Accepted Manuscript

Antimicrobial Coated Implants in Trauma and Orthopaedics

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A Clinical Review and Risk-Benefit Analysis
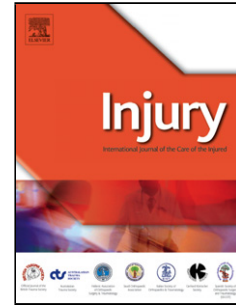
Volker Alt*

*Volker Alt, MD, PhD
Professor and Orthopaedic Trauma Surgeon
Department of Trauma, Hand and Reconstructive Surgery Giessen University Hospital Giessen-Marburg, Campus Giessen, Rudolf-Buchheim-Str. 7, 35385 Giessen, Germany

Correspondence should be sent to:

Prof. Dr. Dr. Volker Alt
Department of Trauma Surgery Giessen University Hospital Giessen-Marburg, Site Giessen
Rudolf-Buchheim-Str. 7
35385 Giessen, Germany
email: volker.alt@chiru.med.uni-giessen.de
tel: +49 641 985 44 601
fax: +49 641 985 44 609

Abstract

Implant-associated infections remain a major issue in orthopaedics and antimicrobial functionalization of the implant surface by antibiotics or other anti-infective agents have gained interest. The goal of this article is to identify antimicrobial coatings, for which clinical data are available and to review their clinical need, safety profile, and their efficacy to reduce infection rates.

PubMed database of the National Library of Medicine was searched for clinical studies on antimicrobial coated implants for internal fracture fixation devices and endoprostheses for bone surgery, for which study design, level of evidence, biocompatibility, development of resistance, and effectiveness to reduce infection rates were analyzed.

Four different coating technologies were identified: gentamicin poly(D, L-lactide) coating for tibia nails, one high (MUTARS®) and one low amount silver (Agluna) technology for tumor endoprostheses, and one povidone-iodine coating for titanium implants. There was a total of 9 published studies with 435 patients, of which 7 studies were case series (level IV evidence) and 2 studies were case series (level III evidence).

All technologies were reported with good systemic and local biocompatibility, except the development of local argyria with blue to bluish grey skin discoloration after the use of high amount silver MUTARS® megaendoprostheses. For the local use of gentamicin, there is contradictory data on the risk of emergence of gentamicin-resistance strains, a risk that does not seem to exist for silver and iodine based technologies. Regarding reduction of infection rates, one case control series showed a significant reduction of infection rates by Agluna low amount silver coated tumor endoprostheses.

Based on socio-economic data, there is a strong need for improvement of infection prevention and treatment strategies, including implant coatings, in fracture care, primary and revision arthroplasty, and bone tumor surgery. The reviewed gentamicin, low amount silver Agluna, and povidone-iodine technologies have shown a good risk benefit ratio for patients. Further data from randomized control trials are desirable, although this will remain challenging in the context of infection prevention due to the required large sample size of such studies.

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Key words: coating, implant, infection, gentamicin, silver

1. Introduction

Orthopaedic implants, such as fracture fixation devices and total joint prostheses have proven their positive effect on patient quality of life. For both indications, metal implants based on their biomechanical properties are primarily used. Despite their known functional benefits, all implants exhibit a certain risk of deep infection. The link between an elevated infection risk in association with an implant was already suggested in 1957 by Elek et al. showing that the threshold for the establishment of an infection after intradermal injection of *S. aureus* was reduced from 1,000,000 bacteria when no foreign body was used to only 100 organisms when a silk suture was placed into the skin [1]. Further papers from Gristina [2] and Costerton et al. [3] identified the so-called "race for the surface" and biofilm formation of bacteria as key elements for the pathophysiology of implant-associated bone infections. The general idea of protection of the implant surface in order to positively influence the "race for the surface" and to prevent biofilm formation, is mainly based on the principle of local delivery of antimicrobial substances from Buchholz who discovered the release of antibiotics from PMMA bone cements into the local surrounding of the implant which paved to way to the prophylactic use of antibiotic-loaded bone cement in total joint arthroplasty [4]. For fracture fixation devices and uncemented total arthroplasty, the principle of local antimicrobial strategies to prevent colonization and biofilm formation on the implant surface is more difficult and the first clinically available technologies only emerged in the last years.

The purpose of this article is to perform a risk benefit analysis for antimicrobial coated implants for patients based on clinical data regarding questions on the clinical need, safety, including allergies and resistance risk, as well as their efficacy to reduce infection rates.

2. Materials and methods

2.1. Literature search

The author searched PubMed (1999 – present) databases of the National Library of Medicine with the following key words: "implant coating bone" (search 1) and "coated implant infection" (search 2) "gentamicin coating" (search 3) "silver coating" (search 4) on May 31, 2016. Only clinical studies on coated implants for internal fracture fixation devices and endoprostheses for bone surgery were included into the further review of data.

2.2. Analysis of clinical data

For all included clinical studies, indication, study design and level of evidence were reviewed [5]. Furthermore, number of patients, and particularly clinical data to identify potential risk and benefits regarding general biocompatibility, allergies, development of resistance and effectiveness to reduce infection rates were analyzed.

3. Results

3.1. Study selection and identified coating technologies

Literature research revealed 1542, 444, 99, and 1263 hits for search 1, 2, 3 and 4, respectively. Most articles on antimicrobial coatings were *in vitro* or *in vivo* animal experiments and most clinical papers reported on non-antimicrobial coatings, such as hydroxyapatite or other porous coatings. The search revealed nine clinical papers with four different antimicrobial coating technologies for which clinical data were reported (Table 1) [6-14].

The first one is a gentamicin poly(D, L-lactide) with 'dipcoating process' for tibia nails [6,7]. The second and third technology are based on different silver strategies with galvanic deposition of a relatively high amount elementary silver on the implant surface of tumor endoprostheses [8-11] or anodization of the titanium alloy followed by absorption of a relatively low amount of silver from an aqueous solution [12] for custom-made tumor endoprostheses. The fourth technology uses a povidone-iodine electrolyte-based process for iodine coating of megaendoprostheses and limb salvage systems [13,14].

3.2. Clinical data for the four different technologies

The 9 published studies included an overall patient number of 502 patients, of whom 20 patients of two studies of Hardes et al. [8,9] and 47 patients of the study of Tsuchiya et al. [13] and of Shirai et al. [14] might have been double included (Table 1). Therefore, with conservative estimate of real patient numbers, an overall number of 435 study patients can be assumed.

Seven of the nine studies are case series with level IV evidence, only the study of Hardest et al. [9] and Wafa et al. [12] on two different silver coating strategies for tumor endoprotheses can be considered as case control series with level III evidence.

3.2.1. Gentamicin poly(D, L-lactide) matrix coating for tibia nails

This coating is based on a fully resorbable poly(D, L-lactide) matrix with gentamicin sulphate with an initial burst release of 40% release of the gentamicin within the first hour, 70% within the first 24 h and 80% within the first 48 h (from a 8 mm thick und 330 mm long UTN PROtect® (Synthes, Bettlach, Switzerland) [15]. The total amount of antibiotic is depending on the surface area of the implant ranging from approximately 10 to 50 mg gentamicin depending on the size of the implant.

This coating was firstly available on the Unreamed Tibia Nail (UTN) PROtect® (UTN PROtect®; Synthes, Bettlach, Switzerland) based on the original UTN titanium alloy (Ti-6Al-7Nb) nail with CE-certification for this coated implant in August 2005.

Fuchs et al. [6] published a prospective, non-randomized case series on clinical, laboratory and radiological outcomes of 21 patients with closed or open tibial fractures, as well as revisions with the UTN PROtect® gentamicin-coated intramedullary nail. The authors reported radiographic union in 11 of 19 patients (58%) who completed the 6-months follow-up with partial fracture healing of at least one cortex of the remaining 8 patients. No implant-associated infections were seen and only one superficial wound healing was reported in one patient. The authors concluded that the use of the gentamicin-coated nail was associated with good clinical, laboratory and radiological outcomes after 6 months and that this implant offered new options for the prevention of infections including revision cases.

Another retrospective case series based on the same gentamicin-poly(D, L-lactide) coating on the Expert Tibia Nail (ETN) ETN PROtect[TM] (DepuySynthes, Johnson/Johnson company, Inc New Jersey, USA) was recently published by Metsemakers et al. [7]. The study included 16 consecutive patients with acute tibia shaft fractures pretreated with external fixation (2 patients), Gustilo-Anderson grade II or grade III open tibia fractures (9 patients) or complex tibia fracture revision cases with infected non-unions (4 patients) and aseptic non-union with soft tissue defect (1 patient) with a follow-up of 18 months. In none of the patients, implant-associated deep infection was noted. Non-union was defined as absence of complete healing after 9 months, which was observed in four of the 16 patients (25 %). This non-union group consisted of one patient that was treated for infected non-union, of two patients with Gustilo-Anderson grade III B open tibia fracture and of one patient with Gustilo-Anderson type II open tibia fracture.

3.2.2. Silver-coated MUTARS for tumor megaendoprostheses and knee arthrodesis nails

Silver coating of the Modular Universal Tumor And Revision System (MUTARS®) megaendoprostheses (Implantcast, Buxtehude, Germany) is achieved by galvanic deposition of elementary silver (with a percentage purity of 99.7%) onto the surface of the titanium–vanadium prostheses with a thickness of the coating of 10 to 15 mm [9]. This first layer is additionally coated with another layer of gold of 0.2 mm thick to ensure sustained release of silver ions.

The first clinical prospective case series consisted of 20 patients with bone tumors of the humerus, femur and tibia were treated with this type of coating with an average silver amount of 0.91 g (range: 0.33 – 2.89 g) [8]. No local or systemic toxic side effects of the silver coating were reported. Blood silver levels did not exceed 56.4

(0,056 µg/ml) parts per billion (ppb), which can be considered as non-toxic. Furthermore, no significant changes in liver and kidney laboratory parameters were found. Histological analysis exhibited no signs of foreign body reaction or chronic inflammation.

In a prospective case series of 51 patients receiving a proximal femur or proximal tibia replacement with a tumor endoprosthesis with the same type of silver coating Hardes et al. found an infection rate of 5.9% (3 of 51 patients) in the silver group after a follow-up time of 5 years compared to a historical control of the same institution with an infection rate of 17.6% (13 of 74 patients) in patients treated with an uncoated implant [9]. In cases of infection of the megaprosthesis, 38.5% of the patients in the uncoated group had finally to be treated with amputation. All infections in patients with a silver-coated implant could be successfully treated without amputation.

In one patient, a blue to gray discoloration of the skin of the previously operated site of the proximal tibia was noted and local argyria, which is a typical dermal side effect of silver with this type of skin discoloration skin could not be excluded.

Glehr et al. [10] reported about the same silver-coated meganedoprostheses in 32 patients undergoing surgery for resection of a bone or soft tissue tumor (26 patients) or revision arthroplasty (6 patients) with a focus on the development of argyria. Seven patients (23%) showed local argyria. Silver serum levels and silver levels of aspirated postoperative seroma were measured in patients with and without argyria and were found not to be different between the two groups. This indicates that local argyria was not linked to an elevated local or systemic silver concentration in those patients. The length of the prosthesis and the associated total amount of silver was not associated with a significant risk of argyria, either. Patients with argyria did not show elevated kidney or liver serum levels and hemoglobin and leucocyte were also

reported not to be significantly different to argyria-free patients. There was an infection risk of 12.5% (4 of 32 patients) in their case series. However, no further details on the underlying details of these infections are given. Three of those infections could be cured by debridement and reimplantation of silver-megaendoprostheses and one proximal amputation of the femur had to be performed. Furthermore, four of the seven patients with local argyria were identified with a peripheral neurological deficit. However, in two of them, this deficit had predated the implantation of the silver-coated prosthesis and no further details on the potential cause of the deficit, e.g. surgical injury vs. silver-related effects in the two remaining patients was given. The electronystagmography in these patients revealed no signs of systemic argyria, such as ocular argyrosis, and no systemic discoloration of the skin was found.

In a recent study, Wilding et al. [11] investigated the effects of a silver-coated knee arthrodesis nail based on the MUTARS silver technology in 8 patients as salvage procedure in complex infected total knee arthroplasty. In 5 of these patients, no further revision surgery was necessary. One patient developed recurrent infection, which could be controlled by singular irrigation and debridement without implant removal and no further need for surgery. Another required incision and drainage of a superficial wound 3 months after arthrodesis hat could also be resolved by a one-stage intervention. The last complication consisted of an intraoperative fracture of the tibia, requiring internal fixation. None of the patients with a mean follow-up of 16 months (3-53 months) had to undergo amputation. Patients reported a significant improvement for pain, night pain and for the ease of standing after seating after the arthrodesis compared to the pre-arthrodesis situation. No adverse events were reported in this study.

3.2.3. Agluna silver coating for tumor megaendoprostheses

Agluna silver-enhanced (Accentus Medical Ltd, Oxfordshire, United Kingdom) custom-made endoprosthesis (Stanmore Implants Worldwide Ltd, Elstree, United Kingdom) are based on ionic silver that is 'stitched' into the surface of the titanium alloy by anodization of the titanium alloy followed by absorption of silver from an aqueous solution [12]. The engineered surface modification is integrated into the substrate and loaded with silver by an ion exchange reaction with formation of circular features of 5 μm. Maximum silver amount for a typical endoprostheses was reported to be 6 mg for a typical endoprostheses.

A retrospective case-control study on a silver-coated tumor prosthesis in 85 patients that were treated between 2006 and 2011 was recently published by Wafa et al. [12] with a minimum follow up of 12 months. These data were matched with outcome in 85 control patients that received an identical but uncoated tumor prosthesis between 2001 and 2011. Indications included 50 primary reconstructions (29.4%), 79 one-stage revisions (46.5%) and 41 two-stage revisions for infection (24.1%). Comparing the matched silver-free control group versus the silver-coated megaendoprosthesis group, there was a significant reduction of the overall post-operative infection rate from 22.4% to 11.8% (p = 0.03) in favor of the silver-coated implant group. For the treatment of these infections, debridement, antibiotic treatment with implant retention was successful in all seven infection cases of the silver group whereas only six of the 19 patients (31.6%) in the control group (p = 0.048) could be treated by this strategy. For the indication of two-stage revision for infection, the overall success rate was 86% (17 of 20) in the silver-coated group and 57.1% in the matched control group (12 of 21) (p=0.05). No implant specific adverse events such as argyria were described by the authors who concluded that the silver coating had an unexpected positive impact in eradication of infections and also in the prevention of infections in

cases with elevated infection risk. They reported about the change of practice by using the silver-coated implants for all revision procedures and primary procedures with a perceived higher risk of infection.

3.2.4. Iodine-coating for tumor endoprostheses

This type of iodine coating uses an anodic oxide film that is produced electrically with a povidone-iodine electrolyte resulting in the formation of an adhesive porous anodic oxide with the antiseptic properties of iodine. The anodic oxide film is between 5 μm and 10 μm thick, exhibits more than 100,000 pores/mm^2 and the capacity to support 10–12 μg iodine/ cm^2 [15].

In a prospective case series, Tsuchiya et al. [13] followed 222 patients with postoperative infections or comprised status with bone tumor cases, limb deformity, degenerative disease, non-unions, or fractures with a mean follow-up of 18.4 months. Different types of implants, e.g. spinal instrumentation (n=82), plates (n=55), external fixator pins (n=36), tumor prostheses (n=32), hip (n=10) and knee (n=4) prostheses, nails (n=2), cannulated screw (n=1) at different anatomical sites were used with the coating. The authors distinguished between "preventive" (n=158) and "therapeutic" cases (n=64) The coated implants were used to prevent infections in cases (n=158) with perceived high infection risk, such as compromised immune status, and also in patients with established postoperative infections for revision (n=64). For preventive indication, 3 of the 158 patients developed an acute infection (1.9%), which could all be cured without implant removal. All of the 64 infection cases could be successfully treated with the iodine-coated implants without recurrence of infection except one who showed signs of a late hematogenous infection 2 years after revision. One case of suspected iodine allergy is reported although all patients were tested pre-operatively with patch tests for potential iodine allergy. To evaluate potential

interactions with iodine, thyroid hormone levels were evaluated which remained without abnormalities as well as thyroid function itself. Further specific adverse events of the coating on CRP levels or white blood cells were not found either. A "mechanical implant failure" rate in 2 cases is described without any further specification, whereas no loosening of the implant and good radiographical bone integration of the implants were reported.

The same type of coating was used in a tumor endoprostheses limb salvage system (Kyocera Limb Salvage (KLS) System (Kyosera, Osaka, Japan) or KOBELCO K-MAX (Kobelco, Kobe, Japan) in 47 patients suffering from malignant bone tumor (11 patients), chronic osteomyelitis due to pyogenic arthritis (6 patients) and loosening of total knee arthroplasty (1 patient) published in a prospective case series of Shirai et al. [14]. The mean age was 53.6 years with a range, 15–85 years and patients were followed up for a mean of 30.1 months (range: 8-50 months). One of the 21 patients in whom the prosthesis was used for prophylactic purposes developed an implant-associated infection with growth of *P. aeruginosa*, whereas all other patient remained infection free. All 26 patients that underwent surgery for one- or two-stage revision procedure for periprosthetic joint infections showed no signs of infection. In line with the study of Tsuchiya et al. [13], no iodine related negative effects on white blood cells and CRP, thyroid hormone levels or thyroid function were reported. Further specific adverse events of the coating were not found either. Also "mechanical implant failure" is reported, with a failure rate of 4.2%.

4. Discussion

4.1. Clinical need

Implant-related musculo-skeletal infections have a severe negative effect on patient quality of life [17]. Therefore, all efforts to reduce infection rates should be undertaken including antimicrobial strategies for implants.

In the orthopaedic trauma patient, particularly open fractures are at risk for implant-associated infections. Mainly open tibia fractures are known to exhibit an elevated infection risk, e.g. the SPRINT trial showed an infection risk of 8.8% for open tibia shaft fractures compared to 2% for closed fractures [18]. Also other stratified data showed the highest infection risk for Gustilo-Anderson type III B open fractures [19]. Relating these facts to recently published costs of US$ 51,364 per infected tibia shaft fracture [20], there is an estimated burden of 1,620 infected tibial shaft fractures with financial costs of US$ 83.3 million in the US per year underscoring the clinical and health-economic need for the improvement of infection prevention, including antimicrobial coatings, in the trauma environment (Table 2).

The high infection rates in endoprosthetic bone tumor surgery of 5 to 13% [21-23] seem to be a logical reason for the use of antimicrobial implants and explain the relatively high percentage of this surgical entity among all patients from published clinical studies (Table 1).

The question arises if the use of antimicrobial implants is warranted not only for patients with an elevated infection risk, such as tumor surgery, but also for standard primary total joint arthroplasty. The number of primary total hip and knee arthroplasty procedures will increase from approximately 916,000 cases in 2010 up to 4,053,000 cases in 2030, mainly driven by the tremendous growth of primary total knee arthroplasty procedures from 663,000 in 2010 to 3,481,000 in 2030 [24]. With

published infection rates of 0.88 % for total hip and 0.92 % for total knee arthroplasty, there will be the threatening total number of approximately 37,000 infected hip and knee prostheses in the United States of America in 2030 compared to only 8,300 cases in 2014 [25] (Table 3). These figures do not even include revision surgery, which can be estimated to double from approximately 130,000 in 2016 up to 260,000 procedures in 2030, and for which a significant higher infection risk compared to primary surgery can be assumed. Furthermore, infections after shoulder, elbow, or ankle arthroplasty are not included in these figures.

Those absolute numbers are obviously linked to a tremendous financial burden on the health care system. Published cost estimations between US$ 43,000 [26] and US$151,000 [28] per case result in approximately total costs between US$ 1.59 to 5.6 billion per year for periprosthetic total knee and hip arthroplasty infections in 2030 in the US (Table 3).

All these figures underscore the strong need for improvement of infection prevention and treatment strategies including implant coatings in fracture care, primary and revision arthroplasty, and bone tumor surgery.

4.2. Safety

Safety considerations for antimicrobial coatings of implants include general biocompatibility, interference with fracture healing or bony integration, allergic potential of the coating and the emergence of resistant bacteria in response to the used antimicrobial agent for the coating.

There is a significant amount of data on several thousand patients available on the use of gentamicin and silver, particularly for gentamicin loaded PMMA bone cements [29] and for silver products in burn wound care [29,30] with a general good biocompatibility of both agents.

All reviewed coating technologies are associated with good systemic biocompatibility and safety, except for the local development of argyria in patients treated with silver-coated MUTARS prosthesis, which will be discussed in the next paragraphs.

4.2.1. General biocompatibility

No systemic biocompatibility problem was reported in 435 patients of the above reviewed studies. Neither gentamicin- nor silver-coated technologies had a negative effect on systemic body functions such as liver or renal function.

Gentamicin poly(D, L-lactide) matrix coating

The two studies on the gentamicin poly(D, L-lactide) matrix coating for tibia nails do not report about any systemic or other general biocompatibility problem of this type of coating [6,7] .

Silver

The study of Hardes et al. [8] reports on comprehensive clinical biocompatibility data with measurement of systemic and local silver concentration measurements in 20 patients for this type of silver-coated megaendoprosthesis with silver loadings between 0.33 g and 2.89 g. The mean preoperative serum silver concentration was 0.37 ppb preoperatively (range, 0.02–3.52). Two weeks postoperatively, the mean silver concentration was 2.80 ppb (range, 0.80–9.12) and varied between the third and 24th postoperative months between 1.93 to 12.98 ppb. The maximum silver concentration in the serum of 56.4 ppb was found in a patient who had received a distal femur prosthesis with silver loading of 0.33 g 15 months before. Interestingly, this is the prosthesis with the lowest silver amount, which led the authors to the conclusion that no correlations between the applied silver amount and silver

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concentrations in the serum could be made. Leukocyte abnormalities and functional impairment of liver and kidney function could be excluded by laboratory parameters. In three patients, in whom the silver-coated megaprostheses had to be revised due to non-coating related complications such as insufficient locking of a humeral stem after 4 months or occurrence of a new osteolysis of the acetabulum six months after implantation of a proximal femur replacement or postoperative hematoma four weeks after implantation, local tissue samples in the vicinity of the implant could be obtained. In all three cases, the prostheses showed normal soft-tissue ingrowth without any macroscopic signs of foreign body granuloma or chronic inflammation. Measurement of the local concentration of silver exhibited distance-dependent function with 1626 ppb, 833 ppb and 473 ppb in 5 mm, 10 mm and 15 mm distance from the prosthesis, respectively, six months after initial surgery with a proximal femur replacement with a total silver mass of 0.45 g. 1185 ppb to 401 ppb were measured at 5 and 15mm distance from a diapyhseal humeral implant, respectively, with a total silver amount of 0.42 g six months after index surgery. In another patient with a silver-coated megaendoprosthesis at the distal femur with a total silver mass of 1.42 g, mean silver concentration of 1626 ppb in the hematoma was measured.

The study of Wilding et al. [11] reported about the recurrence of one deep infection in one and the development of one superficial wound in another of 8 patients after knee arthrodesis with a silver-coated MUTARS arthrodesis nail as salvage procedure after complex total knee arthroplasty. Specific further adverse events in relation to the silver coating were not reported.

The main local biocompatibility issue of the above presented studies seems to be the development of local argyria after the use of MUTARS® megaendoprostheses. The blue to grey discoloration of the skin may be attributable to the stimulation of melanocytes by silver, which can be turned into brownish black under sunlight

exposure, which is comparable to photographic processing, when metallic silver is oxidized to form black silver sulphide [31-33].

Hardes et al. [9] identified a 64-year-old male patient with a gray discoloration of the skin of the previously operated site of the proximal tibia 50 months after surgery with a silver coated megaendoprosthesis in which argyrosis could not be excluded.

The data from Glehr et al. [10] suggest a risk for the development of local argyria of 23% (7 of 32 patients) after the implantation of MUTARS® megaendoprostheses without any systemic toxicity in all 32 patients. Data of this study revealed comparable levels of silver in blood and aspiration fluids between patients with and without local argyria. The median blood levels of silver in the 32 patients were far below 200 µg/kg although some peak values at levels of 200 µg/kg were initially found, which did not persist at follow-up. 4 patients with peripheral neurological deficits are described in the study, of which 2 had predated the implantation of the prosthesis. In the two remaining cases, electronystagmography revealed no signs of systemic argyria and no systemic discoloration of the skin was found. The authors concluded in the abstract that "no neurological symptoms and no evidence of renal or hepatic failure" could be linked to the development of argyria.

Compared to the MUTARS technology with published typical total silver amounts between 0.33 and 2.89 g, Agluna technology with silver loading of only 6 mg has not been reported to cause argyria or other silver-related local or systemic side effects. Therefore, "low dose silver coating" of 6 mg seems to be clinically safer for patients, although a direct dose-depending effect in the "high dose silver" patients treated with MUTARS could not be detected.

Povidone-iodine coating

For the povidone-iodine coating, no specific adverse events were reported [13,14] except one case with suspected povidone-iodine allergy (see below).

The median WBC levels were found to be in the normal range throughout the study period. CRP levels elevated directly post-surgery, however, returned to <0.3 mg/dl within four weeks after surgery. Thyroid hormone levels were not impaired and thyroid function remained intact.

4.2.2. Interference with fracture healing or bony integration

In none of the studies, specific adverse events on fracture healing after the use of a gentamicin-coated tibia nail or bony integration of silver- or povidone-iodine coated prosthesis are reported.

Fuchs et al. [6] reported radiographic union in 11 of 19 patients (58%) after the 6-months follow-up with partial fracture healing of at least one cortex of the remaining 8 patients. Based on the severity of injuries of the included patients in this study, with 12 open fractures (three patients with Gustilo-Anderson type 1, two patients with Gustilo-Anderson type 2 and 7 patients with Gustilo-Anderson type 3, of which three were type 3c open tibial fractures) and the limited follow-up time of only 6 months, fracture healing outcome seems appropriate and not negatively influenced by the coating-layer or gentamicin. These data are comparable to published results on non-coated tibia nails for closed and open fractures with rates for compromised fracture healing of 21%, with even higher risk for open fractures [34].

The study of Metsemakers et al. [7] confirmed these findings with 16 patients with high-risk situations at the tibia, including patients with Gustilo-Anderson type II or type III open tibia fractures (9 patients), or complex tibia fracture revision cases with

infected non-unions (4 patients) and aseptic non-union with soft tissue defect (1 patient). Non-union was noted after 9 months in four of the 16 patients (25 %) including one patient that was treated for infected non-union, two patients with Gustilo-Anderson type III B open tibia fracture and one patient with Gustilo-Anderson type II open tibia fracture.

Regarding silver-technologies, none of the studies reported on impaired bony integration of the prosthesis or early loosening of the implants after a median follow up of up to 53 months [8]. However, long-term results are lacking and should carefully evaluated.

The povidone-iodine coating was reported to exhibit good bony integration based on radiographic findings with spot welds in direct vicinity to the implant surface [13,14]. No implant loosening was reported, however, a "mechanical implant failure in 2 cases" was not specified by the authors. It is likely that those two cases are identical in the study of Shirai et al. [14] and Tsuchiya et al. [13] as the former study reports on an implant failure rate of 2.4% (2 of 47 cases) and the latter exactly on two implant failure cases.

Overall, there is no significant evidence that the available gentamicin-coated tibia nails or silver-coated and iodine-coated megaendoprostheses have a negative effect on fracture healing or bony integration of the prosthesis.

4.2.3. Allergic potential

Allergies against components of the coated implant preclude its use in such a case and only materials with a low allergic profile should generally be used.

There are no reports in the literature of documented allergies against gentamicin [35] or poly(D, L-lactide).

Regarding silver, contact dermatitis is rare and has been reported mainly on previous sensitized population, such as silver miners, jewelers and photographers [36,37]. Furthermore, the pathogenesis of contact dermatitis is likely to be different compared to deep soft-tissue and bone reactions with silver. Hypersensitivity to silver sulfadiazine is also known, however, this is mainly attributed to sulfadiazine and not the silver [38].

In general, a low rate with a prevalence of 0.4% of allergic reactions against povidone-iodine has been found in the literature [39,40]. Patients subjected to treatment with povidone-iodine prostheses in the studies of Tsuchiya et al. [13] and Shirai et al. [14], were pre-operatively tested with patch tests to diagnose potential allergies. One case of suspected allergy against the coating was reported from Tsuchiya et al. [13] with clinical appearance of an acute infection. No further details on the allergy, treatment or outcome of this case are given.

4.2.4. Development of resistance

The emergence of drug-resistance in microorganisms is a natural consequence of selection pressure by the use of therapeutic agents. There is some evidence that the frequent use of locally applied antibiotic-loaded biomaterials, particularly antibiotic loaded PMMA bone cement, has contributed to the problem of drug-resistance in bone surgery in the last decades. In the 1980's and 1990's, several authors have described high gentamicin resistance rates in bacteria in periprosthetic infections in which gentamicin-loaded PMMA was previously used [41-43]. These findings were recently confirmed in patients treated by 2-stage revision procedures in periprosthetic joint infections with aminoglycoside loaded PMMA spacers [44]. The main reason for the development of antibiotic resistance in the context of antibiotic-loaded bone

cement is seen in the fact of unfavorable elution kinetics of antibiotics from the PMMA allowing for subinhibitory levels of the antibiotics over months or even years that stimulate mutational resistance to occur [45-47].

However, these observations were recently contradicted by Hansen et al. [48] that reported the absence of resistance development in 174 cases with periprosthetic joint infections that had initially received prophylactic antibiotic-loaded cement in their primary joint arthroplasty.

As the reviewed fully resorbable poly(D, L-lactide) matrix for tibia nails exhibits considerable elution kinetic differences compared to PMMA, e.g. burst release with 80% release of gentamicin within the first 48 h [15], the creation of subinhibitory levels with subsequent development of drug-resistance should not be set equal to PMMA and needs to be specifically addressed by further clinical investigations for gentamicin-coated implants.

Despite the extensive use of silver in medicine and non-medical applications, only little resistance against silver has emerged, which is considered not to be a major clinical concern [30]. There are only a few cases on silver resistance of different bacteria, such as *Pseudomonas aeruginosa*, *Enterobacter cloacae*, *Klebsiella pneumonia* etc. that were recently reviewed by Sterling [30]. This low resistance risk is believed to be associated with the multi-target effects of silver including corruption of DNA replication, cell wall formation, functional protein precursors and the electron transport chain [49,50]. This multilevel antimicrobial mode ensures that resistance cannot be easily acquired by single point mutations in contrast to aminoglycoside antibiotics, where resistance can be selected much easier [51].

The analyzed studies of this article did not report in cases of infection after the implantation of the coated implant on the antibiotic susceptibility of the identified bacteria. Therefore, there is no data whether in the few cases of infection, resistance

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against gentamicin, silver or povidone-iodine occurred in the infection causing bacteria.

4.3. Evidence of reduction in infection rates

There is no prospective randomized control trial that investigates postoperative infection rates of the reviewed coatings vs. uncoated control implants.

There are only one case control series for the silver Agluna [12] and one case control series for the silver MUTARS technology [9] (Level III evidence) (Table 4).

Wafa et al. [12] compared infection rates of the Agluna silver coated implants with case matched historical controls of their own institution that had been treated by the same surgical technique with a non-coated implant in terms of anatomical site and implant type. They found a significant reduction of infection rate from 22.4% to 11.8% (p = 0.033) by the silver coating.

Also Hardes et al. [9] found in their case control study a decrease of implant-infections in the MUTARS silver group to 5.9% (3 of 51 patients) versus 17.4 % (17 of 91 patients) in the uncoated control group with comparable pre-operative leucocyte levels and resection length. However, this difference did not reach statistical significance (p=0.062).

A further interesting point is the difference in outcome of infected silver coated vs. infected uncoated implants with a more successful treatment outcome in silver-coated prostheses. Hardes et al. [9] reduced amputation rates in megaendoprosthesis-related infections from 38.5 % (5 of 16 patients) in the non-coated group to 0% in the silver group.

For postoperative infections, Wafa et al. [12] reported a significant higher rate of successful implant retention of the silver-coated group (100% success rate, 7 of 7

cases) compared to controls (31% success rate; 6 of 19 cases) (p = 0.048). For two-stage revision, the difference between the success rate of 86% in the silver group to 57.1% in the control group with a p-value of 0.05 almost reached statistical significance.

Wilding et al. [11] also described a positive outcome in 8 patients with knee arthrodesis with silver-coated nail for complex total knee arthroplasty infection that did not require amputation. Two infection and would healing complication could be treated with single wash out and debridement procedures.

It must be considered that these data were shown for tumor endoprostheses and complex infected total knee arthroplasty cases with a relatively high (re)infection risk and should not be directly transferred to standard primary hip or knee arthroplasty. Furthermore, these results rely on historical control comparisons and further data from prospective randomized control trials are desirable. However, adequately powered randomized controlled clinical trial remain challenging in the context of infection prevention due to the large sample size and long follow-up of such studies [52].

Overall, these findings can be considered as first hint for the effects of antimicrobial coatings and a "proof of concept" for implants in bone surgery.

5. Conclusion

In conclusion, there is a strong need for improvement of infection-prevention and infection treatment in fracture care, primary and revision arthroplasty, and bone tumor surgery. Overall, it can be concluded the reviewed gentamicin-, low amount silver Agluna, and povidone-iodine technologies have shown the "proof of concept" for antimicrobial coatings of implants with a good risk benefit ratio, resulting good systemic and local biocompatibility data and some first evidence for the reduction of infection rates by coated implants mainly in patients with a high infection risk. The only major safety risk was identified for the use of high amount silver coating (MUTARS), which seems to be associated with the development of local argyria with blue to bluish grey discoloration of the skin.

Further data from randomized control trials particularly on the effects on the reduction of infection rates are desirable, although this will remain challenging in the context of infection prevention due to large sample sizes and long follow-up of such studies.

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Table 1. Published clinical data of different antimicrobial coated internal fixation devices and endoprostheses
*20 patients of two studies of Hardes et al. and 47 patients of the study of Tsuchiya et al., 2012 and of Shirai et al., 2012, might have been included in two studies

Coating technology	Authors	Implant	Concentrations/ loadings	Indications	Study type	Evidence level	Number of patients
Gentamicin poly(D, L-lactide) with 'dip coating process'	Fuchs et al., 2011	Tibia nail (UTN PROtect®, Synthes)	10 to 50 mg gentamicin per implant	Closed or open tibial fractures and tibia revision cases	Case series	IV	21
	Metsemakers et al., 2015	Tibia nail (ETN PROtect™; DepuySynthes, Johnson/Johnson Company, Inc New Jersey, USA)	Not specifically given, but same technology as described by Fuchs et al. (2011)	Acute tibia shaft fractures or complex tibia fracture revision cases	Case series	IV	16
Silver (elementary silver with percentage purity of 99.7%) with galvanic deposition on the implant surface	Hardes et al. 2007	Mutars® tumor endoprosthesis (Implantcast, Buxtehude,Germany)	0.33 - 2.89 g of silver per implant	Bone metastases or or systemic lymphatic disease in humerus, femur or tibia	Case series	IV	20
	Hardes et al. 2010	Mutars® tumor endoprosthesis (Implantcast, Buxtehude,Germany)	Not specifically given, but same technology as described by Hardes et al. (2007)	Bone sarcoma of proxmial femur or proximal tibia	Case control series	III	51
	Glehr et al., 2013	Mutars® tumor endoprosthesis (Implantcast, Buxtehude, Germany)	Not specifically given, but same technology as described by Hardes et al. (2007)	Bone or soft tissue tumor surgery, revision arthroplasty with bone loss	Case series	IV	32
	Wilding et al., 2016	Knee arthrodesis nail based on MUTARS technology	Not specifically given, but same technology as described by Hardes et al. (2007)	Infected total knee arthroplasty	Case series	IV	8

Silver with anodisation of the titanium alloy followed by absorption of silver from an aqueous solution	Wafa et al., 2015	Agluna silver-enhanced (Accentus Medical Ltd, Oxfordshire, United Kingdom) custom-made tumor endoprostheses (Stanmore Implants Worldwide Ltd, Elstree, United Kingdom).	0.006 g silver for an "average" prosthesis	Primary reconstructions, one-stage and two-stage revisions for infection	Case control study	III	85
Povidone-iodine electrolyte-based process	Tsuchiya et al., 2012	Spinal instrumentation, plates, external fixator pins, tumor prostheses, hip and knee prostheses, 2 nails, cannulated screw	$10–12$ µg iodine/cm^2	Bone tumor cases, limb deformity, degenerative disease, osteomyelitis, non-unions, fractures	Case series	IV	222
	Shirai et al. 2014	Kyocera Limb Salvage (KLS) System (Kyosera, Osaka, Japan) and KOBELCO K-MAX (Kobelco, Kobe, Japan)	$10–12$ µg iodine/cm^2	Malignant bone tumor, infected total knee arthroplasty, chronic osteomyelitis due to pyogenic arthritis, and loosening of total knee arthroplasty	Case series	IV	47
Total number of patients							502
Total numer of patients with deduction of patients with possible double inclusion*							**435**

Table 2. Estimated financial costs for infected tibial shaft fractures in the US
* US population of 318 million, incidence for tibial shaft fractures of 17/100.000 (Weiss et al., 2008) and distribution of 85% of closed vs. 15% of open fractures (Weiss et al., 2008)
**SPRINT investigators, 2008
*** Based on costs of 51,364 US$ per case (Thakore et al., 2015)

	Estimated number of closed and open tibia shaft fractures*	Infection rate**	Estimated number infected tibia fractures	Costs
Closed	46,000	2 %	920	US$ 47.2 M
Open	8,000	8.8%	700	US$ 36.1 M
Total	54,000		1,620	US$ 83.3 M

Table 3. Estimated number of total hip (THA) and total knee arthroplasty (TKA) infections in 2010 and 2030 with related economic burden.

* Kurtz et al., 2008
** Kurtz et al., 2007
*** Based on costs between 43,000 US$ (Klouche et al., 2010) and 151,000 US$ (Hebert et al., 1996) per infection case

	Estimated number of primary THA*	Infection rate**	Estimated number infected of primary THA	Estimated number of primary TKA*	Infection rate**	Estimated number infected of primary TKA	Estimated total number of infected THA + TKA	Range of estimated overall costs
2010	253,000	0.88%	2,226	663,000	0.92%	6,100	8,326	US$ 360 – 1,260 M
2030	572,000	0.88%	5,034	3,481,000	0.92%	32,025	37,059	US$ 1,590 – 5,600 M

Table 4. Evidence of reduction of infection rates by coated implants.

Coating technology	Authors	Implant	Indications	Infection rate with coated implant	Infection rate of matched control group with uncoated impalnt	p-value	Evidence level
Silver (elementary silver with percentage purity of 99.7%) with galvanic deposition on the implant surface	Hardes et al. 2010	Mutars® tumor endoprosthesis (Implantcast, Buxtehude,Germany)	Bone sarcoma of proxmial femur or proximal tibia	5.9% (3 of 51 patients)	17.6% (13 of 74patients)	p= 0.062	III
Silver with anodisation of the titanium alloy followed by absorption of silver from an aqueous solution	Wafa et al., 2015	Agluna silver-enhanced (Accentus Medical Ltd, Oxfordshire, United Kingdom) custom-made tumor endoprostheses (Stanmore Implants Worldwide Ltd, Elstree, United Kingdom).	Primary reconstructions, one-stage and two-stage revisions for infection with tumor implants	11.8% (10 of 85 patients)	22.4% (19 of 85 patients)	p= 0.033	III