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*Original Article*

# Titanium oxide nanotubes embedded with silver dioxide nanoparticles for staphylococcus aureus infections after prosthetic joint replacement in animal models

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**Abstract:** Objective: The aim of this study was to determine the effects of novel antibacterial coatings made from composite material titanium oxide nanotubes embedded with silver dioxide nanoparticles ($Ag_2O$-$TiO_2$-NTs) on staphylococcus aureus infections after artificial joint replacement in animal models. Methods: Eighty New Zealand rabbits were selected to construct animal models of prosthetic infections after prosthetic joint replacement. The animal models were randomly divided into an experimental group and control group. Animals in the experimental group were implanted with artificial joint prostheses with $Ag_2O$-$TiO_2$-NTs composite coatings, whereas those in the control group were implanted with common artificial joint prostheses. Fifteen days after prosthetic joint replacement, staphylococcus aureus supernatant (1 mL) was injected into the affected articular cavity of the knee joint of each animal in both groups. Anti-infection effects of $Ag_2O$-$TiO_2$-NTs composite coatings were evaluated. These included body temperature, serum C-reactive protein (CRP) concentration, erythrocyte sedimentation rate (ESR), procalcitonin (PCT), and infection rates of the prostheses. Any underlying causes were also analyzed. Results: Measured values of body temperature, CRP, ESR, and PCT of animals in the experimental group were remarkably lower than in the control group, at different time points after bacterial inoculation (all $P<0.05$). Infection rates of prostheses of animals in the experimental group were also lower than the control group ($P<0.001$). Conclusion: Artificial joint prostheses with novel antibacterial coatings, made from $Ag_2O$-$TiO_2$-NTs composites, can effectively relieve the inflammatory reaction in animal models and have better performance regarding anti-staphylococcus aureus infections.

**Keywords:** Titanium oxide nanotubes embedded with silver dioxide nanoparticles, animal model, prosthetic joint replacement, staphylococcus aureus, novel antibacterial coating

## Introduction

Prosthetic joint replacement is a major technique used for improving and restoring knee joint function in patients with end-stage arthrosis [1]. With increased aging of the population, incidence of end-stage arthrosis is on the rise. As the physiological function of elderly patients declines, most develop morbidities (including obesity, diabetes, and cardiovascular and cerebrovascular diseases). As a result, they are at higher risk for onset of periprosthetic infections following prosthetic joint replacement [2]. Although a variety of effective prophylactic measures have been taken, clinically, incidence of post-operative infections remains at 1% and infection rates after revision surgery have reached up to 4%, with 70% of infections caused by staphylococcus aureus [3]. Infections after prosthetic joint replacement bring bigger challenges to relevant clinicians with heavier economic burden and physical and psychological torture for patients [4].

Periprosthetic infections are closely related to adhesion of bacteria to the surface of material and biofilm formation. Once a patient is infected, bacterial biofilms on the surface of the prosthesis will impede the infiltration of antibiotics. Bacteria around the lesions are difficult to kill, even with highly-sensitive drugs. As a result, patients develop recurrent infections after surgery and inflammation is poorly controlled, leading to failure of the surgery [5]. Clinically,

the most common infection prophylaxis is to apply antibiotic coatings on joint prostheses or to use antibiotic bone cement [6]. Although these measures can effectively prevent infections, long-term exposure of antibiotics to bacteria enhances risks for generation of drug-resistant strains. Moreover, antibiotics and bone cement on the surface of prosthesis have a short duration of effect, resulting in an unsatisfactory antimicrobial effect. Some patients may even develop toxic effects and hypersensitivity [7].

With advances in medical technology, artificial joint prostheses, made of nanometer materials, have gradually been applied in the fields of medicine and biology. Nanomaterials have special biological effects and physical and chemical properties. Nano-silver oxide has a long-acting antibacterial mechanism and shares a broad-spectrum antibacterial activity with silver nanomaterials. Hence, it can kill a variety of bacteria [8, 9]. Titanium dioxide nanomaterials have a clean and neat three-dimensional structure. With high mechanical strength and excellent biological compatibility, they can be used as drug carriers [10]. To date, few reports have investigated the clinical application of artificial joint prosthesis with novel antibacterial coatings, prepared by composite material titanium oxide nanotubes embedded with silver dioxide nanoparticles ($Ag_2O$-$TiO_2$-NTs). The aim of this study was to construct animal models with staphylococcus aureus infections, following total knee arthroplasty, to explore the antibacterial effects of artificial joint prosthesis with $Ag_2O$-$TiO_2$-NTs coatings, providing more evidence for its clinical practice.

## Materials and methods

### *Experimental animals*

A total of 120 healthy adult New Zealand rabbits (body weight, 2.3-3.8 kg), male and female, were purchased from Shanghai Fengxian Brilliant Farm, China (product certification: SYXK (Shanghai) 2013-0047). They were raised in a clean environment at a room temperature of 21-25°C, and humidity of 52-57%, for 2 weeks before the experiment. No food or drink restrictions were applied to the rabbits. This experimental study strictly complied with Animal Welfare and Ethics principles.

### *Main materials, instruments, and reagents*

$Ag_2O$-$TiO_2$-NTs was prepared by the College of Mechanical Engineering, Zhejiang University, China. Artificial joint prostheses (spikes) were prepared by Smith & Nephew, Suzhou, China. Artificial joint prostheses with $Ag_2O$-$TiO_2$-NTs coatings were also prepared using pulsed electrochemical deposition by the College of Mechanical Engineering, Zhejiang University. Staphylococcus aureus (ATCC25923) strains were purchased from Hoepbio in Qingdao Hightech Industrial Park, China. AU5800 automatic biochemical analyzers were purchased from Beckman Coulter, China and C-reactive protein (CRP) and procalcitonin (PCT) kits were purchased from Shanghai AIYUE Biotechnology, Shanghai, China. DRAGONMED erythrocyte sedimentation rate (ESR) analyzers were purchased from Shanghai Queensland Biotechnology, Shanghai, China and SteriIGARD III Advance Biosafety cabinet was purchased from Beckman Coulter, USA.

### *Staphylococcus aureus cultivation and suspension preparation*

Staphylococcus aureus (ATCC25923) strains were seeded in preservation medium and stored in a low temperature refrigerator at -20°C. They were removed and rewarmed 1 day before use. The colonies of bacteria were picked up with an inoculating loop from the biosafety cabinet. LB nutrient agar medium was treated on the three-sector streak plate. The plate was incubated in an incubator at 37°C for 24 hours. White, smooth, and opaque isolated colonies were picked up with an inoculating loop from the biosafety cabinet, incubated with TBS, and shaken overnight at 37°C. Twenty-four hours later, purebred bacteria were rinsed with sterile normal saline 3 times, diluted into $1*10^6$ CFU/mL bacterial suspensions, and stored for use.

### *Randomization and animal modeling*

Eighty New Zealand rabbits were included for the construction of animal models of prosthesis infections following artificial joint replacement. They were randomly assigned to an experimental group or control group. Specific procedures of modeling were as follows: Morphine hydrochloride injection was intravenously injected at 2 mg/kg into rabbit ear edges

**Table 1.** General data of animal models

| Variable | Experiment group (n=38) | Control group (n=38) | $t/X^2$ | P |
|---|---|---|---|---|
| Sex | | | | |
| Male (%) | 19 (50.00) | 24 (63.16) | 1.339 | 0.355 |
| Female (%) | 19 (50.00) | 14 (36.84) | | |
| Age | | | 0.517 | 0.632 |
| ≤25 weeks | 23 (60.53) | 26 (68.42) | | |
| >25 weeks | 15 (39.47) | 12(31.58) | | |
| Body weight | | | 0.844 | 0.491 |
| ≤3.1 kg | 22 (57.89) | 18 (47.37) | | |
| >3.1 kg | 16 (42.11) | 20 (52.63) | | |
| Room temperature (°C) | 25.09 ± 0.83 | 24.86 ± 0.71 | 1.298 | 0.198 |
| Room humidity (%) | 55.63 ± 2.03 | 54.79 ± 2.56 | 1.585 | 0.117 |

for adequate anesthesia. The right lower limbs of rabbits were cut off, followed by routine skin preparation, disinfection with iodine tincture and alcohol, as well as sterile draping. Intraoperative procedures strictly followed the principles for aseptic operations [11]. A 3-cm midline vertical incision was made at the right knee joint. The patella and bent-knee were everted to expose the knee joint. Cruciate ligaments were resected along the medial patellar, followed by resection of the proximal tibia, metaphyseal and articular surface, as well as distal femoral condyle. Intercondylar fossa of the femur was exposed. A 2.5 mm drill was used to expand the femoral medullary cavity along the long axis of femur in the center of the intercondylar fossa of femur. Artificial joint prostheses, coated by $Ag_2O$-$TiO_2$-NTs composites, were implanted into the animals in the experiment group, while common artificial joint prostheses were implanted into those in the control group. After implantation, the wounds were rinsed with normal saline. The joint capsule was closed by layered suturing and the wounds were bandaged by aseptic dressings, followed by fixation of surgical limbs. After the operation, gentamicin at 40,000 U/mg was injected into the affected articular cavity of the knee joint for prophylaxis infections 3 times per day, for 3 consecutive days. Two weeks after the operation, synovial fluid was extracted and bacterial culture was conducted for confirmation of bacterial infection. Staphylococcus aureus suspension (1 mL) was injected into the affected articular cavity of the knee joint of each animal in both groups, 15 days postoperatively.

*Body temperature, CRP, ESR and PCT measurement*

Rectal temperatures of the animals were measured 1 day before and 1 day, 3 days, 5 days, 7 days, 9 days, 11 days and 14 days after bacterial injection, respectively. Venous blood (7 ml) was drawn from the ear edges of each rabbit in both the experiment group and control group 1 day before and 1 day, 3 days, 7 days and 14 days after bacterial injection. Of the drawn venous blood, 4 mL was applied for detection of serum CRP and PCT (Immunological transmission turbidimetry) and the remaining 3 mL for detection of ESR (Capillary optics). Index tests and instrument operations were performed in strict accordance with manufacturer instructions.

*Periprosthetic tissue bacterial culturing*

Two weeks after injection of bacterial suspensions, the animals were sacrificed by aeroembolism. Joint capsule and periprosthetic tissues were extracted for bacterial culturing in a strict aseptic setting. Five samples were taken from each animal. Infection was indicated when the cultures of more than two samples were positive for bacteria. To prevent false negativity, samples were extracted and placed in a nutrient broth for enrichment culturing, namely, the samples were incubated in a bacterial incubator at 37°C for 24 hours. Subsequently, colonies of bacteria were inoculated in blood agar culture-media and incubated in a bacterial incubator at 37°C. At 24-48 hours, the colonies were taken out for observation.

*Statistical analysis*

Statistical data analyses were carried out using SPSS software, version 17.0 (Tianjin Ksoft Tech, China). Measurement data are presented as mean ± sd and were compared by two independent samples t-tests. Data at multiple time points were compared using repeated measures ANOVA. Count data are expressed as percentages and were compared by Chi-square tests. P levels less than 0.05 were deemed to be statistically significant.

**Table 2.** Changes in body temperature of animal models (mean ± sd, °C)

| Time point | Experiment group (n=38) | Control group (n=38) | t | P |
|---|---|---|---|---|
| 1 d before bacterial inoculation | 38.4 ± 0.2 | 38.3 ± 0.3 | 1.710 | 0.091 |
| 1 d after bacterial inoculation* | 40.3 ± 0.4 | 41.4 ± 0.7 | 8.411 | <0.001 |
| 3 d after bacterial inoculation* | 40.6 ± 0.4 | 41.3 ± 0.8 | 4.824 | <0.001 |
| 5 d after bacterial inoculation* | 40.7 ± 0.6 | 41.1 ± 0.6 | 2.906 | 0.004 |
| 7 d after bacterial inoculation* | 40.6 ± 0.5 | 41.3 ± 0.7 | 5.016 | <0.001 |
| 9 d after bacterial inoculation* | 40.3 ± 0.3 | 40.9 ± 0.8 | 4.329 | <0.001 |
| 11 d after bacterial inoculation* | 39.4 ± 0.3 | 41.2 ± 0.6 | 16.540 | <0.001 |
| 14 d after bacterial inoculation* | 38.7 ± 0.4 | 40.8 ± 0.7 | 16.060 | <0.001 |
| F | 194.800 | 89.890 | - | - |
| P | <0.001 | <0.001 | - | - |

Note: *P<0.05, compared with 1 d before bacterial inoculation.

**Table 3.** Serum CRP changes in animal models before and after bacterial inoculation (mean ± sd, mg/L)

| Time point | Experiment group (n=38) | Control group (n=38) | t | P |
|---|---|---|---|---|
| 1 d before bacterial inoculation | 0.81 ± 0.15 | 0.84 ± 0.21 | 0.716 | 0.475 |
| 1 d after bacterial inoculation* | 1.54 ± 0.23 | 1.95 ± 0.26 | 7.281 | <0.001 |
| 3 d after bacterial inoculation* | 2.37 ± 0.28 | 3.29 ± 0.46 | 10.530 | <0.001 |
| 7 d after bacterial inoculation* | 2.16 ± 0.21 | 3.08 ± 0.37 | 13.330 | <0.001 |
| 14 d after bacterial inoculation* | 1.93 ± 0.23 | 3.01 ± 0.29 | 17.990 | <0.001 |
| F | 286.300 | 371.500 | - | - |
| P | <0.001 | <0.001 | - | - |

Note: *P<0.05, compared with 1 d before bacterial inoculation.

## Results

*General data*

Sex, age, body weight, indoor feeding temperature, and humidity of New Zealand rabbits had no effect on this experiment (all P>0.05; **Table 1**). After injection of bacterial suspensions into the articular cavity of the animals, 38 infection models were successfully constructed in each group. Neither swelling nor any abscess was observed in the knee joints of animals in the experimental group during the observation period. Conversely, focal knee joint swelling and ulceration-post purulent discharge were noted in 20 rabbits in the control group.

*Body temperature changes in animal models before and after bacterial inoculation*

Repeated measures ANOVA indicated that measured values for body temperature of animals varied significantly at different time points and corresponding values of animals in the control group were remarkably higher than the experimental group (all *P*<0.05). Values at 1 day, 3 days, 5 days, 7 days, 9 days, 11 days and 14 days after bacterial inoculation rose compared to those before bacterial inoculation in animals of both groups (all P<0.05), with strikingly lower body temperature among animals in the experiment group (all P<0.05; **Table 2**).

*Serum CRP changes in animal models before and after bacterial inoculation*

Repeated measures ANOVA revealed that serum CRP values of animals at different time intervals differed considerably. Corresponding values were remarkably higher in the control group than the experimental group (all P<0.05). Serum CRP values of animals at 1 day, 3 days, 7 days and 14 days after bacterial inoculation were elevated compared with those before bacterial inoculation in both groups (all P<0.05), with substantive lower serum CRP values in the experimental group (all P<0.05; **Table 3**).

*Serum ESR changes in animal models before and after bacterial inoculation*

Repeated measures ANOVA also showed that serum ESR measurements of animals were statistically different at diverse time points and measurements were substantially higher in the control group than the experimental group (all P<0.05). Serum ESR measurements of animals at 1 day, 3 days, 7 days and 14 days after bacterial inoculation were increased compared with those before bacterial inoculation in both groups (all P<0.05), with remarkably lower mea-

**Table 4.** Serum ESR changes in animal models before and after bacterial inoculation (mean ± sd, mm/h)

| Time point | Experiment group (n=38) | Control group (n=38) | t | P |
|---|---|---|---|---|
| 1 d before bacterial inoculation | 1.22 ± 0.33 | 1.31 ± 0.35 | 1.153 | 0.252 |
| 1 d after bacterial inoculation* | 4.16 ± 0.93 | 5.18 ± 1.16 | 4.229 | <0.001 |
| 3 d after bacterial inoculation* | 4.51 ± 0.85 | 11.46 ± 1.63 | 23.310 | <0.001 |
| 7 d after bacterial inoculation* | 5.11 ± 1.24 | 14.73 ± 2.09 | 24.400 | <0.001 |
| 14 d after bacterial inoculation* | 4.03 ± 0.35 | 10.82±1.87 | 9.421 | <0.001 |
| F | 128.200 | 457.500 | - | - |
| P | <0.001 | <0.001 | - | - |

Note: *P<0.05, compared with 1 d before bacterial inoculation.

surements in the experimental group (all P<0.05; **Table 4**).

*Serum PCT changes in animal models before and after bacterial inoculation*

Repeated measures ANOVA also demonstrated that there was a statistical disparity in serum ESR values of animals at different time points and that serum PCT values of animals in the control group were significantly higher than the experimental group (all P<0.05). In both groups, serum PCT levels at 1 day, 3 days, 7 days and 14 days after bacterial inoculation were elevated compared to those before bacterial inoculation (all P<0.05) and values in the experimental group were remarkably lower (all P<0.05; **Table 5**).

*Bacteriological examinations of prostheses in animal models*

Infection occurred in 4 prostheses after bacterial inoculation in the experiment group, with an infection rate of 10.53%. Infections were reported in 38 prostheses in the control group, with an infection rate of 100%. A remarkably lower infection rate was noted in the experimental group ($X^2$=61.524, P<0.001; **Table 6**).

## Discussion

Prosthetic joint replacement is an indispensable surgical technique for management of severe knee joint disease. The clinical response is favorable with a 10-year success rate of over 80%. Nevertheless, due to surgical trauma, foreign matter implantation, the patient's own vulnerability, and other factors, loose prosthesis and periprosthetic infections have often occurred after surgery [12, 13]. Incidence of infection has recently declined, to some extent, due to improvements in the operation for artificial joint replacement, material selection, and higher patient awareness of infection prevention. However, with the population aging, the number of patients with severe osteoarthrosis is increasing and bacterial infections caused by arthritic surgery are also on the rise [14]. Staphylococcus aureus is a major factor inducing severe periprosthetic infections. Biofilms of staphylococcus aureus are decisive in the development of severe infections in prosthetic joints. Biofilms can protect the bacteria from being attacked by the immunity system of the organisms and antibiotics, resulting in recurrent infections [15]. Therefore, finding a method to prevent infections after artificial joint replacement is an important subject in clinical research.

Patients with infections, following artificial joint replacement, are predisposed to fevers, inflamed skin, and inflammation, typical symptoms of joint infection. Hence, such patients are easy to diagnose. However, patients with low-toxicity and subacute infections have unclear clinical signs and symptoms and low sensitivities of respective clinical indexes (CRP, ESR, and PCT) [16, 17]. CRP is an acute protein synthesized by hepatocytes and a crucial marker for evaluating the inflammatory response of the body. The content of CRP is low in healthy humans or animals. CRP levels rise gradually when the body is present with a postoperative stress reaction, tissue injury, or infection, and they rapidly decrease to normal levels when triggering factors are ablated [18]. ESR denotes the rate at which red blood cells sediment in a period of an hour. When ESR increases, various inflammatory diseases are present, such as connective tissue inflammation and tuberculosis. ESR can also rise in the short term when tissues in the body are infected, injured, and degenerated or necrotic [19]. When the body is infected by bacteria, in

**Table 5.** Serum PCT changes in animal models before and after bacterial inoculation (mean ± sd, ng/mL)

| Time point | Experiment group (n=38) | Control group (n=38) | t | P |
|---|---|---|---|---|
| 1 d before bacterial inoculation | 141.28 ± 39.67 | 159.52 ± 43.09 | 1.920 | 0.058 |
| 1 d after bacterial inoculation* | 328.54 ± 107.28 | 624.59 ± 131.68 | 10.740 | <0.001 |
| 3 d after bacterial inoculation* | 276.46 ± 99.67 | 567.16 ± 112.59 | 11.920 | <0.001 |
| 7 d after bacterial inoculation* | 169.26 ± 87.46 | 418.62 ± 126.38 | 10.000 | <0.001 |
| 14 d after bacterial inoculation* | 146.65 ± 53.64 | 316.75 ± 107.54 | 8.725 | <0.001 |
| F | 40.830 | 113.500 | - | - |
| P | <0.001 | <0.001 | - | - |

Note: *P<0.05, compared with 1 d before bacterial inoculation.

**Table 6.** Infection rates in bacteriological examination in the experimental group and control group

| Group | Infected | Uninfected | $X^2$ | P |
|---|---|---|---|---|
| Experiment group (n=38) | 4 (10.53) | 34 (87.4) | 61.524 | <0.001 |
| Control group (n=38) | 38 (100.00) | 0 | | |

response to stimuli from cytokines (LPS, IL-6 and TNF), cells in the tissue rapidly secrete PCT. CT pre-peptide substances are present in the serum and PCT precursors gradually enter the endoplasmic reticulum of the cell endomembrane system. PCT is generated during glycosylation under the control of enzymes. Therefore, PCT has a high specificity for judging bacterial infections in the body, thus, it can be utilized to adjudicate the severity of infections [20]. In the present study, measured values for body temperature, CRP, ESR, and PCT of animals differed insignificantly before bacterial inoculation between the experiment group and control group. Values rose remarkably, however, after inoculation. This indicated that, prior to bacterial inoculation, surgery had no effect on the four above indexes but the sensitivity to staphylococcus aureus was high. Measured values for body temperature, CRP, ESR, and PCT at different time points after bacterial inoculation in the experimental group were strikingly lower than those in the control group, as was infection rate. This suggests that $Ag_2O$-$TiO_2$-NTs composite coatings on artificial joint prostheses effectively relieves inflammation in animals and has excellent antibacterial properties. Cell plasma membranes of bacteria are negatively charged and nano-silver oxide has a potent adsorptive capacity, so they can act in synergy [21]. The integration of silver ions and plasma membranes contribute to changes in the structures of bacterial nuclear membranes and cell walls, resulting in changes in biofilm permeability of cells and, ultimately, in bacterial apoptosis [22]. Silver ions can bind to protein via the cell membrane to form S-Ag compounds and inactivate enzymes in the bacteria, leading to further development and death of bacteria after protein coagulation and denaturation. With the disintegration of bacteria, anions can again combine with other bacteria to exert a long-term bactericidal effect [23]. This is in alignment with findings reported by Wei et al., that the preparation of artificial joint prosthesis coated by composites hydroxyapatite-nano-silver has favorable antibacterial activity. Wei et al. analyzed the histocompatibility of the materials, but the present study does not provide an in-depth investigation on the histocompatibility of $Ag_2O$-$TiO_2$-NTs [24]. This warrants further verification.

In the present study, Zealand rabbits were enrolled as animal models. Modeling was simple and reliable, with a high surgery success rate. Total knee arthroplasty in New Zealand rabbits is similar to the same procedure in humans. Infection models, prepared by injecting staphylococcus aureus, guaranteed the reliability of the experiment as they could reflect environmental changes in the body. In the present study, there were no *in vitro* antibacterial activity experiments of $Ag_2O$-$TiO_2$-NTs, and a paucity of long-term observation on the toxicity of materials. Therefore, the study was not free of limitations. It is hoped that, in future experiments, more profound exploration can be done to support the findings of this present study.

In summary, artificial joint prostheses, with novel antibacterial coatings made from $Ag_2O$-

$TiO_2$-NTs composites, are associated with effective alleviation of the inflammatory response in animal models and have better performance regarding anti-staphylococcus aureus infections.

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## Disclosure of conflict of interest

None.

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## References

[1] Sanders TL, Maradit Kremers H, Schleck CD, Larson DR and Berry DJ. Subsequent total joint arthroplasty after primary total knee or hip arthroplasty: a 40-year population-based study. J Bone Joint Surg Am 2017; 99: 396-401.

[2] Otto-Lambertz C, Yagdiran A, Wallscheid F, Eysel P and Jung N. Periprosthetic infection in joint replacement. Dtsch Arztebl Int 2017; 114: 347-353.

[3] Grosso MJ, Berg A, LaRussa S, Murtaugh T, Trofa DP and Geller JA. Silver-impregnated occlusive dressing reduces rates of acute periprosthetic joint infection after total joint arthroplasty. J Arthroplasty 2017; 32: 929-932.

[4] Iorio R and Osmani FA. Strategies to prevent periprosthetic joint infection after total knee arthroplasty and lessen the risk of readmission for the patient. J Am Acad Orthop Surg 2017; 25 Suppl 1: S13-s16.

[5] Kunutsor SK, Beswick AD, Peters TJ, Gooberman-Hill R, Whitehouse MR, Blom AW and Moore AJ. Health care needs and support for patients undergoing treatment for prosthetic joint infection following hip or knee arthroplasty: a systematic review. PLoS One 2017; 12: e0169068.

[6] Amerstorfer F, Fischerauer S, Sadoghi P, Schwantzer G, Kuehn KD, Leithner A and Glehr M. Superficial vancomycin coating of bone cement in orthopedic revision surgery: a safe technique to enhance local antibiotic concentrations. J Arthroplasty 2017; 32: 1618-1624.

[7] Tschon M, Sartori M, Contartese D, Giavaresi G, Aldini NN and Fini M. Use of antibiotic loaded biomaterials for the management of bone prosthesis infections: rationale and limits. Curr Med Chem 2017; [Epub ahead of print].

[8] Besinis A, Hadi SD, Le HR, Tredwin C and Handy RD. Antibacterial activity and biofilm inhibition by surface modified titanium alloy medical implants following application of silver, titanium dioxide and hydroxyapatite nanocoatings. Nanotoxicology 2017; 11: 327-338.

[9] Mao S, Chang J, Pu H, Lu G, He Q, Zhang H and Chen J. Two-dimensional nanomaterial-based field-effect transistors for chemical and biological sensing. Chem Soc Rev 2017; 46: 6872-6904.

[10] Tsang MP, Hristozov D, Zabeo A, Koivisto AJ, Jensen ACØ, Jensen KA, Pang C, Marcomini A and Sonnemann G. Probabilistic risk assessment of emerging materials: case study of titanium dioxide nanoparticles. Nanotoxicology 2017; 11: 558-568.

[11] Wu D, Zhou S, Hu S and Liu B. Inflammatory responses and histopathological changes in a mouse model of staphylococcus aureus-induced bloodstream infections. J Infect Dev Ctries 2017; 11: 294-305.

[12] Kunutsor SK, Whitehouse MR, Blom AW and Beswick AD. Systematic review of risk prediction scores for surgical site infection or periprosthetic joint infection following joint arthroplasty. Epidemiol Infect 2017; 145: 1738-1749.

[13] Duchman KR, Pugely AJ, Martin CT, Gao Y, Bedard NA and Callaghan JJ. Operative time affects short-term complications in total joint arthroplasty. J Arthroplasty 2017; 32: 1285-1291.

[14] Dennison T, Alentorn-Geli E, Assenmacher AT, Sperling JW, Sánchez-Sotelo J and Cofield RH. Management of acute or late hematogenous infection after shoulder arthroplasty with irrigation, débridement, and component retention. J Shoulder Elbow Surg 2017; 26: 73-78.

[15] Chirca I and Marculescu C. Prevention of infection in orthopedic prosthetic surgery. Infect Dis Clin North Am 2017; 31: 253-263.

[16] Alazzawi S, Khan O and Haddad FS. Periprosthetic infection in the hip joint. 2017.

[17] Falzarano G, Piscopo A, Grubor P, Rollo G, Medici A, Pipola V, Bisaccia M, Caraffa A, Barron EM, Nobile F, Cioffi R and Meccariello L. Use of common inflammatory markers in the long-term screening of total hip arthroprosthesis infections: our experience. Adv Orthop 2017; 2017: 9679470.

[18] Sousa R, Serrano P, Gomes Dias J, Oliveira JC and Oliveira A. Improving the accuracy of synovial fluid analysis in the diagnosis of prosthetic

joint infection with simple and inexpensive biomarkers: C-reactive protein and adenosine deaminase. Bone Joint J 2017; 99-B: 351-357.
[19] Jitmuang A, Yuenyongviwat V, Charoencholvanich K and Chayakulkeeree M. Rapidly-growing mycobacterial infection: a recognized cause of early-onset prosthetic joint infection. BMC Infect Dis 2017; 17: 802.
[20] Memar MY, Varshochi M, Shokouhi B, Asgharzadeh M and Kafil HS. Procalcitonin: the marker of pediatric bacterial infection. Biomed Pharmacother 2017; 96: 936-943.
[21] Dizaj SM, Lotfipour F, Barzegar-Jalali M, Zarrintan MH and Adibkia K. Antimicrobial activity of the metals and metal oxide nanoparticles. Mater Sci Eng C Mater Biol Appl 2014; 44: 278-284.
[22] Kalan LR, Pepin DM, Ul-Haq I, Miller SB, Hay ME and Precht RJ. Targeting biofilms of multidrug-resistant bacteria with silver oxynitrate. Int J Antimicrob Agents 2017; 49: 719-726.
[23] Falconer JL and Grainger DW. In vivo comparisons of silver nanoparticle and silver ion transport after intranasal delivery in mice. J Control Release 2018; 269: 1-9.
[24] Wei B, Shi Z, Xiao J, Xu Y and Lv L. In vivo and in vitro antibacterial effect of nano-structured titanium coating incorporated with silver oxide nanoparticles. Journal of Biomaterials & Tissue Engineering 2017; 7: 418-425.