European Journal of Orthopaedic Surgery & Traumatology
https://doi.org/10.1007/s00590-018-2270-3

ORIGINAL ARTICLE • HIP - TUMORS

Silver-coated megaprostheses in the proximal femur in patients with sarcoma

Arne Streitbuerger[1,2] · Marcel P. Henrichs[3] · Gregor Hauschild[1] · Markus Nottrott[1] · Wiebke Guder[1,2] · Jendrik Hardes[1,2]

Received: 29 April 2018 / Accepted: 14 June 2018

Abstract

Background Proximal femur replacements in patients with sarcoma are associated with high rates of infection. This study is the largest one comparing infection rates with titanium versus silver-coated megaprostheses in sarcoma patients.

Methods Infection rates were assessed in 99 patients with proximal femur sarcoma who underwent placement of a titanium ($n=35$) or silver-coated ($n=64$) megaprosthesis. Treatments administered for infection were also analyzed.

Results Infections occurred in 14.3% of patients in the titanium group, in comparison with 9.4% of those in the silver group, when the development of infection was the primary end point. The 5- and 10-year event-free survival rates for the prosthesis relative to the parameter of infection were 90% in the silver group and 83% in the titanium group. The overall infection rates were 10.9% in the silver group and 20% in the titanium group. Two patients each in the silver and titanium groups ultimately had to undergo amputation. The need for two-stage prosthesis exchanges (57.1% in the titanium group) declined to 14.3% in the silver group.

Conclusion Using a silver-coated proximal femoral replacement nearly halved the overall infection rate. When infections occurred, it was usually possible to avoid two-stage prosthesis exchanges in the silver group.

Keywords Prosthesis-related infections · Bone neoplasms · Silver · Implantation · Proximal femur · Sarcoma

Introduction

Proximal femoral replacement is increasingly being used not only in sarcoma surgery, but also in surgery for metastases and in revision procedures [1–3]. In addition to mechanical complications such as luxation, aseptic loosening, and periprosthetic fracture, periprosthetic infection continues to be a frequent complication [1, 2, 4, 5]. Treatment options for periprosthetic infection range from rinsing the prosthesis alone and exchanging the polyethylene components, to a one-stage exchange of the prosthesis with or without exchanging the prosthesis stems, to two-stage prosthesis exchanges, or even a need for secondary amputation [2, 5, 6]. Periprosthetic infection is thus usually associated with a prolonged burden of suffering for the patient, sometimes with multiple revision operations, a protracted postoperative rehabilitation period, and in the worst case also with a permanent loss of function [2]. For medical insurance companies, periprosthetic infection of primary implants (total hip arthroplasty, THA; total knee arthroplasty, TKA) also usually represents a substantial cost burden [7], depending on the severity of the condition. However, no data on this relating to megaendoprostheses are currently available.

There is therefore a clear need to reduce the numbers of periprosthetic infections. Antimicrobial silver coating on the surface of prostheses may be capable of reducing the rate of periprosthetic infections by preventing bacterial colonization. In a previous study, our own group reported a reduction in the rate of periprosthetic infection when silver-coated tumor endoprostheses were used in the proximal tibia and

Arne Streitbuerger, Marcel P. Henrichs have contributed equally to the paper.

✉ Jendrik Hardes
jendrik.hardes@uk-essen.de

[1] Department of Orthopedics and Tumor Orthopedics, Münster University Hospital, Münster, Germany

[2] Department of Oncologic Musculoskeletal Surgery, Essen University Hospital, Hufelandstr. 55, 45147 Essen, Germany

[3] Department of Orthopedics, Paracelsus Clinic, Osnabrück, Germany

Published online: 20 June 2018

femur [8]. However, the number of patients included in the study was small and the follow-up period was short. When infection developed nevertheless, the silver coating on the prostheses led to a lower rate of revision operations being needed and to better final outcomes in relation to possible reinfection.

To the best of our knowledge, no studies have been published on the use of silver-coated proximal femur tumor endoprostheses as a method of preventing infection. The aim of the present study was therefore to compare the actual infection rate among patients with titanium tumor prostheses and the infection rate in patients in whom silver-coated prostheses were placed in the proximal femur as the primary implant. Possible differences in the treatment of periprosthetic infections were also documented.

Materials and methods

A total of 99 patients were treated with a proximal femur replacement (MUTARS®, Implantcast Ltd., Buxtehude, Germany). Sixty-four patients (median age 37 years, range 5–82) received a silver-coated prosthesis between 2005 and 2014, and 35 patients (median age 38 years, range 7–71) received a titanium prosthesis between 1996 and 2004. Some of the patients were included in the previous study, but now have a longer follow-up period [8]. The silver-coated prosthesis used has been described in previous studies [9]. No silver coating was applied on the articulating surfaces or prosthetic stems.

Patients with a silver-coated replacement had median follow-up periods of 34.5 months (mean 43 months, range 3–135 months) and 42 months for the surviving patients. At the final follow-up, 43 patients had no evidence of disease, four were alive with disease, and 17 patients had died of the disease (median follow-up period of 23 months). Patients with a titanium replacement had median follow-up periods of 96 months (mean 95 months, range 3–216 months) and 120 months for the surviving patients. At the final follow-up, 21 patients had no evidence of disease and 14 patients had died of the disease (median follow-up period of 18 months).

Only patients with bone or soft-tissue tumors with osseous infiltration were included. Patients who had previously undergone treatment with an intralesional procedure (e.g., curettage, arthroplasty in the case of an overlooked sarcoma, osteosynthesis due to a pathologic fracture) were also included. In contrast, patients who received their current megaprosthesis after a failed previous megaprosthesis were excluded. Patients with extra-articular resection were included (titanium $n=4$, silver $n=3$). The clinical charts for the 64 patients treated with a silver-coated megaprosthesis were assessed prospectively, with particular attention being given to demographic data, diagnosis, preoperative intralesional procedures, pathologic fracture, preoperative leukocyte count, adjuvant or neoadjuvant therapy, reconstruction length, operating time, and complications. Special emphasis was given to revision operations due to mechanical failure (e.g., dislocation, aseptic loosening, and periprosthetic fracture) (Table 1).

In the titanium group, there were seven previous operations (curettage, $n=4$, with osteosynthesis in one case; osteosynthesis, $n=2$; hip arthroplasty, $n=1$). In the silver group, there were seven previous intralesional operations (hip arthroplasty, $n=3$; curettage, $n=2$; soft-tissue sarcoma resection, $n=2$) (Table 1).

Table 1 also shows the patients' mean age and the characteristics of the surgical procedures in the titanium and silver groups, including preoperative intralesional surgical procedures, adjuvant or neoadjuvant treatment modalities, and postoperative complications (wound healing complications—superficial/epifascial versus deep wound healing disturbances; aseptic loosening, change of the cup, periprosthetic fracture).

Surgery was carried out in both groups in the same laminar airflow operating rooms; staff did not use body-exhaust suits. Postoperatively, all patients received an intravenous third-generation cephalosporin for 3–7 days, followed by oral therapy with a second-generation cephalosporin until wound healing was achieved. The proximal femur replacements were routinely combined with a reattachment tube for soft-tissue refixation [10].

Table 1 Data for patients with proximal femur replacements

	Titanium ($n=35$)	Silver ($n=64$)
Leukocytes (median)	6.1	5.0
Pathologic fracture	17.1%	20.3%
Previous intralesional operations (%)	20.0%	10.9%
Diagnoses (most common)	CS 40.0% OS 28.6% ES 25.7%	ES 29.7% CS 25.0% OS 18.8% STS 12.5% PSB 9.4%
Chemotherapy	57.1%	68.8%
Radiotherapy	22.9%	29.7%
Extra-articular resection	11.4%	4.9%
Median reconstruction length (mm)	200	200
Median operating time (min.)	262	214
Wound healing problems		
Superficial	0%	9.4%
Deep/hematoma	0%	4.7%
Revision operations (mechanical failure)	8.6%	15.6%

CS chondrosarcoma; *ES* Ewing's sarcoma; *OS* osteosarcoma; *PSB* pleomorphic sarcoma of bone; *STS* soft-tissue sarcoma

An implant-associated infection was diagnosed in accordance with the Musculoskeletal Infection Society (MSIS) criteria [11]. However, using the MSIS criteria some of our patients would have had no infection in the silver and titanium groups (Table 2). However, all of these patients had clear clinical signs of infection (e.g., redness, wound secretion) and/or clearly elevated CRP levels—but without a clear fistula and without the finding of the causative bacteria. Therefore, we evaluated this clinical scenario in immunocompromised patients as a periprosthetic infection. In patients with periprosthetic infection, cure with no clinical signs of inflammation and negative C-reactive protein (CRP) findings were assessed by the treating clinician at the date of the last available follow-up. Treatment for periprosthetic infection was documented at the final follow-up.

Statistical analysis

The primary end point of the study was a periprosthetic infection without any previous revision surgery. The secondary end point was the outcome of treatment for any periprosthetic infection that occurred. Event-free survival of the prosthesis relative to the parameter of infection was assessed using Kaplan–Meier survivorship analysis. Possible risk factors for periprosthetic infection were screened using univariate analysis for the whole patient group and for the titanium and silver subgroups. The infection rates in the silver and titanium groups were compared using the Chi-square test.

Results

Statistically significant risk factors for periprosthetic infection

Univariate analysis of the study group as a whole ($n=99$) only identified radiotherapy administration as a significant risk factor for infection ($P=0.007$).

Incidence of periprosthetic infection

Infections were observed in the titanium group in 14.3% of the patients (five of 35), when the occurrence of infection was the primary end point. In the silver group, infections developed in only 9.4% (six of 64). The 5- and 10-year event-free survival rates for the prostheses relative to the parameter of infection were 90% (95% CI 82.5–97.7) in the

Table 2 Time of infection, possible previous revision operations before the development of infection and parameters indicating periprosthetic infection

Patient	Age (years)	Silver coating	Time since primary operation (months)	Any revision surgery due to mechanical failure before infection	Type of revision surgery	Time interval between revision surgery and infection (months)	Fistula	Isolated microorganism	C-reactive protein (mg/dL)
1	55	Yes	17	No	–	–	No	*S. aureus*	24.6
2	41	Yes	44	Yes	Change of stem	3	Yes	*S. epidermidis, E. faecalis*	5.9
3	71	Yes	0.5	No	–	–	No	None	10.0
4	14	Yes	1.5	No	–	–	No	None	6.8
5	21	Yes	12	No	–	–	No	*S. epidermidis*	5.4
6	80	Yes	1	No	–	–	No	None	10.2
7	19	Yes	6	No	–	–	No	*S. anginosus, S. constellatus*	19.1
8	7	No	70	Yes	Salter osteotomy due to chronic dislocation	2	No	None	–
9	60	No	2	No	–	–	No	*S. epidermidis*	10.0
10	31	No	11	No	–	–	No	*S. epidermidis*	2.0
11	12	No	24	No	–	–	No	*S. epidermidis, S. hominis*	–
12	21	No	55	No	–	–	No	None	–
13	46	No	4	No	–	–	No	*E. faecalis*	–
14	39	No	168	Yes	Change of stem	64	No	*S. epidermidis*	11.9

silver group and 83% (95% CI 69.4–97.0) in the titanium group ($P = 0.568$).

Overall, seven of the 64 patients in the silver group (10.9%) developed a periprosthetic infection, as one patient became infected after revision surgery due to a mechanical failure of the prosthesis (Table 3). In the titanium group, two patients developed periprosthetic infection after revision surgery due to mechanical prosthesis failures, resulting in an overall infection rate of 20.0% (seven of 35).

In the silver group, none of the patients who died of disease over a median of 23 months postoperatively had any periprosthetic infection, whereas two patients (patients 9 and 13) with titanium prostheses developed periprosthetic infections and died 4 and 24 months, respectively, after the primary implantation.

Time to periprosthetic infection

In the titanium group, periprosthetic infection led to a surgical intervention at a median of 11 months (range 2–55 months) after implantation of the prosthesis in five patients without any previous revision surgery. In the silver group, periprosthetic infection occurred at a median of 4 months (range 0.5–17 months) after primary implantation of the prosthesis in six patients without any previous revision surgery (Table 2). In one patient with periprosthetic infection after a revision operation for mechanical failure, infection developed 3 months postoperatively. In the titanium group, two patients developed infection after revision surgery 2 and 64 months postoperatively. Overall, 10 of 11 (91%) periprosthetic infections in both groups occurred within the first two postoperative years, if no later revision surgery due to mechanical failure was necessary.

Treatment of periprosthetic infection

Finally, two patients (28.6%) each in the silver group and titanium group had to undergo amputation or rotationplasty. Stump lengthening procedures were carried out with cement spacers in three patients and BIIIb rotationplasty in one. All of these patients had poor soft-tissue conditions due to previous radiotherapy.

However, a two-stage prosthesis exchange was required much less often in the silver group, at 14.3% of the patients ($n = 1$), in comparison with the titanium group, at 57.1% ($n = 4$). In the silver group, two patients each (28.6%) instead underwent debridement, antibiotics, irrigation, and retention (DAIR) of the prosthesis, or a one-stage prosthesis exchange with retention of the stems.

In the silver group as well, however, a one-stage exchange of the prosthesis body without removal of the stems ($n = 1$) and an attempt at two-stage reimplantation without removing the stem ($n = 1$) were not successful. Both of these patients had undergone radiotherapy after the primary prosthesis implantation.

Discussion

Despite the use of systemic antibiotic therapy and additional individual measures against periprosthetic infection, it is not always possible to prevent infection as a complication [1, 2, 4, 12]. In contrast to a primary endoprosthesis in the hip, megaprostheses require a larger surgical access and larger implants. In addition, the majority of the patients have immune suppression as a result of receiving (neo-) adjuvant chemotherapy. Whereas infection rates of 0.5–1.1% are reported with primary endoprostheses (THA) [13], megaendoprostheses in the proximal femur are associated with infections in 6–19.5% of tumor patients [1, 2, 4]. A more detailed distinction between patients with sarcoma and those with metastases by Funovics et al. [2] showed that patients with sarcoma suffered infection in 15.3% of cases, in contrast to only 1.1% of patients with bone metastases. Calabro et al. [14] could demonstrate that proximal femur replacements in oncologic patients have higher infection rates, if the megaprosthesis is used in revision cases (11.5%) compared to primary cases (3.9%).

Table 3 Infection rates and ultimately successful treatment of infection

	Titanium ($n = 35$)	Silver ($n = 64$)	Total
Patients with infection as primary end point (n)	5	6	11
Infection rate in patients with no revision surgery (%)	14.3	9.4	11.1
Patients with infection over whole study period (n)	7	7	14
Secondary infection rate (%)	20.0	10.9	14.1
DAIR	0	2 (28.6%)	2 (14.3%)
One-stage prosthesis change without stem removal	0	2 (28.6%)	2 (14.3%)
Two-stage change of whole prosthesis	4 (57.1%)	1 (14.3%)	5 (35.7%)
Explantation of prosthesis and permanent spacer	1 (14.3%)	0	1 (7.1%)
Amputation/rotationplasty	2 (28.6%)	2 (28.6%)	4 (28.6%)

DAIR debridement, antibiotics, irrigation, and retention

The high rates of infection reported particularly in patients with sarcoma make it clear that it is urgently necessary to reduce the infection rates. In addition to optimizing systemic antibiotic treatment [12], antimicrobial silver coating might be able to reduce the rates, as silver has been used as an antimicrobial agent for centuries [15]. Silver has been used successfully in the topical treatment of burns and chronic wounds and as a coating on medical devices [16]. However, negative results with silver-coated devices have also been reported in the literature [17–19]. There is as yet no conclusive evidence of the potential benefit of silver-coated orthopedic hardware [16].

Silver coating of orthopedic megaprostheses was first reported by our group in an animal trial in 2004 [20] and in humans in 2007 [9]. In the animal trial, a statistically significant reduction in the infection rate was demonstrated after artificial inoculation of *Staphylococcus aureus* into a rabbit model, using silver-coated diaphyseal femur spacers in comparison with uncoated titanium prostheses [20]. Hardes et al. [9] and Glehr et al. [21] showed that toxic levels of silver in the blood do not occur and that silver-coated megaprostheses do not have any toxicological side effects, apart from asymptomatic argyria in a few patients.

Silver-coated megaprostheses have mainly been used in published studies in patients with previous periprosthetic infection or other types of revision surgery, rather than as the primary implants [21, 22]. In a recently published matched-control study, Wafa et al. [22] compared the infection rates with an uncoated tumor prosthesis (Stanmore Implants, Elstree, UK) and a silver-coated implant (Agluna®; Stanmore Implants). In this study as well, however, most of the patients were treated with silver-coated prostheses for one-stage or two-stage revisions after periprosthetic infection. The key message of the study was that the reinfection rate is significantly ($P=0.05$) lower after a two-stage revision with silver-coated implants (15%, three of 20 patients) in comparison with uncoated implants (42.9%, nine of 21 patients).

To the best of our knowledge, the first and still the only study on silver-coated megaprostheses, in the proximal femur and proximal tibia, for prevention of periprosthetic infection, was published by our own group in 2010 [8]. The study compared the infection rate with silver-coated proximal femur replacements ($n=22$) with the data for 33 patients who received titanium prostheses. In the titanium group, proximal femur replacement was associated with an overall infection rate of 18.2%—infection of the primary implant or after revision surgery for the primary implant due to mechanical failure. The rate was reduced to 4.5% in the silver group ($P=0.222$). However, both due to the short follow-up period with a median of only 16 months and also due to the small numbers of patients, the results were only able to provide preliminary evidence of the potential efficacy of silver coating.

Within a period of 6 years, we have been able both to increase the numbers of patients receiving silver-coated proximal femoral replacements for this rare tumor location and also to achieve a much longer follow-up period with a median of 42 months in the surviving patients. Although the overall infection rate in the silver group increased to 10.9% in comparison with the 2010 publication [8], it was nearly half the figure for the titanium group, in which there was a mean infection rate of 20%. Infections were observed in the titanium group in 14.3% of the patients when the occurrence of infection was the primary end point. In the silver group, the rate was only 9.4% (six of 64 patients). Wafa et al. [22] reported on 10 patients who received silver-coated proximal femoral replacements. However, all of the patients received the silver-coated prostheses during one-stage ($n=9$) or two-stage ($n=1$) exchanges. No reinfection occurred in any of the patients.

Revision surgery for a tumor endoprosthesis may also be associated with a substantial risk of periprosthetic infection [2, 5], with bacterial contamination occurring during the revision procedure. In the study by Funovics et al. [2], as many as seven of 12 infections (58.3%) occurred within a mean of 6 months after revision surgery. In the present study, by contrast, previous revision surgery might have been responsible for periprosthetic infection in only three (silver group, $n=1$; titanium group, $n=2$) of 14 patients with periprosthetic infection (21.4%). A significant risk factor was not evident in the study, although it can of course not be excluded in the future.

In the present study, 10 of 11 (91%) periprosthetic infections in both groups occurred within the first two postoperative years if later revision surgery due to mechanical failure was not necessary. The initial hypothesis [8] that due to possible dissociation of silver ions from the prosthesis surface, infection becomes apparent at a later time point with silver-coated prostheses than in the titanium group has not so far been confirmed in this study. Whereas periprosthetic infection led to surgical intervention in the titanium group at a median of 11 months after prosthesis implantation in patients with no previous revision surgery, in the silver group periprosthetic infection occurred earlier, at a median of 4 months postoperatively. We would therefore assume that despite the shorter follow-up period in the silver group, no further substantial change in the infection rate can be expected—as long as additional revision operations due to mechanical complications are not necessary. In general, comparison with the study by Funovics et al. [2], with a mean infection time point of 39 months postoperatively, shows that the infections became clinically apparent at an earlier point in the present study.

Although it was not possible to demonstrate a statistically significant reduction in the rate of periprosthetic infection, the present study confirms the initial results from 2010

showing that silver-coated tumor prostheses can apparently reduce the infection rate. But why is the decline not clearer? In our view, this may be explained by the fact that active free silver ions bind to proteins and become inactivated [23]. This means that the surgeon has to avoid hematoma and poor muscle coverage of the prosthesis, resulting in superficial wound healing problems, which can lead to bacterial colonization. In these areas, the silver coating is unable to develop an adjuvant effect. The silver coating may inhibit bacterial colonization of the prosthetic body, but is inactivated by binding to proteins (e.g., in a hematoma). For example, patient no. 3 in the study developed an increase in CRP values of up to 10 mg/dL in the second postoperative week. A clear hematoma was found during the revision operation that was carried out. Following rinsing of the hematoma, the CRP normalized and the patient has no evidence of reinfection 34 months after the revision operation. A silver coating of the stems might result in a further reduction in the infection rate. However, up to now our group failed to develop such a coating due to the toxic effects of silver ions against osteoblasts in a dog model [24].

In addition to the reduction in the rate of periprosthetic infections as the primary end point of the study, attention also needs to be given to the effects of infection when it develops nevertheless, as a secondary end point. Jeys et al. [25] reported that secondary amputation was necessary after proximal femoral replacement in five of 264 patients (1.9%). Although two patients each in the silver group and the titanium group ultimately required amputation (an amputation rate of 4%), DAIR or one-stage revision was more frequently successful in the silver group than in the titanium group. Although Funovics et al. [2] also reported successful infection eradication in 62.5% of cases even in proximal femoral tumor prostheses without silver coating, Wafa et al. [22] in the study mentioned above were able to avoid reinfection in all patients ($n=9$) with silver-coated tumor prostheses in the proximal femur, implanted for the first time during one-stage exchanges.

Both Jeys et al. [25] and also Funovics et al. [2] report that radiotherapy is a risk factor for infection. In the study by Jeys et al. [26], the risk was even statistically significant. In the present study as well, radiotherapy correlated significantly with the development of periprosthetic infection. It was also found that all patients who underwent amputation in the study had previously received radiotherapy. In the present authors' view, this is explained by the poor soft-tissue conditions resulting from radiotherapy, meaning that silver coating is not able to have a positive effect in these cases.

The most important limitation of the present study is the retrospective character of the titanium group, whereas the data for the silver group were collected prospectively. The patient numbers are of course still small, although in our view they are sufficiently large for such a rare procedure. The advantage of this study lies in the fact that only one implant system was used over many years, always in the same surgical setting and only by a few experienced surgeons.

Conclusions

In conclusion, although silver coating is not always able to prevent periprosthetic infections, silver does appear to represent a reasonable addition to the armamentarium for treating periprosthetic infection without systemic toxic effects. In our view, the results of this study justify the further use of silver-coated proximal femur replacements. Infections that develop nevertheless do not result from ineffectiveness of the silver coating or even resistance to it [14]. Rather, the silver ions can only act directly on the surface of the prosthesis, since in the periprosthetic environment they are directly bound to proteins and thus inactivated. Appropriate systemic antibiotic therapy and other methods of reducing periprosthetic infection are therefore of particular importance. In some cases of periprosthetic infection of silver-coated prostheses, minor revision surgery or even adequate antibiotic therapy alone may be successful instead of an explantation of the prosthesis. In the future, studies with larger numbers of patients and longer follow-up periods are warranted in order to confirm these results. It will be of particular interest to see the extent to which silver-coated proximal femoral replacements will be capable of reducing the rates of infection and reinfection after revision surgery.

Compliance with ethical standards

Ethical approval Ethical approval was obtained from the local ethic committee of the University of Muenster.

Conflict of interest Authors A.S., M.P.H., M.N., W.G. and J.H. declare that they have no conflict of interest. Author G.H. has a honorarium from Implantcast Company for scientific consulting and clinical reviewing.

References

1. Chandrasekar CR, Grimer RJ, Carter SR et al (2009) Modular endoprosthetic replacement for tumours of the proximal femur. J Bone Joint Surg Br 91:108–112
2. Funovics PT, Hipfl C, Hofstaetter JG et al (2011) Management of septic complications following modular endoprosthetic reconstruction of the proximal femur. Int Orthop 35:1437–1444. https://doi.org/10.1007/s00264-010-1054-0
3. Hardes J, Budny T, Hauschild G et al (2009) Proximal femur replacement in revision arthroplasty. Z Orthop Unfall 147:694–699
4. Gosheger G, Gebert C, Ahrens H et al (2006) Endoprosthetic reconstruction in 250 patients with sarcoma. Clin Orthop 450:164–171

5. Jeys LM, Kulkarni A, Grimer RJ et al (2008) Endoprosthetic reconstruction for the treatment of musculoskeletal tumors of the appendicular skeleton and pelvis. J Bone Joint Surg Am 90:1265–1271
6. Hardes J, Gebert C, Schwappach A et al (2006) Characteristics and outcome of infections associated with tumor endoprostheses. Arch Orthop Trauma Surg 126:289–296
7. Kamath AF, Ong KL, Lau E et al (2015) Quantifying the burden of revision total joint arthroplasty for periprosthetic infection. J Arthroplasty 30:1492–1497. https://doi.org/10.1016/j.arth.2015.03.035
8. Hardes J, von Eiff C, Streitbuerger A et al (2010) Reduction of periprosthetic infection with silver-coated megaprostheses in patients with bone sarcoma. J Surg Oncol 101:389–395
9. Hardes J, Ahrens H, Gebert C et al (2007) Lack of toxicological side-effects in silver-coated megaprostheses in humans. Biomaterials 28:2869–2875
10. Gosheger G, Hillmann A, Lindner N et al (2001) Soft tissue reconstruction of megaprostheses using a Trevira tube. Clin Orthop 393:264–271
11. Parvizi J, Gehrke T, International Consensus Group on Periprosthetic Joint Infection (2014) Definition of periprosthetic joint infection. J Arthroplasty 29:1331. https://doi.org/10.1016/j.arth.2014.03.009
12. Racano A, Pazionis T, Farrokhyar F et al (2013) High infection rate outcomes in long-bone tumor surgery with endoprosthetic reconstruction in adults: a systematic review. Clin Orthop 471:2017–2027. https://doi.org/10.1007/s11999-013-2842-9
13. Dale H, Fenstad AM, Hallan G et al (2012) Increasing risk of prosthetic joint infection after total hip arthroplasty. Acta Orthop 83:449–458. https://doi.org/10.3109/17453674.2012.733918
14. Calabro T, van Rooyen R, Piraino I et al (2016) Reconstruction of the proximal femur with a modular resection prosthesis. Eur J Orthop Surg Traumatol 26:415–421. https://doi.org/10.1007/s00590-016-1764-0
15. Randall CP, Gupta A, Jackson N et al (2015) Silver resistance in Gram-negative bacteria: a dissection of endogenous and exogenous mechanisms. J Antimicrob Chemother 70:1037–1046. https://doi.org/10.1093/jac/dku523
16. Politano AD, Campbell KT, Rosenberger LH et al (2013) Use of silver in the prevention and treatment of infections: silver review. Surg Infect 14:8–20. https://doi.org/10.1089/sur.2011.097
17. Dahlberg PJ, Agger WA, Singer JR et al (1995) Subclavian hemodialysis catheter infections: a prospective, randomized trial of an attachable silver-impregnated cuff for prevention of catheter-related infections. Infect Control Hosp Epidemiol 16:506–511
18. Riley DK, Classen DC, Stevens LE et al (1995) A large randomized clinical trial of a silver-impregnated urinary catheter: lack of efficacy and staphylococcal superinfection. Am J Med 98:349–356
19. Tokmaji G, Vermeulen H, Müller MCA et al (2015) Silver-coated endotracheal tubes for prevention of ventilator-associated pneumonia in critically ill patients. Cochrane Database Syst Rev 8:CD009201. https://doi.org/10.1002/14651858.cd009201
20. Gosheger G, Hardes J, Ahrens H et al (2004) Silver-coated megaendoprostheses in a rabbit model—an analysis of the infection rate and toxicological side effects. Biomaterials 25:5547–5556
21. Glehr M, Leithner A, Friesenbichler J et al (2013) Argyria following the use of silver-coated megaprostheses: no association between the development of local argyria and elevated silver levels. Bone Joint J 95-B:988–992. https://doi.org/10.1302/0301-620X.95B7.31124
22. Wafa H, Grimer RJ, Reddy K et al (2015) Retrospective evaluation of the incidence of early periprosthetic infection with silver-treated endoprostheses in high-risk patients: case-control study. Bone Joint J 97-B:252–257. https://doi.org/10.1302/0301-620X.97B2.34554
23. Schierholz JM, Lucas LJ, Rump A et al (1998) Efficacy of silver-coated medical devices. J Hosp Infect 40:257–262
24. Hauschild G, Hardes J, Gosheger G et al (2015) Evaluation of osseous integration of PVD-silver-coated hip prostheses in a canine model. Biomed Res Int 2015:292406. https://doi.org/10.1155/2015/292406
25. Jeys LM, Grimer RJ, Carter SR et al (2003) Risk of amputation following limb salvage surgery with endoprosthetic replacement, in a consecutive series of 1261 patients. Int Orthop 27:160–163
26. Jeys LM, Grimer RJ, Carter SR et al (2005) Periprosthetic infection in patients treated for an orthopaedic oncological condition. J Bone Joint Surg Am 87:842–849