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Original Research Article

Ultrathin silver-polysiloxane-coated plates for treatment of infected femur non-union

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Abstract: The prevalence of fracture-related infections (FRI) poses a significant challenge in healthcare, with patients experiencing poor outcomes and lower quality of life compared to non-FRI patients. The antimicrobial coating HyProtect was applied on plates for the treatment of infected femur non-unions. The study was conducted at the Department of Septic Trauma and Orthopaedic Surgery at BG Klinikum Hamburg, Hamburg, Germany. The study aimed to address the need for infection prevention systems by applying antibacterial coatings to orthopedic implants. The silver-polysiloxane coating is a unique method combining Physical Vapor Deposition (PVD) and Chemical Vapor Deposition (CVD) techniques to embed silver aggregates in a plasma polymer matrix. The coating demonstrated antimicrobial efficacy, no cytotoxicity, and prevention of biofilm growth in in vitro and in vivo studies. The results of the prospective non-interventional case series involving 8 patients with infected femur non-unions treated with the silver-coated implants showed positive healing outcomes with no reinfections and improved quality of life scores. The systemic silver levels remained low at 0.014 ppm in blood, indicating good biocompatibility. Conclusion: The results suggest that the silver-coated implant technology could significantly improve patient outcomes and safety during FRI surgeries. The coating process was found to be suitable for various substrates, including 3D printed implants.

I. Introduction

Fracture-related infection (FRI) still presents a major challenge in terms of the treatment, for the physicians as well as personnel in health care. In Germany, 7253 cases of FRI were listed in 2018 [1], but this number only applies to the initial indication during the admission; later FRI cases do not appear in the statistics.

According to a study performed by Iliaens et al. [2] direct hospital-related costs associated with FRI were eight times that of non-FRI patients and indirect costs were four times that of patients without FRI.

Patients with FRI showed significantly poorer outcomes on both physical function (35.6 vs. 48.4, $p < 0.001$) and pain interference (60.4 vs. 46.3, $p < 0.001$) PROMIS scales [2].

In an ambidirectional cohort study performed by Buijs et al. [3], 134 patients were examined, with 28% of them being FRI patients and 72% being non-FRI patients. FRI patients had significantly lower quality of life scores compared to non-FRI patients in various domains. FRI patients also experienced more postoperative complications compared to non-FRI patients. Over a 14.5-month follow-up period, FRI patients developed multiple complications including nonunion, infections, and implant failure [3].

Walter et al. evaluated a total of 37 FRI patients [4]. In all patients successful eradication of infection and stable bone consolidation after long bone FRI was achieved. After 4.2 years (mean) follow-up time, FRI patients reported significantly lower quality of life in comparison to normative data.

The risk of FRI increases dramatically with the severity of the soft tissue damage. In closed tibial shaft fractures, the infection rate is approx. 1-2%. In open fractures with extensive soft tissue injuries, the infection rate increases dramatically to 42.9% [1]. Hematogenous infections are less common in FRI [5]. Bacteria that enter the situs during surgery or bacteria that enter via the open fractures are the main cause. These pathogens become particularly problematic when they are able to form biofilms.

Plantonic bacterial cells, which are easier to treat, become sessile bacterial cells that behave quite differently phenotypically. During biofilm formation, the bacterial population is embedded in a matrix of extracellular polymeric substances (EPS), which is partly responsible for the formation and maintenance of biofilm structures [6], as well as for the adherence onto surfaces. As soon as this bacterial layer grows into the third dimension, it becomes difficult to treat with antibiotics.

According to Baertl et al., it does not depend on the pathogen spectrum whether an FRI is an acute or chronic infection [7]. In the presence of a foreign body material like an implant, 100 pathogens are already sufficient to cause a severe infection [8]. This way the implant becomes the breeding ground for infection. Therefore, it is of great interest to reduce the number of vital germs on the implant surface to prevent also the biofilm formation. This means that the implant surface should be protected against bacterial colonization by an antibacterial coating.

I.I. Silver as an antimicrobial compound

Silver is an antimicrobial compound in which free silver ions bind non-specifically to Sulphur sidechains (SH groups) in proteins (cysteine side chains providing a particularly large number of SH groups). This disrupts bacterial energy production and other processes based on cysteine-containing enzymes, damages the cell membrane and affects the cell wall [9, 10, 11, 12]. These effects are responsible for cell disruption and the cells can then no longer divide and die [9, 10, 11, 12]. However, when using silver in an antibacterial implant coating, the two diametrically opposed factors of antibacterial efficacy vs. biocompatibility/toxicity must be considered [13, 14]. High silver concentrations carry the risk of side effects such as argyria. Too low concentrations can lead to poor or limited antibacterial efficacy [15,16]. Only a few silver-based antibacterial coatings are available in the clinic [17]. These include, for example, the MUTARS® (Implantcast, Buxtehude, Germany) tumor prosthesis (m(Ag) = 0.33 – 2.89 g) [17, 18] and the Ag-PROTEX® (Kyocera, Kyoto, Japan) coating (m(Ag) = 1.9 to 2.9 mg) [17, 19] of implants for hip joint prostheses.

I.II. The antibacterial HyProtect coating

The antibacterial HyProtect™ coating (silver multilayer coating (SML)) (Bio-Gate, Nuremberg, Germany) is an ultra-thin coating, that can be applied to both metal and polymer components.

This coating was used on implants in the present study in humans. Khalilpour et al. reported various successful tests of the HyProtect™ coating (SML), such as in vitro antimicrobial activity, no cytotoxicity according to ISO 10993-5 and ex vivo antimicrobial activity [20]. Two publications from 2016 and 2024 describe the ability of the HyProtect coating to prevent biofilm growth in vitro [21, 22].

The silver concentration of 2.7 µg/cm^2 enables the HyProtect coating to osseointegrate [23, 24]. Especially the osseointegration of orthopedic implants under load resulted in no significant differences between uncoated and HyProtect coated implants [24]. This good biocompatibility was also confirmed in the presented human study, where the HyProtect coating did not negatively influence the osteosyntheses.

In 2020 the antibacterial efficacy was evaluated in vivo in an infection model in rabbits [25], resulting in 97.5% germ reduction.

In the last 10 years more than 100 patients worldwide (EU, USA, Switzerland, Australia, New Zealand) received HyProtect coated implants (trauma, joint replacement, tumor and spine implants). These cases consist of customized implants and compassionate care cases based on standard implants coated with HyProtect. Several cases with different implants like Knee Arthrodesis', Total Femur, intramedullary nails and fracture plates were published [26, 27, 28, 29, 30].

Almost 50% of the customized implants were manufactured via 3D printing with Titanium substrates. This demonstrates that the HyProtect coating process can be used on several substrates including 3D printed substrates.

II. Material and methods

In low-pressure processes, a combination of a PVD (Physical Vapor Deposition) and CVD (Chemical Vapor Deposition), metallic silver aggregates are embedded in a SiO_xC_y plasma polymer, resulting in the HyProtect coating.

The plasma polymer/SiO_xC_y (Fig. 1) is grown from the precursor hexamethyldisiloxane (HMDSO, $C_6H_{18}Si_2O$) in radiofrequency (RF) plasma onto the substrate.

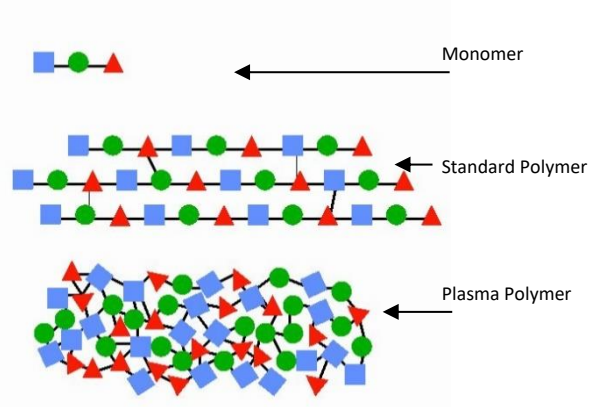

Figure 1: Differences between monomer, standard polymer and plasma polymer

The silver aggregates are sputtered from a pure silver target onto an underlying first layer of plasma polymer also known as amorphous modified polysiloxane. The second plasma polymer layer (3rd layer) is applied on top in a way that the sputtered silver aggregates remain interwoven by the plasma polymer. The term "layer" just describes the

process of the coating. As can be seen in Fig. 2, the result is a composite coating formed by the involved steps.

The silver content is nominal 2.7 µg/cm2 and the total coating thickness is nominal 90 nm. The entire coating dissolves completely over a period of 6 months.

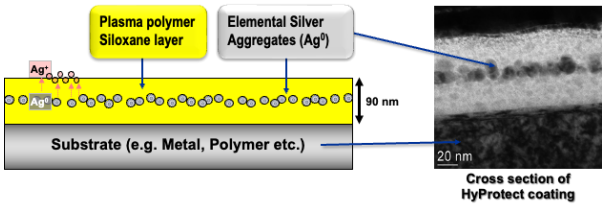

Figure 2: Differences between monomer, standard polymer and plasma polymer

The plasma polymer (SiO_xC_y) is grown from the precursor hexamethyldisiloxane (HMDSO, C6H18Si2O) in radio-frequency (RF) plasma onto the substrate. As long as the RF plasma is switched on, the HMDSO and O2 are converted into the plasma polymer.

Elemental reactions occurring in plasma polymerization are the fragmentation of monomer molecules, the formation of active sites (radicals) from the monomer, and recombination of the activated fragments (together with a reaction gas) to form a polymer. This process is a rapid step growth of polymers due to fragmentation of monomers. This process is attributed to the various types of collisions occurring simultaneously or separately in the reaction chamber. If fragmentation and recombination operate in plasma, the starting molecules for plasma polymerization will not be restricted to unsaturated compounds, saturated compounds can also deposit plasma polymers. The fragmentation of starting molecules in plasma is mainly represented by two types of reactions, namely the elimination of the weak hydrogen atom and the scission of the C–C bond. Silver atoms are sputtered from a pure grade silver target onto the substrate.

III. Results and discussion

First clinical results were generated in a prospective, non-interventional single arm case series including all patients in a time-frame.

As part of the REFECT study project, a prospective, non-interventional analysis was conducted encompassing all patients who received internal stabilization with a silver-coated plate (HyProtect™, Bio-Gate AG, Nuremberg) from 01/2023 to 01/2024 as part of the three-stage treatment for infected non-union of the femur.

Patients were included, if an infected non-union was diagnosed and treated by a silver coated implant at the BG Klinikum Hamburg. 15 patients were screened for the study, 8 patients were enrolled after informed consent (follow up not finished yet).

6 male and 2 female patients in accordance with the male predominance of infected bone non-union (Fig. 3) were included. An infected non-union was defined as a lack of bony healing 6 months after trauma. Age group evaluation showed a quite even distribution (see Fig. 4).

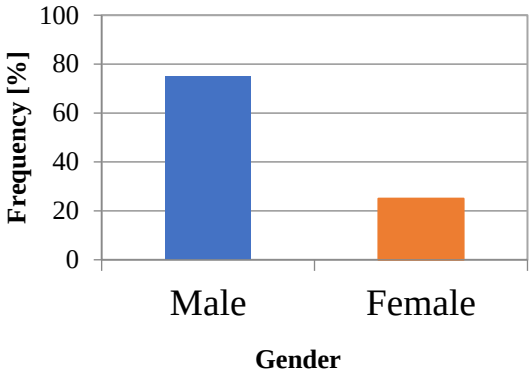

Figure 3: sex distribution

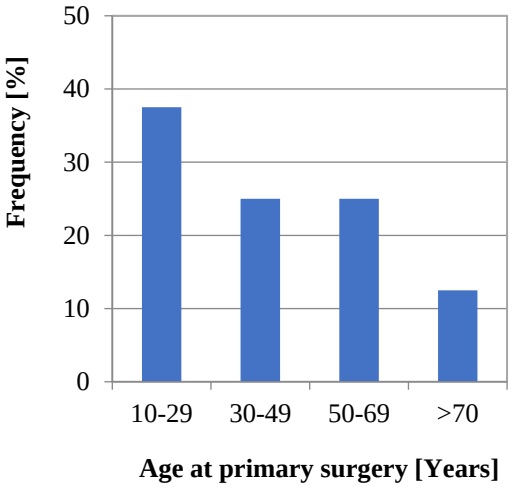

Figure 4: Age groups

According to this classification, we included 8 patients with an infected non-union. All patients were treated with a standardized 3-stage treatment of the infected femur ending in a re-osteosynthesis with a coated implant.

The implants were measured on radiographs using templates. The fitting implants were then sent for surface coating at Bio-Gate (see Fig. 5 and 6 before and after coating).

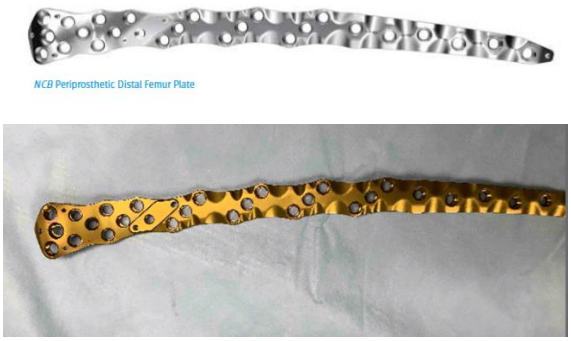

Figure 5: Distal femur plate made from Ti6Al4V before (top) and after antibacterial surface coating (bottom)

The NCB Periprosthetic Femur Plate Sytem implant (Zimmer Biomet, Warsaw, USA) was utilized in all patients using different sizes and variations in order to meet the needs to the respective patient. The surgical treatment included a thorough debridement followed by a re-osteosynthesis (Fig. 6).

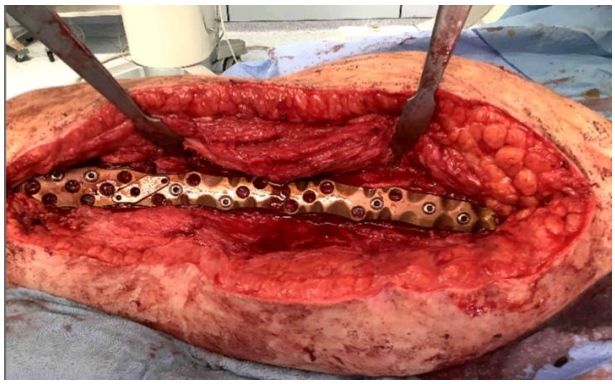

Figure 6: Re-Osteosynthesis of a distal femoral infected non-union of the left leg.

Standardized clinical follow-up including X-ray was performed 3 and 6 (12 and 24 months pending) postoperatively. At each follow up examination, the WOMAC and LEFS score was evaluated. The WOMAC (Western Ontario and McMaster Universities Arthritis Index) includes scores for each subscale which are summed up, with a possible score range of 0-20 for Pain, 0-8 for Stiffness, and 0-68 for Physical Function. Usually, a sum of the scores for all three subscales gives a total WOMAC score.

The LEFS (Lower Extremity Functional Scale) consists of a total score range from 0 to 80 points. Higher scores represent better function. The minimum detectable change (MDC) for the LEFS is 9 points. That is, a change of more than 9 points re-presents a true change in the patient's condition.

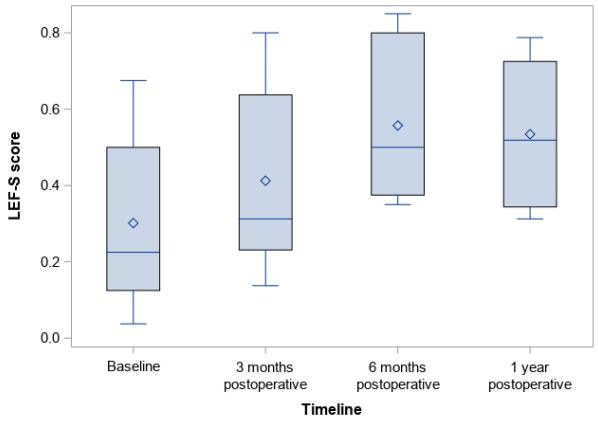

Figure 8: Lower Extremity Functional Scale results up to 12 months.

The mean follow-up of the 8 included patients was 10 months (as of 06/24). The concentration of silver ions in the blood serum reached a maximum of 0.014 mg/l in the postoperative laboratory controls. Clinically, all patients showed a positive healing process postoperatively with no sign of re-infection and no adverse procedure-associated events.

The WOMAC as well as LEFS scores showed improved results after 3,6 and 12 months (see figure 8).

IV. Conclusions

There is a great need for infection prevention systems that can improve the safety of patients undergoing FRI surgery. The high number of infections, especially in open fractures, can only be addressed by a comprehensive treatment strategy that includes hygiene management, debridement, antibiotic therapy and infection prophylaxis systems for implants.

The HyProtect coating, which is compatible with a wide range of different substrate materials, including 3D printed implants, demonstrated excellent biocompatibility with systemic silver levels as low as 0.014 ppm in blood. The absence of re-infections in patients also proves its good efficacy as a prevention technology and is a promising candidate for an infection prophylaxis system for orthopaedic and trauma applications.

Acknowledgments

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Author's statement

Conflict of interest: T. Konradt is employee of the manufacturer Bio-Gate. All other Authors state no conflict of interest. Informed consent: Informed consent has been obtained from all individuals included in this study. Ethical approval: The research related to human use complies with all the relevant national regulations, institutional policies and was performed in accordance with the tenets of the Helsinki Declaration, and has been approved by the authors' institutional review board or equivalent committee.

References

1. M. Rupp, N. Walter, S. Bärtl, R. Heyd, F. Hitzenbichler, V. Alt. Fracture-Related Infection-Epidemiology, Etiology, Diagnosis, Prevention, and Treatment. Dtsch Arztebl Int. 2024 Jan 12;121(1):17-24. doi: 10.3238/arztebl.m2023.0233. PMID: 37970721; PMCID: PMC10916768.
2. J. Iliaens, J. Onsea, H. Hoekstra, S. Nijs, W.E. Peetermans, W.J. Metsemakers. Fracture-related infection in long bone fractures: A comprehensive analysis of the economic impact and influence on quality of life. Injury. 2021 Nov;52(11):3344-3349. doi: 10.1016/j.injury.2021.08.023. Epub 2021 Aug 25. PMID: 34474918.
3. M.A.S. Buijs, S. Haidari, F.F.A. IJpma, F. Hietbrink, G.A.M. Govaert. What can they expect? Decreased quality of life and increased postoperative complication rate in patients with a fracture-related infection. Injury. 2024 Apr;55(4):111425. doi: 10.1016/j.injury.2024.111425. Epub 2024 Feb 14. PMID: 38402709.
4. N. Walter, M. Rupp, K. Hierl, C. Pfeifer, M. Kerschbaum, T. Hinterberger, V. Alt. Long-term patient-related quality of life after fracture-related infections of the long bones. Bone Joint Res. 2021 May;10(5):321-327. doi: 10.1302/2046-3758.105.BJR-2020-0532. PMID: 34008424; PMCID: PMC8160029.
5. Trampuz, W. Zimmerli. Diagnosis and treatment of infections associated with fracture-fixation devices. Injury 2006; 37 (Suppl 2): 59–66.
6. I.W. Sutherland. (2001) The biofilm matrix - an immobilized but dynamic microbial environment. Trends Microbiol 9: 222-227.
7. S. Baertl, N. Walter, U. Engelstaedter. What is the most effective empirical antibiotic treatment for early, delayed, and late fracture-related infections? Antibiotics (Basel) 2022; 11: 287.

8. S.D. Elek, P.E. Conen. The Virulence of Staphylococcus pyogenes for Man.: A Study of the Problems of Wound Infection. Br. J. Exp. Pathol. 1957, 38, 573–586.
9. D.E. Marx, D.J. Barillo. Silver in medicine: the basic science. Burns. 2014 Dec;40 Suppl 1:S9-S18. doi: 10.1016/j.burns.2014.09.010. PMID: 25418438.
10. M. Aldabaldetrecu, L. Tamayo, R. Alarcon, M. Walter, E. Salas-Huenuleo, M.J. Kogan, J. Guerrero, M. Paez, M.I. Azócar. Stability of Antibacterial Silver Carboxylate Complexes against Staphylococcus epidermidis and Their Cytotoxic Effects. Molecules. 2018 Jul 4;23(7):1629.
11. J.W. Alexander. History of the medical use of silver. Surg Infect (Larchmt). 2009 Jun;10(3):289-92.
12. I.X. Yin, J. Zhang, I.S. Zhao. The Antibacterial Mechanism of Silver Nanoparticles and Its Application in Dentistry. Int J Nanomedicine 2020;15(2555-2562, doi: 10.2147/IJN.S246764
13. L. Pauksch, S. Hartmann, M. Rohnke, G. Szalay, V. Alt, R. Schnettler, K.S. Lips. Biocompatibility of silver nanoparticles and silver ions in primary human mesenchymal stem cells and osteoblasts. Acta Biomater. 2014, 10, 439–449, doi: 10.1016/j.actbio.2013.09.037.
14. V. Alt. Antimicrobial coated implants in trauma and orthopaedics – A clinical review and risk-bene fi t analysis. Injury, Int J Care Injured 2017;48(599-607, doi: 10.1016/j.injury.2016.12.011
15. C.R. Rathbone, J.D. Cross, K.V. Brown, C.K. Murray, J.C. Wenke. Effect of various concentrations of antibiotics on osteogenic cell viability and activity. J. Orthop. Res. 2011, 29, 1070–1074, doi:10.1002/jor.21343.
16. L. Pauksch, S. Hartmann, M. Rohnke, G. Szalay, V. Alt, R. Schnettler, K.S. Lips. Biocompatibility of silver nanoparticles and silver ions in primary human mesenchymal stem cells and osteoblasts. Acta Biomater. 2014, 10, 439–449, doi:10.1016/j.actbio.2013.09.037.
17. H. Li, D. Wang, W. Zhang. Potential side effects of antibacterial coatings in orthopaedic implants: A systematic review of clinical studies. Front Bioeng Biotechnol 2023;11(1111386, doi:10.3389/fbioe.2023.1111386
18. J. Hardes, H. Ahrens, C. Gebert, A. Streitbuerger, H. Buerger, M. Erren, A. Gunsel, C. Wedemeyer, G. Saxler, W. Winkelmann. Lack of toxicological side-effects in silver-coated megaprostheses in humans. Biomaterials 2007, 28, 2869–2875, doi:10.1016/j.biomaterials.2007.02.033
19. S. Eto, S. Kawano, S. Someya. First Clinical Experience With Thermal-Sprayed Silver Oxide-Containing Hydroxyapatite Coating Implant. J Arthroplasty 2016;31(7):1498-503, doi:10.1016/j.arth.2015.12.034
20. P. Khalilpour, K. Lampe, M. Wagener. Ag / SiO x C y plasma polymer coating for antimicrobial protection of fracture fixation devices. 2010.
21. M.A. Azab, M.J. Allen, J.B. Daniels. Evaluation of a silver-impregnated coating to inhibit colonization of orthopaedic implants by biofilm forming methicillin-resistant Staphylococcus pseudintermedius. Vet Comp Orthop Traumatol 2016;29(4):347-50, doi: 10.3415/VCOT-15-08-0134
22. S.W.G. van Hoogstraten, J. Fechter, R. Bargon, J.L. van Agtmaal, L.C.W. Peeters, J. Geurts, J.J.C. Arts. The Antibacterial Properties of a Silver Multilayer Coating for the Prevention of Bacterial Biofilm Formation on Orthopedic Implants—An In Vitro Study. Coatings. 2024; 14(2):216. https://doi.org/10.3390/coatings14020216
23. R. Smeets, C. Precht, M. Hahn, O. Jung, P. Hartjen, M. Heiland, A. Gröbe, M.G. Holthaus, H. Hanken. Biocompatibility and Osseointegration of Titanium Implants with a Silver-Doped Polysiloxane Coating: An In Vivo Pig Model. Int J Oral Maxillofac Implants. 2017 November/December;32(6):1338–1345. doi: 10.11607/jomi.5533. Epub 2017 Oct 13. PMID: 29028852.
24. S. Stein, L. Kruck, D. Warnecke. Osseointegration of titanium implants with a novel silver coating under dynamic loading. European Cells and Materials 2020;39(249-259
25. M. Fabritius, A.A. Al-Munajjed, C. Freytag. Antimicrobial silver multilayer coating for prevention of bacterial colonization of orthopedic implants. Materials 2020;13(doi:10.3390/ma13061415
26. V. Alt, C. Heiss, M. Rupp. Treatment of a Recurrent Periprosthetic Joint Infection with an Intramedullary Knee Arthrodesis System with Low-Amount Metallic Silver Coating. J Bone Jt Infect. 2019 Apr 20;4(3):111-114. doi: 10.7150/jbji.34484. PMID: 31192109; PMCID: PMC6536804.
27. Ismat, V. Alt, C. Heiss, M. Rupp. Limb-saving Knee Arthrodesis with a Silver-coated Arthrodesis Rod in a Patient with Aspergillus Osteomyelitis of the Knee. Strategies Trauma Limb Reconstr. 2020 May-Aug;15(2):121-125. doi: 10.5005/jp-journals-10080-1445. PMID: 36466308; PMCID: PMC9679594.
28. J. E. Lenz, F. Baumann, V. Alt. Therapy of a Chronically Infected Total Femur Prothesis in a 40-year-old Patient. Z Orthop Unfall. 2022 Apr 4. English, German. doi: 10.1055/a-1754-0051. Epub ahead of print. PMID: 35378563.
29. V. Alt,. Treatment of an infected nonunion with additional fresh fracture of the femur with a silver-coated intramedullary nail: A case report. Trauma Case Rep. 2022 Mar 23;39:100641. doi: 10.1016/j.tcr.2022.100641. PMID: 35345781; PMCID: PMC8957057.
30. V. Alt, C. Pfeifer, M. Rupp, N. Walter. Treatment of a Gustilo-Anderson type II open tibia shaft fracture with an ultrathin silver plasma-coated plate: A case report. Trauma Case Rep. 2022 Oct 17;42:100715. doi: 10.1016/j.tcr.2022.100715. PMID: 36299855; PMCID: PMC9589016.