■ ONCOLOGY

Retrospective evaluation of the incidence of early periprosthetic infection with silver-treated endoprostheses in high-risk patients

CASE-CONTROL STUDY

H. Wafa,
R. J. Grimer,
K. Reddy,
L. Jeys,
A. Abudu,
S. R. Carter,
R. M. Tillman

From The Royal Orthopaedic Hospital NHS Trust, Birmingham, United Kingdom

■ H. Wafa, MSc (Orth), MD, FRCSEd(Tr & Orth), Consultant Orthopaedic Surgeon
Glasgow Royal Infirmary, 84, Castle Street, Glasgow, G4 0SF, UK.

■ R. J. Grimer, DSc, FRCS (Trauma & Orth), Professor
■ L. Jeys, FRCS(Tr&Orth), Consultant Orthopaedic Surgeon
■ A. Abudu, FRCS(Tr&Orth), Consultant Orthopaedic Surgeon
■ S. R. Carter, FRCS, Professor
■ R. M. Tillman, FRCS(Tr&Orth), Consultant Orthopaedic Surgeon
Royal Orthopaedic Hospital, Bristol Road South, Northfield, Birmingham, B31 2AP, UK.

■ K. Reddy, MS (Orth), MCh (Orth), FRCSEd (Tr&Orth), Orthopaedic Surgeon
Vanderbilt Orthopaedic Institute, 1215 21st Avenue South, Medical Center East, S Tower, Suite 4200, Nashville, Tennessee, 37232-8774, USA.

Correspondence should be sent to Mr H Wafa; e-mail: hazem.wafa@nhs.net

doi:10.1302/0301-620X.97B2.34554 $2.00

Bone Joint J 2015;97-B:252–7.
Received 29 May 2014; Accepted after revision 21 October 2014

We conducted a case-control study to examine the merit of silver-coated tumour prostheses. We reviewed 85 patients with Agluna-treated (silver-coated) tumour implants treated between 2006 and 2011 and matched them with 85 control patients treated between 2001 and 2011 with identical, but uncoated, tumour prostheses.

In all, 106 men and 64 women with a mean age of 42.2 years (18.4 to 90.4) were included in the study. There were 50 primary reconstructions (29.4%); 79 one-stage revisions (46.5%) and 41 two-stage revisions for infection (24.1%).

The overall post-operative infection rate of the silver-coated group was 11.8% compared with 22.4% for the control group (p = 0.033, chi-square test). A total of seven of the ten infected prostheses in the silver-coated group were treated successfully with debridement, antibiotics, and implant retention compared with only six of the 19 patients (31.6%) in the control group (p = 0.048, chi-square test). Three patients in the silver-coated group (3.5%) and 13 controls (15.3%) had chronic periprosthetic infection (p = 0.009, chi-square test).

The overall success rates in controlling infection by two-stage revision in the silver-coated group was 85% (17/20) compared with 57.1% (12/21) in the control group (p = 0.05, chi-square test). The Agluna-treated endoprostheses were associated with a lower rate of early periprosthetic infection. These silver-treated implants were particularly useful in two-stage revisions for infection and in those patients with incidental positive cultures at the time of implantation of the prosthesis.

Debridement with antibiotic treatment and retention of the implant appeared to be more successful with silver-coated implants.

Cite this article: *Bone Joint J* 2015;97-B:252–7.

Endoprosthetic reconstruction after tumour resection provides immediate stability and allows early weight-bearing.[1] These prostheses have also been used in the reconstruction of selected patients with segmental skeletal defects caused by fracture nonunion in the elderly and revision arthroplasty with significant bone loss.[2-4] Deep periprosthetic infection remains one of the most difficult complications to treat after this type of reconstruction, and is reported to occur in between 5% and 13% of patients.[5-10] A significant number of these will require an amputation if the infection is uncontrolled.[5,7,8,10]

Biofilm formation protects the bacteria from the immune response of the host and the effect of antibiotics.[11,12] Because colonisation of the prosthesis precedes clinical infection, one approach to minimising the risk of infection is to coat the surface of the prosthesis with an antimicrobial substance. The biocidal effects of silver are well known. Silver molecules have been incorporated into the surfaces of a number of medical devices including vascular and urinary catheters, endotracheal tubes, vascular grafts, prosthetic heart valve sewing rings, surgical sutures, and different orthopaedic implants.[13-17]

The purpose of this study was to compare the incidence of periprosthetic infection at 12 months in patients who had undergone endoprosthetic reconstruction with a silver-coated prosthesis with a control group who had a matched but untreated implant. We also investigated the management of infection which arose either in the post-operative period, or, unexpectedly, at the time of revision surgery, and reviewed the outcome of this group of patients.

Patients and Methods

Ethical approval for this study was obtained from the local ethics committee (NRES Committee East of England, Essex).

Between 2006 and 2011, 85 consecutive patients underwent endoprosthetic replacement

Table I. The type of and indication for endoprosthetic replacement by silver-coated or control group.

		Silver group (n = 85)			Control group (n = 85)		
Anatomical location	**No. patients**	**Primary**	**Single-stage revision**	**Two-stage revision**	**Primary**	**Single-stage revision**	**Two-stage revision**
Distal femur	63	3	20	8	3	19	10
Proximal tibia	36	9	4	5	9	3	6
Proximal femur	19	-	9	1	-	9	-
Total femur	6	-	3	-	-	2	1
Combined femur/tibia	8	-	1	3	-	2	2
Proximal humerus	6	-	1	2	-	1	2
Hemipelvis	16	7	-	1	7	1	-
Distal humerus	2	-	1	-	1	-	-
Distal radius	2	1	-	-	-	1	-
Intercalary	12	6	-	-	4	2	-
Total	170	26	39	20	24	40	21

using an Agluna silver-enhanced (Accentus Medical Ltd, Oxfordshire, United Kingdom) custom-made endoprosthesis (Stanmore Implants Worldwide Ltd, Elstree, United Kingdom). All were at least 18 years old at the time of surgery and were followed for a minimum of 12 months. In each case, we used a silver-coated implant because the patient was perceived to be at high risk of infection, either on the grounds of site (e.g. tibia or pelvis) or other risk factors (e.g. previous surgery, revision surgery, the use of radiotherapy or poor soft-tissue cover.)

A control series of 85 patients were selected using the search engine of a prospective database of our oncology service which contains data about all 31188 patients who have been treated in the department. Casematching was carried out on the basis of the anatomical location of the implant and the type of surgery performed (primary, one-stage revision or two-stage revision). The patients in this group had all been treated between 2001 and 2011. The case matching was carried out by an independent data manager. All patients in the control group had the same type of custom implant and the same indication for surgery, but the endoprosthesis did not have a silver coating.

There were, therefore, 170 patients in the study overall, 106 men and 64 women with a mean age of 42.2 years (18.4 to 90.4) at the time of implant insertion. In all, 50 patients (29.4%) had a primary reconstruction, 79 (46.5%) a one-stage revision and 41 (24.1%) a two-stage revision for periprosthetic infection. The site of and reasons for endoprosthetic replacement are shown in Table I.

Because of the wide variety of indications for surgery, the rates of infection were analysed based both on the site of, and indication for surgery (primary, one-stage revision (presumed to be aseptic) and two-stage revision for infection). Of the 50 patients having a primary endoprosthesis, 40 were for a primary bone tumour: 16 had undergone chemotherapy, (six of 26 (23.1%) in the silver group and ten of 24 in the control group (41.7%) ($p = 0.16$)). All prostheses were implanted using antibiotic-laden cement; usually Palacos R+G (Heraeus Medical, Hanau, Germany) and all patients had routine peri-operative antibiotic prophylaxis according to the hospital guidelines in place at the time of the surgery. This was usually Cefuroxime (1.5 g IV at induction and a further two doses of 750 mg at eight-hourly intervals) for primary procedures and aseptic revisions but targeted to the identified bacteria for a two-stage revision for infection.

In the Agluna coating process, ionic silver is 'stitched' into the surface of the titanium alloy using a patented method. This is achieved by anodisation of the titanium alloy followed by absorption of silver from an aqueous solution. The engineered surface modification is integrated into the substrate and loaded with silver by an ion exchange reaction. This results in the formation of circular features of 5 µm diameter in the surface of the implant, containing an amorphous titania species within which the bulk of the ionic silver has been stored. Using this technique, the maximum inventory of silver for a typical endoprosthesis is 6 mg, more than 300 times lower than the no-observed-adverse-effect level.[18] This treatment enables the steady release of silver ions from the surface of the implant over several months by dissolution into body fluids, eventually leaving a silver-free implant that has long-term durability and biocompatibility.

All patients were followed up for a minimum of 12 months. Data collected during the post-operative period, and at three, six, nine and 12 month post-operatively were analysed. Deep infections were classified according to the criteria established by the United States, Center for Disease Control (CDC). The CDC defines a deep surgical site infection as one occurring within 30 days of an operation, or within one year if the implant is in place and the infection appears to be related to the operation.[19] A periprosthetic infection was confirmed if three of the following five criteria were met:[20]

- C-reactive protein level of > 10 mg/dL.
- Erythrocyte sedimentation rate of > 30 mm/hr.
- Positive joint aspiration culture.
- Purulent intra-operative tissue appearance.
- Positive intra-operative culture.

Table II. The post-operative infection rate split both by site, indication and by silver-coated *versus* control group.

		Silver group n = 85				Control group n = 85	
		Primary	Single-stage revision	Two-stage revision	Primary	Single-stage revision	Two-stage revision
Anatomical location	No. patients	Infected (%)	Infected (%)	Infected (%)	Infected (%)	Infected (%)	Infected (%)
Distal femur	63	0/3*(0)*	2/20 *(10)*	1/8 (*13)*	0/3 (*0)*	2/19 *(11)*	4/10 *(40)*
Proximal tibia	36	1/9 *(11)*	0/4 *(0)*	1/5 (*20)*	0/9 *(0)*	1/3 *(33)*	3/6 *(50)*
Proximal femur	19	-	0/9 *(0)*	0/1 *0)*	-	1/9 *(11)*	-
Total femur	6	-	0/3 *(0)*	-	-	1/2 *(50)*	1/1 *(100)*
Combined femur/tibia	8	-	0/1 (*0)*	1/3 (*33)*	-	0/2 *(0)*	1/2 *(50)*
Proximal humerus	6	-	0/1 (*0)*	0/2 (*0)*	-	0/1 (*0)*	0/2 *(0)*
Hemipelvis	16	4/7 *(57)*	-	0/1 (*0)*	4/7 *(57)*	0/1 *(0)*	-
Distal humerus	2	-	0/1*(0)*	-	0/1 *(0)*	-	-
Distal radius	2	0/1 *(0)*	-	-	-	0/1 *(0)*	-
Intercalary	12	0/6 *(0)*	-	-	1/4 *(25)*	0/2 *(0)*	-
Total	170	5/26 (*19)*	2/39 (*5)*	3/20 (*15)*	5/24 *(21)*	5/40 *(13)*	9/21 *(43)*

Table III. Types of infecting micro-organisms split by silver and control groups.

Isolated micro-organism	Silver-coated group	Control group
Gram positive bacteria (n, %)		
Coagulase-negative staphylococcus	4 *(40)*	5 + 2* (*36.8)*
Staphylococcus aureus	2 + 1* *(30)*	1 + 3* (*21.1*)
Streptococcus viridans	1 *(10)*	-
Enterococcus faecalis	1* *(10)*	1* *(5.3)*
Beta hemolytic streptococcus	-	1 + 2* *(15.8)*
Gram negative bacteria (n, %)		
Pseudomonas aeruginosa	2 + 1* *(30)*	-
Enterobacter cloacae	-	2 + 1* *(15.8)*
Escherichia coli	-	1* *(5.3)*
Proteus mirabilis	-	1* *(5.3*)
Brevundimonas vesicularis	-	1 *(5.3)*
Raoultella planticola	-	1 *(5.3)*
Negative culture (n, %)	-	3 *(15.8)*

* indicates those cases with polymicrobial infection in patients affected by an infected prosthesis according to the definition from the Center for Disease Control

The management of patients with an infection was initially by washout and antibiotics. If this failed then further surgery was usually undertaken, usually in the form of a two-stage revision or amputation depending on the clinical situation and the wishes of the patient.

Statistical analysis. This was performed using Prism version 5.04 (GraphPad Software, Inc., La Jolla, USA). Comparisons between groups were undertaken using the chi-squared test with statistical significance set at a p-value < 0.05.

Results

The overall rate of periprosthetic infection at one year in patients who received a silver-treated implant was 11.8% (10/85) compared with 22.4% (19/85) in the control group (p = 0.033, chi-square test). This does not include the patients who had positive cultures at revision but did not fulfil the criteria. The rates of infection by site and indication for the two groups are shown in Table II.

The organisms infecting the two groups were largely similar (Table III). There was a higher incidence of Pseudomonas infection in patients in the silver-treated group than in the control group. All of these patients had a pelvic prosthesis.

In each group, 15 patients had a positive culture of the joint aspirate and/or tissue samples taken at the time of implant insertion. These were treated with a prolonged course of antibiotics. In the control group, six of the 15 patients (40%) had a post-operative infection compared with two patients (13.3%) in the silver-coated group (p = 0.099, chi-square test).

In the silver-coated group, seven of the ten infected prostheses (70%) were successfully treated with debridement, antibiotics, and implant retention compared with six of the 19 infected implants (31.6%) in the control group (p = 0.048, chi-square test).

In the control group, 13 of the 85 patients (15.3%) had a persistent periprosthetic infection which required

Table IV. Outcome for patients with post-operative infection split by silver-coated *versus* control group

	Silver-coated group (n = 10)	Control group (n = 19)
Resolved	7	6
Chronic antibiotic suppression	1	7
Prosthetic revision for infection	1	3
Amputation	1	3

removal of the implant, amputation, or long-term antibiotic suppression at the time of latest follow-up, as compared with three patients in the silver group (3.5%) (Table IV) (p = 0.009, chi-square test).

The rate of infection after a primary procedure was dramatically higher in the pelvis than in other sites both in the silver-coated and control groups (eight out of 14; 57%). The rate of infection for other sites was 1/19 (5.3%) for the silver-coated implants and 1/17 (5.9%) for the control group.

Only three of the 16 patients (18.8%) who received adjuvant chemotherapy developed an early periprosthetic infection (one of six (16.7%) in the silver-coated group and two of ten in the control group (20%) (p = 0.869, chi-square test).

Periprosthetic infection occurred in two of the 39 patients (5.1%) who had a single-stage revision procedure with a silver-treated implant and in five of the 40 patients (12.5%) in the control group (p = 0.249 by chi-square test).

In the silver-coated group, the infection relapsed in three of the 20 patients (15%) who underwent a two-stage revision surgery compared with nine of the 21 patients in the control group (42.9%) (p = 0.05, chi-square test).

Discussion

Periprosthetic infection is a devastating complication after endoprosthetic replacement. Bacterial colonisation of the surface of the implant makes it very difficult to eradicate infection while retaining the prosthesis. A two-stage revision is a massive undertaking for the patient, who needs a prolonged period of hospitalisation and rehabilitation, and carries considerable financial implications for the treating hospital. Moreover, these procedures are not consistently successful: more than 20% of those undergoing a two-stage revision with a conventional implant have a relapse of their periprosthetic infection.[21,22] Jeys et al[5] reported on 1240 patients who underwent endoprosthetic reconstruction. Periprosthetic infection was identified in 136 patients (11%) at a mean follow-up of 5.8 years: amputation was needed in 50 (37%) of the 136 patients.[5] Flint et al[22] removed 15 of 180 (8%) uncemented endoprostheses of the lower extremity for infection: five patients subsequently had an amputation.

Costerton, Montanaro and Arciola[23] described how bacterial adherence to an implant and the production of a biofilm proceeds in two steps: first, by attachment of the bacteria to the surface of the implant and, second, by proliferation of the bacteria with production of an extracellular polymeric matrix consisting of various monomolecular components including the polysaccharide intercellular adhesin (PIA), proteins and extracellular DNA. Biofilm formation is partially controlled by quorum sensing, an interbacterial communication mechanism dependent on population density.[22,24,25]

The type of alloy from which the endoprosthesis is made seems to have an influence on the rate of infection. Gosheger et al[26] have reported a significantly higher rate of infection when the endoprosthesis is made of a cobalt–chrome alloy (24 of 77, 31.2%) rather than a titanium alloy (17 of 120, 14.2%). In an experimental study, porous-coated cobalt–chromium implants required a concentration of *Staphylococcus aureus* that was 15 times less than that needed to infect a porous-coated titanium implant.[27] Once a glycoprotein film has formed on the titanium oxide surface, it is rapidly colonised by osteoblasts which may protect the surface against colonisation by bacterial pathogens. The cobalt–chromium alloy is less readily colonised by host osteoblasts and consequently more readily colonised by the bacteria.[26]

Silver has the ability to exert its bactericidal/bacteriostatic activity at very low concentrations. Silver ions interact with sulphur or phosphorous-containing groups belonging to proteins of the bacterial cell wall or plasma membrane, creating membrane holes through which the contents of the cytoplasm flow out of the cell, causing bacterial cell death. Silver ions inhibit cytochromes of the electron transport chain, bind to and damage DNA, RNA, and ribosomes, and also lead to the formation of reactive oxygen species, which are toxic to both bacterial cells and eukaryotic host cells.[28] Moreover, bacterial resistance to silver is rare and develops slowly compared with antibiotic resistance. This may be due to the effect of multiple antimicrobial mechanisms which mediate the bactericidal activity of silver, whereas antibiotics have usually only one mechanism of action.[27] Silver has therefore been widely used as an anti-infective coating in a variety of medical devices.

The Agluna process is different to the silver coating used by Hardes et al.[29] In their process 0.33 g to 2.89 g of silver is coated onto the implant compared to a maximum of 6 mgs in the Agluna process for a typical megaprosthesis. Local argyria has been reported in 23% of the patients (7/31) with the use of this type of silver-coated prostheses (Implantcast, Buxtehude, Germany): the level of silver in Agluna-coated implants is highly unlikely ever to cause this level of toxicity.[30]

In this study, the overall rate of periprosthetic infection in patients who received silver-treated implants was 11.8%, which is almost half of that in the control group (22.4%).

Our results match those of Hardes et al[13] who reported a reduction in the rate of periprosthetic infection from 17.6% in uncoated titanium endoprostheses to 5.9% in the silver-coated group. Their significantly lower infection rates could be explained by our study design as we only included very high risk patients.

In this small series we have not been able to show that silver coating reduced the rate of infection of primary implants or one-stage revisions when infection was not anticipated (e.g. for aseptic loosening or prosthesis breakage). Nevertheless, we have not disproved that silver coating may have a beneficial role. Racano et al[31] recently carried out a review of reported rates of infection after endoprosthetic replacement and suggested an overall rate of 10% at one year. They also suggested that the duration of antibiotic administration may be a contributory factor. As a result they are currently carrying out an international randomised control trial to examine the relationship between the duration of antibiotic prophylaxis and the risk of infection. If silver coating does indeed reduce the rate of infection by half, then this is likely to have a far greater effect than the duration of antibiotics.

There are many limitations to this study, the largest of which is the small number of patients in each group. Given the rarity of bone tumours, and even with an infection risk of 10%, carrying out a randomised trial to identify if silver coating was beneficial or not would take many years to complete, which is why we undertook a case-controlled series. The length of time (five years) taken to accrue just 85 patients in the silver-coated group gives an idea of the rarity of the indications for doing so.

The most impressive results by far in this series have been the reduced rate of infection after two-stage revisions and the far greater ease with which infection can been controlled should it arise in all patients. This was an unexpected result and suggests that the combination of silver coating with a debridement and implant retention as well as antibiotic administration can be successful in eradicating infection in a much greater proportion of cases than prior to the advent of silver-coated implants. This alone could justify the use of a silver-treated implant in any case where a high risk of infection is likely.

As a result of this experience, we currently use silver-treated implants for all revision procedures and any primary procedure where there is a perceived higher risk of infection.

Author contributions

H. Wafa: Data collection and CRFs, data analysis, writing the manuscript.
R. J. Grimer: Data analysis, writing the manuscript.
K. Reddy: Revising the manuscript.
L. Jeys: Revising the manuscript.
A. Abudu: Revising the manuscript.
S. R. Carter: Revising the manuscript.
R. M. Tillman: Revising the manuscript.

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

This article was primary edited by G. Scott and first proof edited by A. C. Ross.

References

1. **Wafa H, Grimer RJ.** Surgical options and outcomes in bone sarcoma. *Expert Rev Anticancer Ther* 2006;6:239–248.
2. **Dietz SO, Nowak TE, Burkhart KJ, et al.** Fractures of the distal humerus in the elderly; pros and cons of endoprosthetic replacement. *Unfallchirurg* 2011;114:801–814 (In German).
3. **Paniker J, Abudu A, Carter SR, Tillman RM, Grimer RJ.** Treatment of non-union with massive endoprosthesis. *J Bone Joint Surg [Br]* 2008;90-B(SuppIII):403.
4. **Saidi K, Ben-Lulu O, Tsuji M, et al.** Supracondylar periprosthetic fractures of the knee in the elderly patients: a comparison of treatment using allograft-implant composites, standard revision components, distal femoral replacement prosthesis. *J Arthroplasty* 2014;29:110–114.
5. **Jeys LM, Grimer RJ, Carter SR, Tillman RM.** Periprosthetic infection in patients treated for an orthopaedic oncological condition. *J Bone Joint Surg [Am]* 2005;87-A:842–849.
6. **Gosheger G, Gebert C, Ahrens H, et al.** Endoprosthetic reconstruction in 250 patients with sarcoma. *Clin Orthop Relat Res* 2006;450:164–171.
7. **Sim IW, Tse LF, Ek ET, et al.** Salvaging the limb salvage: management of complications following endoprosthetic reconstruction for tumours around the knee. *Eur J Surg Oncol* 2007;33:796–802.
8. **Shehadeh A, Noveau J, Malawer M, et al.** Late complications and survival of endoprosthetic reconstruction after resection of bone tumors. *Clin Orthop Relat Res* 2010;468:2885–2895.
9. **Shin DS, Weber KL, Chao EY, An KN, Sim FH.** Reoperation for failed prosthetic replacement used for limb salvage. *Clin Orthop Relat Res* 1999;358:53–63.
10. **Zeegen EN, Aponte-Tinao LA, Hornicek FJ, et al.** Survivorship analysis of 141 modular metallic endoprostheses at early followup. *Clin Orthop Relat Res* 2004;420:239–250.
11. **Albers CE, Hofstetter W, Siebenrock KA, et al.** In vitro cytotoxicity of silver nanoparticles on osteoblasts and osteoclasts at antibacterial concentrations. *Nanotoxicology* 2013;7:30–36.
12. **Valour F, Trouillet-Assant S, Rasigade JP, et al.** Staphylococcus epidermidis in orthopedic device infections: the role of bacterial internalization in human osteoblasts and biofilm formation. *PLoS One* 2013;8:67240.
13. **Hardes J, von Eiff C, Streitbuerger A, et al.** Reduction of periprosthetic infection with silver-coated megaprostheses in patients with bone sarcoma. *J Surg Oncol* 2010;101:389–395.
14. **Schierholz JM, Lucas LJ, Rump A, et al.** Efficacy of silver-coated medical devices. *J Hosp Infect* 1998;40:257–262.
15. **Kollef MH, Afessa B, Anzueto A, et al. NASCENT Investigation Group** Silver-coated endotracheal tubes and incidence of ventilator-associated pneumonia: the NASCENT randomized trial. *JAMA* 2008;300:805–813.
16. **Collinge CA, Goll G, Seligson D, et al.** Pin tract infections: silver vs uncoated pins. *Orthopedics* 1994;17:445–448.
17. **Riley DK, Classen DC, Stevens LE, et al.** A large randomized clinical trial of a silver-impregnated urinary catheter: lack of efficacy and staphylococcal superinfection. *Am J Med* 1995;98:349–356.
18. **Lansdown AB.** A pharmacological and toxicological profile of silver as an antimicrobial agent in medical devices. *Adv Pharmacol Sci* 2010;2010:910686.
19. **Horan TC, Gaynes RP, Martone WJ, et al.** CDC definitions of nosocomial surgical site infections, 1992: a modification of CDC definitions of surgical wound infections. *Am J Infect Control* 1992;20:271–274.
20. **Parvizi J, Ghanem E, Menashe S, et al.** Periprosthetic infection: what are the diagnostic challenges? *J Bone Joint Surg [Am]* 2006;88-A:138–147.
21. **Grimer RJ, Belthur M, Chandrasekar C, Carter SR, Tillman RM.** Two-stage revision for infected endoprostheses used in tumor surgery. *Clin Orthop Relat Res.* 2002;395:193–203.
22. **Flint MN, Griffin AM, Bell RS, et al.** Two-stage revision of infected uncemented lower extremity tumor endoprostheses. *J Arthroplasty* 2007;22:859–865.
23. **Costerton JW, Montanaro L, Arciola CR.** Biofilm in implant infections: its production and regulation. *Int J Artif Organs* 2005;28:1062–1068.
24. **Arciola CR, Campoccia D, Speziale P, et al.** Biofilm formation in Staphylococcus implant infections; a review of molecular mechanisms and implications for biofilm-resistant materials. *Biomaterials* 2012;33:5967–5982.
25. **Montanaro L, Poggi A, Visai L, et al.** Extracellular DNA in biofilms. *Int J Artif Organs* 2011;34:824–831.
26. **Gosheger G, Goetze C, Hardes J, et al.** The influence of the alloy of megaprostheses on infection rate. *J Arthroplasty* 2008;23:916–920.

27. Cordero J, Munuera L, Folgueira MD. Influence of metal implants on infection; an experimental study in rabbits. *J Bone Joint Surg [Br]* 1994;76-B:717–720.

28. Taglietti A, Arciola CR, D'Agostino A, et al. Antibiofilm activity of a monolayer of silver nanoparticles anchored to an amino-silanized glass surface. *Biomaterials* 2014;35:1779–1788.

29. Hardes J, Ahrens H, Gebert C, et al. Lack of toxicological side-effects in silver-coated megaprostheses in humans. *Biomaterials* 2007;28:2869–2875.

30. Glehr M, Leithner A, Friesenbichler J, et al. Argyria following the use of silver-coated megaprostheses: no association between the development of local argyria and elevated silver levels. *Bone Joint J* 2013;95-B:988–992.

31. Racano A, Pazionis T, Farrokhyar F, et al. High infection rate outcomes in long-bone tumor surgery with endoprosthetic reconstruction in adults: a systematic review. *Clin Orthop Relat Res* 2013;471:2017–2027.