixed with 1.0 g of tobramycin as a sulphate in 40 g powder, Stryker-Howmedica-Osteonics, Rutherford, NJ) was inserted in the right tibial medullary canal. In the same manner, plain Simplex-P bone cement was used in Groups 2 and 3. The animals in Group 3 received also systemic antibiotics (cefazolin, 30 mg/kg, injected subcutaneously every 8 hours for 14 days total, from day 28 through day 42). The rabbits in Group 2 did not receive any form of antibiotic treatment. The bone cement (precooled at 4°C) was vacuum-mixed for 60 seconds (tobramycin-containing bone cement) or 100 seconds (plain bone cement) on the surgical table. Approximately 1.2 ml cement was injected gently into the medullary canal, while the syringe was slowly being retracted. The exact amount of

Figure 1. Example of implant used to create an infection.
injected cement was determined by weighing the syringe containing the cement. After polymerization of the cement and wound drainage with saline, the joint capsule and skin were closed in layers with Vicryl 3-0.

**Follow-up**
The follow-up period after revision surgery was 14 days (42 days after the first operation). Routine AP and lateral X-rays of the right femur were obtained after the first operation and before and after revision surgery on day 28. Body weight and body temperature were recorded on a regular basis. Blood samples from the auricular vein on erythrocyte sedimentation rate (ESR) and white blood cell counts (WBC) were taken prior to the first operation and at day 1, 7, 14, 21, 28 (prior to revision), 35 and 42 postoperatively. The animals were killed with an overdose pentobarbital sodium intravenously.

**Autopsy and sample acquisition**
After the animals were killed, the skin of the both legs was clipped, disinfected with povidone-iodine and isolated by sterile drapes. The right and left (not operated on) tibia were excised and cleaned from soft tissue debris. First, bone samples were taken from the left tibia from a region corresponding to the right tibia samples. Secondly, the external surface of the right tibia was notched circumferentially at each end of the shaft and longitudinally on two sides, posterior and anterior. An osteotome was used to break off each metaphysis and then to free the medial half of the bone from the lateral half. Care was taken not to damage the cement.

**Bacteriological culture**
Both the medial bone half of the right tibia adjacent to the cement plug and bone from the corresponding region of the left tibia were submitted for quantification of bacteria. The bone samples were homogenized in a sterile phosphate buffered saline solution (pH 7.4) using a Polytron tissue grinder (Kinetica, Best, The Netherlands) and the number of bacteria per gram of bone was determined by dilution and plating techniques.

**PCR hybridization assay**
A part of the medial half of the right tibial cortex adjacent to the cement plug was collected for molecular biological analysis for the presence of bacterial DNA. These samples were incubated for 18 hours at 60°C in 1.5 ml digestion buffer (500 mM Tris (pH 9), 20 mM EDTA, 10 mM NaCl, 1% SDS, 0.5 mg/ml proteinase K) to release total DNA. A volume of 200 µl of the extracted DNA
was used for DNA isolation the QIAamp Tissue Kit (Qiagen, Hilden, Germany). The last step in the isolation of the DNA included the elution of DNA in an end-volume of 400 µl. Subsequently, 2.5 µl of the dissolved DNA was amplified by the technique described by Wilbrink et al. [Wilbrink, 1998]. Broad range biotin-labeled primers, targeting conserved regions of the gene for the 16S subunit of ribosomal RNA (16S rRNA), were used to set up an eubacteria-specific polymerase chain reaction (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. We used the reverse line blot hybridization technique as described by Kaufhold et al. [Kaufhold, 1994]. For this purpose, we used a genus-specific staphylococcal oligonucleotide probe (5'-AACCTAC-CTATAAGACTGG-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). Ten microliter of PCR products were hybridized to the oligonucleotide probes on the membrane for 1 hr at 42 °C, using a miniblotter system (MN45, Immunetics, Cambridge, MA). Subsequently, 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 could be visualized on a film (Hyperfilm ECL) by using an enhanced chemoluminescent detection system (ECL, Amersham international, Little Chalfont, England).

Statistics
The probability of a positive culture was compared between the three groups of rabbits using the Fisher’s exact test. Furthermore, to account for inoculum dose, also a more sophisticated analysis by using a stratified two by two chi-squared test was performed. One-sided tests were performed for comparison of each antibiotic group (tobramycin-bone cement and systemic cefazolin) with the control group. Two-sided tests were performed for comparison of the two antibiotic groups. A P-value of less than 0.05 was considered significant. Exact P-values have been computed using the statistical program StatXact 4.
I Results

General
Three rabbits were lost before the time of revision. Two of these rabbits died in the first week after the initial operation, the third showed signs of severe sepsis and was killed in the third postoperative week. In all three rabbits the culture revealed an overwhelming S. aureus infection at the side of the implant. All other rabbits had a good recovery from both operations. The

Figure 2. Lateral radiographs of the right tibia of the same rabbit at day-28, before (left) and after (right) revision surgery. Periostal reactive bone formation as a sign of local response to infection is seen in the proximal half of the tibia. At the time of revision surgery, the implant was removed and bone cement was injected into the tibial canal after debridement.
inserted cement (mean ± standard deviation) weighed 0.97±0.17 g in Group 1 (tobramycin cement), 1.03±0.13 in Group 2 (systemic antibiotic), and 1.02±0.16 g in Group 3 (control).

The development of an infection in all rabbits was confirmed at the time of revision by the presence of pus macroscopically and/or positive cultures of debrided tissue or the revised implant. The X-rays of all rabbits taken on day 28 all showed clear signs of reactive bone tissue predominantly at the proximal half of the right tibia, indicating a response to the presence of a local fulminant infection at the site of the implant (Figure 2).

No signs of side effects of systemic cefazolin, like diarrhea caused by pseudomembranous colitis, were seen in rabbits treated with cefazolin.

No clear differences between the three treatment groups were seen in body temperature and loss of body weight, ESR and WBC. Table 1 shows the results of ESR and WBC.

## Table 1: Erythrocyte sedimentation rate and white blood cell count

<table>
<thead>
<tr>
<th>Group of rabbits</th>
<th>ESR (mm/hr, mean±SD)</th>
<th>WBC (x 10⁹/l, mean±SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 0</td>
<td>Day 7</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>1.3±0.5</td>
<td>42.9±34.7</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>1.1±0.4</td>
<td>35.3±27.2</td>
</tr>
<tr>
<td>Control</td>
<td>1.5±0.5</td>
<td>41.9±26.5</td>
</tr>
</tbody>
</table>

ESR = erythrocyte sedimentation rate; WBC = white blood cell count

### Bacteriological culture

The outcome of cultures is presented in Table 2. Results of culture of the cortex of the right tibia adjacent to the cement (weight 1.03 ± 0.03 g, mean ± SD) showed a decrease for both antibiotic groups (tobramycin-cement and systemic cefazolin) in comparison with the control group. Since in both antibiotic groups most rabbits (7 out of 9 and 8 out of 8, respectively)
showed negative culture results, no statistical analysis was performed on the mean culture results to point out the difference. The rate of infection in both antibiotic groups was significantly lower than in the control group, $p < 0.01$. The rate of infection in the tobramycin-cement group was slightly higher (2/9) but not significantly different from the systemic cefazolin group (0/8), $p = 0.47$. When the inoculum dose ($10^5$ or $10^6$ CFU) was taken into account, the statistical analysis also showed significant differences between both antibiotic groups and the control group, $p < 0.01$, but no significant difference between the two antibiotic treatment groups, $p = 0.5$.

**Reverse line blot hybridization assay**

No PCR sample at 42 days follow-up was obtained in 6 out of the 27 rabbits of which culture results were available at that time. Figure 3 shows a detail of

![Figure 3](image)

**Figure 3.** 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

<table>
<thead>
<tr>
<th>Group of rabbits</th>
<th>Infection rate</th>
<th>Culture (mean ± SD, $10^5$ CFU/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tobramycin</td>
<td>2/9</td>
<td>1.1 ± 2.2</td>
</tr>
<tr>
<td>Control</td>
<td>10/10</td>
<td>5.7 ± 1.4</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>0/8</td>
<td>0</td>
</tr>
</tbody>
</table>

CFU/g = colony forming units per gram of bone
Table 3. Outcome of reverse line blot hybridization

<table>
<thead>
<tr>
<th></th>
<th>Culture -</th>
<th>Culture +</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RLB -</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tobramycin</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Control</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><strong>RLB +</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tobramycin</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Control</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>5</td>
<td>0</td>
</tr>
</tbody>
</table>

The results (in number of rabbits) of the reverse line blot hybridization compared by culture. RLB = reverse line blot hybridization assay; - = negative result; + = positive result.

In the present investigation, we demonstrated that both tobramycin-containing bone cement and systemic cefazolin reduce size and rate of infection in the treatment of an infected prosthesis by a one-stage revision procedure in rabbits, based on the results of bacteriological culture. This model was designed to mimic a one-stage revision procedure for an infected joint arthroplasty, so that a high efficacy of an antibiotic treatment would be required to clear the infection. We did not incorporate a two-stage revision model in this study, since our main objective was to test a specific antibiotic-containing cement. The temporary treatment between removal of the implant and insertion of the cement at a subsequent operation, may be a confounding factor for this purpose. Furthermore, this model differs from previous efficacy studies done by us and many other authors, in that the treatment did not start immediately after inoculation, but after a prolonged time period. This delay of treatment was introduced to create an established infection with the subse-
quent inflammatory responses and alterations in microcirculation and bone morphology. Therefore, in comparison with the ‘direct-infection’ models, this model is more similar to the clinical situation in which antibiotic treatment is started only after the infection has settled itself. Only a few studies have addressed an animal model to evaluate the option of treating an established prosthesis-related infection with antibiotic-containing bone cement. Fitzgerald showed that gentamicin-containing bone cement could effectively prevent, but not treat Staphylococcus aureus infections around injected PMMA in tibiae of dogs [Fitzgerald, 1983]. In three out of five infections, the one-stage revision failed as a treatment. Gerhart et al. showed that gentamicin- and/or vancomycin- loaded bone cement had some, but no absolute efficacy in the treatment of Staphylococcus aureus infections in 34 rat tibiae, based upon the number of colony-forming units [Gerhart, 1993]. The number of failed treatments however, was not mentioned. The use of pre-formed cement to create an infection in this model could have made the removal of the cement easier as compared to the model of Fitzgerald, who inserted the initial cement in as dough.

In the present study, systemic cefazolin was effective in treating the infection in rabbits after revision of the implant. Salez-Mghir et al. studied the treatment with either systemic vancomycin or teicoplanin of a tibia implant infection in rabbits [Salez-Mghir, 1998]. Neither of these antibiotics could fully clear the infection in the majority of rabbits. In contrast with our study, these rabbits were inoculated with methicillin-resistant S. aureus and treated only for one week. Notably, also in contrast with our study, the implants in these rabbits were not revised before starting treatment, stressing the need for revising the prosthesis once infected. In present study, systemic antibiotic treatment was not significantly superior to local antibiotic treatment, although higher numbers of animals may have revealed such a difference. In another animal model, tobramycin-containing bone cement could prevent all infections [Nijhof, 2000b]. In the present study, the same cement could not fully treat 2 out of 9 infected rabbits. This can be explained by the more extensive spread of infection at the time of revision, i.e. not restricted only to the local area around the bone cement. Destruction of the cortex might be severe, and remaining necrotic tissue some distance from the antibiotic-containing bone cement may cause treatment failure [Fitzgerald, 1983]. In such a case, it is doubtful whether an antibiotic course of more than two weeks would have been more successful, although a previous study has shown that antibiotic elution from tobramycin-containing bone cement could be detected up to 4 weeks in vivo [Nijhof, 1997]. Clinically, in patients with such an
extensive implant infection, few surgeons will opt for only local antibiotics. For this matter, a combination of both antibiotic-containing bone cement and systemic antibiotic might be optimal: Systemic antibiotics for the wound problems and bacteria outside the operative area, and antibiotic-containing bone cement for local, high release of antibiotic. Indeed, this combination of antibiotic administration was predominantly used in many series reporting on one-stage revision, although an important early study of Buchholz et al. reported success rates of 77 to 90 per cent in one-stage revisions mainly without administration of systemic antibiotics [Buchholz, 1981, Loty, 1992, Miley, 1982, Mulcahy, 1996, Salvati, 1982a, Ure, 1998, von Foerster, 1991, Wroblewski, 1986].

In addition to culture, we have determined the presence of staphylococcal DNA in the samples of the tibial cortex of the rabbits by means of a reverse line blot hybridization assay. PCR-based assays like RLB might become valuable complements of conventional microbiological techniques, or even improve diagnostic accuracy [Hoeffel, 1999, Mariani, 1996, Mariani, 1998, Tunney, 1999]. In 9 out of 12 rabbits with negative culture results, reverse line blot hybridization showed the presence of *S. aureus* DNA in the right tibia, 14 days after treatment with antibiotics (either systemically or with antibiotic-containing bone cement). Do these reverse line blot hybridization results demonstrate the sensitivity of DNA-based detection methods, or should these findings be interpreted as false-positive results based upon the outcome of culture? The sensitivity of a PCR-based detection method, using broad range bacterial primers, is at the same time its Achilles heel: PCR does not only amplify DNA of viable bacteria, present at the site of the implant, but also contaminating DNA or small quantities of DNA that can still be present shortly after antimicrobial killing of the bacteria. Strict policies in handling the samples should be and have been obtained in this study to exclude false-positive results due to contamination, either from contaminated reagents or from previously amplified bacterial DNA products. We think that the presence of *S. aureus* DNA as confirmed by the reverse line blot hybridization in rabbits with negative culture can be explained to a large extent by non-viable bacteria after antibiotic treatment. Clearance of all bacterial DNA after antibiotic treatment may be species specific, but van der Heijden et al. have shown that it can take up to 26 days after initiation of therapy that PCR of non-staphylococcal DNA becomes negative in septic joints [van der Heijden, 1999b]. In a previous animal model we studied the infection prophylaxis with systemic cefazolin or tobramycin-containing bone cement after inoculation of the rabbit tibia with *S. aureus* [Nijhof, 2000b]. *S. aureus* DNA
could not be detected 7 days after the procedure. These findings may implicate that the clearance of DNA after antibiotic treatment is dependent on bacterial load, since in the present model, the therapy was started only after a full-blown infection had developed. Further studies should be employed to address the persistence of bacterial DNA after antibiotic treatment, because DNA-based diagnosis will become increasingly important in the near future [Rantakokko-Jalava, 2000]. Important clinical decisions based on this type of diagnosis regarding the continuation of antibiotic therapy, whether systemically or locally via antibiotic-containing bone cement or beads, will benefit from more insight on this matter. Furthermore, the viability of microorganisms can be studied using molecular techniques targeting RNA. Reverse transcriptase PCR and nucleic acid sequence amplification (NASBA) have been used for this purpose [Sheridan, 1998, van der Vliet, 1994]. Both ribosomal RNA (rRNA) and messenger RNA (mRNA) can be targeted, but rRNA has been shown to persist longer than mRNA in mycobacteria after chemotherapy [Hellyer, 1999]. In situ hybridization for staphylococcal 16S rRNA can give additional information whether the detection of bacterial DNA represents the presence of the causative organism at the site of an implant or that it is caused by contamination [Krimmer, 1999].

RLB confirmed the presence of S. aureus DNA in only 6 of the 9 rabbits in which S. aureus was cultured 14 days after revision. Since we added an internal spike in the PCR samples, we could exclude inhibition of amplification in the 3 control rabbits with a negative reverse line blot hybridization result and a positive culture. These rabbits had a relatively low bacteria load as compared to the 6 rabbits with a positive reverse line blot hybridization result and positive cultures (respectively 3.8±0.8 and 6.3±0.6, mean 10^log CFU/g). The PCR samples of the three rabbits with negative reverse line blot hybridization results may have originated from a part of the tibial cortex where infection was minimal, causing sampling error. Furthermore, the differences between the weights of the bone samples taken for culture or PCR, and the magnitude of dilution of the original volumes during the two techniques should be considered. The amount of a bone used for a PCR sample was approximately 500 times less than that for culture.

It is concluded from the current study that both tobramycin-containing bone cement and systemic cefazolin used in a one-stage revision for an infected implant can reduce size and rate of infection. However, in cases of virulent infections, a combination of systemic and local antibiotics may be necessary in a one-stage revision procedure. Further studies on the feasibility of PCR-reverse line blot hybridization are advised.