MENTORS IN ORTHOPEDICS

ANTIBACTERIAL COATING OF IMPLANTS: WHAT SURGEONS SHOULD KNOW

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SUMMARY

Background: Biofilm-associated infections represent a substantial burden in orthopedic and trauma surgery, with periprosthetic joint infection serving as a primary etiology for arthroplasty failure. Bacterial colonization and subsequent biofilm maturation occur within hours of implantation, creating a protective matrix that sequesters microorganisms from systemic antimicrobial agents and host immune responses.

Objective: This review examines the pathogenesis of implant-related infections and evaluates the classification, clinical efficacy, and limitations of current antibacterial coating technologies designed to inhibit bacterial adhesion and biofilm formation.

Key Points: Antibacterial strategies are categorized into passive surface modifications, active surface modifications, and local antibacterial carriers. Silver-coated megaprostheses demonstrate reduced infection rates in oncological reconstructions but face limitations regarding ion toxicity and incomplete implant coverage. Iodine-supported titanium implants show clinical safety in trauma and tumor cases. Antibiotic-loaded polymethylmethacrylate remains a standard for cemented fixations but is inapplicable to cementless components. A fast-resorbable hydrogel composed of hyaluronan and poly-L-lactic acid allows for intraoperative application across diverse biomaterials, including titanium and polyethylene. Preclinical and clinical data indicate that this hydrogel, when loaded with antibiotics, significantly reduces bacterial colonization and early postoperative infection rates without compromising osseointegration or bone healing.

Conclusion: Despite the rising incidence of septic complications, few antibacterial coating technologies have achieved widespread clinical adoption. Implementing these technologies, supported by robust post-marketing surveillance and specific reimbursement frameworks, is essential to reduce the clinical and economic burden of orthopedic infections.

KEYWORDS

Prosthesis-Related Infections; Biofilms; Coated Materials, Biocompatible; Anti-Bacterial Agents; Orthopedic Procedures

THE IMPACT OF BIOFILM- AND IMPLANT-RELATED INFECTIONS IN ORTHO-TRAUMA

Up to 80% of human bacterial infections are biofilm-related, according to the U.S. National Institutes of Health [1]. Among these, implant-related infections in orthopaedics and trauma still have a tremendous impact [2]. In fact, peri-prosthetic joint infection (PJI) is among the first reasons for joint replacement failure [3], posing challenging diagnostic and therapeutic dilemmas [4], with extremely high economic and social associated costs (Table 1). [5]

Leading reason for revision: Peri-prosthetic hip and knee infection is among the first three reasons for joint replacement failure, according to the registers; [6]
Infection risk after joint arthroplasty: the incidence of peri-prosthetic joint infection (PJI) **ranges from 1 to 2% after primary implant and up to 10% after revision surgery and in oncological reconstructions** [3].
Infection risk after osteosynthesis: the incidence of surgical site infection (SSI) after osteosynthesis for closed fractures of the long bones **range from 2% to 10%** [9]. The incidence of SSI after Gustilo 2 or 3 open fractures of the long bones is > 20% [10]
Mortality risk: the adjusted relative mortality risk (RR) for patients with hip revision for PJI, compared with the patients who did not undergo revision surgery is 2.18 [7]. The RR for patients undergoing hip revision for PJI, compared with aseptic hip revision range from 1.87 to 3.10; [8]
Additional costs: the average cost of management of infection after hip fracture surgery is **> 30,000 Euros** [8]. The cost of any single case of hip or knee PJI management ranges from **40,000 to > 100,000 Euros** [11, 12].

Table 1. Impact of implant-related infections in orthopedics and trauma: facts and figures.

PATHOGENESIS OF IMPLANT-RELATED INFECTIONS AND ANTIBACTERIAL COATING RATIONALE

Whenever a biomaterial is implanted, a competition starts between the host's and the bacterial cells for surface colonization. In the event of bacterial adhesion to an implant, immediate biofilm formation starts, making the bacteria extremely resistant to host's defense mechanisms and to antimicrobials[13]. In fact, in a wet environment, like the human body is, bacteria are capable to immediately adhere on a surface and to produce a protective intercellular matrix (the "biofilm"), which is completely formed in few hours. Once established, the biofilms efficiently protect the microorganisms both from the host's immune system and from the systemically administered antibiotics.

This immediate colonization of the implant from the bacteria can happen at time of surgery soon after the biomaterial is implanted in the body [14], even if the clinical consequences of the implant colonization may only become evident weeks, months or even years after the initial bacterial adhesion. The pathological consequences of the bacterial adhesion on an implanted biomaterial, generically termed as "post-surgical infection", features the

presence of variable inflammatory signs and markers, pain and progressive implant loosening, whose timing and extent depends very much on the balance between bacterial behavior and the host's individual inflammatory response.

This observation, grounds the basis for providing all the implantable devices with a surface finishing or a coating, specifically designed to selectively prevent bacterial adhesion and biofilm formation at the very time of surgery, without interfering with the biocompatibility and the long-term duration and function of the implant [15]. Despite this urgent need, the development of antibacterial coating technologies for large scale use appears particularly challenging, due to the many requirements that they must fulfill [16]. In fact, while antibacterial coating of implants is advocated by many as a possible solution to reduce the burden of implant-related infection in orthopedics, remarkably few technologies are currently available in the market, with proven clinical safety and efficacy.

ANTIBACTERIAL COATING TECHNOLOGIES CLASSIFICATION

Various technologies have been investigated in the last decades and can be classified according to their mechanism of action in 3 groups (Table 2):

1. Passive surface finishing/modification (PSM)

This approach aims at preventing or reducing bacterial adhesion to implants through surface chemistry and/or physical modifications, without the use of any pharmacologically active substance. Examples of this approach include modified titanium dioxide surface or polymer coatings.

2. Active surface finishing/modification (ASM)

Pharmacologically active pre-incorporated bactericidal agents, such as antibiotics, antiseptics, metal ions, or other organic and inorganic substances, are actively released from the implant to reduce bacterial adhesion. Examples of this approach are 'contact killing' active surface with silver- or iodine-coated joint implants.

3. Local carriers or coatings (LCC)

This strategy employs local antibacterial carriers, or coatings, that are not built into the device, but rather are applied during surgery, immediately prior to the insertion of the implant. They may have direct or synergistic antibacterial/antiadhesive activity or may deliver high local concentrations of loaded antibiotics or antibacterial agents [15].

Despite several products found effective at a research level, translating preclinical findings into clinical practice appears particularly challenging, time-consuming, and expensive. As a result, many promising coating technologies fail to reach the market due to regulatory, commercial or economic restrictions, denying the potential benefit to the patients and for the health care systems.

Features/examples	Development stage
Passive Surface/Finishing Modifications (PSM)	
Prevention of bacterial adhesion	
Hydrophilic surface	Preclinical
Superhydrophobic surface	Preclinical
Anti-adhesive polymers	Preclinical
Nanopatterned surface	Preclinical
Albumin	Preclinical
Hydrogels	Preclinical
Biosurfactants	Preclinical
Active Surface/Finishing Modifications (ASM)	
Inorganic	
Silver ions and nanoparticles	Market
Other metals (copper, zinc, titanium dioxide, etc.)	Preclinical
Non-metals: iodine	Clinical
Other non-metal ions (selenium, graphene, etc.)	Preclinical
Organic	
Coated/linked antibiotics	Market
Covalently linked antibiotics	Preclinical
Antimicrobial peptides	Preclinical
Cytokines	Preclinical
Enzymes and biofilm-disrupting agents	Preclinical
Chitosan derivatives	Preclinical
Synthetic	
Non-antibiotic antimicrobial compounds	Preclinical
'Smart' coatings	Preclinical
Combined Multilayer coating	Preclinical
Local Carriers or Coatings (LCC)	
Non-biodegradable	
Antibiotic-loaded poly(methyl methacrylate)	Market
Biodegradable	
Antibiotic-loaded bone grafts and substitutes	Market
Fast-resorbable hydrogel (acting both as passive surface modification system and as local antibiotic carrier)	Market

ANTIBACTERIAL COATING: CURRENT TECHNOLOGIES

Only few technologies are currently available in orthopedics and trauma for clinical use, or at least with reported clinical results (Table 3). These include silver and iodine coatings, antibiotic-loaded bone cement, gentamicin poly-l-lactic acid (PLLA) coating and a fast-resorbable hydrogel coating composed of covalently linked hyaluronan and PLLA (Defensive Antibacterial Coating -DAC® Novagenit Srl, Mezzolombardo, Italy).

Technology	Regulatory phase	Trademark and manufacture company	Mechanism of action	Main applications
Silver	Market	Agluna® (Accentus Medical Ltd, Didcot, United Kingdom); Mutars® (Implantcast GmbH, Buxtehude, Germany); PorAg (Waldemar Link GmbH & Co. KG, Hamburg, Germany)	Silver ion release	Tumour mega-prosthesis
Iodine	Clinical trials	Not applicable	Iodine release	Titanium implants including spine instrumentation, hip and knee joint arthroplasties, plates and screws
Gentamicin poly (D, L-lactide) matrix	Market	UTN PROtect Tibial Nail® (DePuy Synthes, Bettlach, Switzerland); Expert Tibial Nail (ETN) PROtect® (DePuy Synthes, Johnson & Johnson, New Brunswick, New Jersey)	Gentamicin release	Tibial nail for the treatment of tibial fractures and non-unions
Hyaluronic acid and poly (D, L-lactide) hydrogel	Market	Defensive Antibacterial Coating (DAC®) (Novagenit Srl, Mezzolombardo, Italy)	Antifouling activity with ancillary antibiotic release	Orthopaedics, traumatology, dentistry, and maxillofacial implants

SILVER COATINGS

Different technologies are currently used to apply the silver coating to metallic orthopedic implants [17-19]. Comparative and prospective studies are not available and only retrospective case series have been published, with coating application restricted to tumor prostheses [20,21].

Wafa et al. [22] reported the results of silver-coated tumour prostheses in 85 patients compared with 85 matched control patients. Indications included 50 primary reconstructions (29.4%), 79 one-stage revisions (46.5%), and 41 two-stage revisions for infection (24.1%). At a minimum follow-up of 12 months, there was a significant reduction in the overall postoperative infection rate from 22.4% to 11.8% ($p = 0.03$) in favor of the silver-coated implant group, with a mean reduction of approximately 48% in infection rate.

The routine use of silver-coated implants remains rather limited for several reasons, including possible toxicity of silver ions [23], and selective coating, thereby providing incomplete protection of the implant, since the intramedullary part of the prosthesis and some modular components cannot be coated. Moreover, silver coating is currently available only for few implant designs and the high costs of this technology has resulted in limited use outside the oncology applications [24].

IODINE COATING

Povidone-iodine can be used as an electrolyte, resulting in the formation of an adhesive, porous anodic oxide with the antiseptic properties of iodine [25]. Besides extensive preclinical studies [25-27], excellent clinical efficacy was reported for iodine coating of titanium alloys in a continuous, non-comparative series of 222 patients [28]. Preoperative diagnoses included tumour in 95 cases (42.8%), 34 limb deformities (15.3%), 29 cases of degenerative disease (13.1%), 27 osteomyelitis (12.2%), 24 nonunions (10.8%), and 16 fractures (7.2%). A variety of implants were used: 82 spinal instrumentations, 55 plates for osteosynthesis, 36 external fixations (pins and wires), 32 tumour prostheses, ten hip prostheses, four knee prostheses, two nails, and one cannulated screw. At a mean follow-up of 18.4 months (3 to 44), acute infection developed in three tumour cases (1.9%).

Two more recent non-comparative studies – one investigating iodine coating and megaprosthesis [29], the other investigating total hip arthroplasty (THA) [30] – confirmed the safety and efficacy of the technology at longer follow-ups. Based on these findings, clinical trials are currently ongoing to meet the regulatory requirements for market approval (Fig. 1). While no adverse event has been reported to date, the longer-term effects of local application of iodine coating and the application to materials other than titanium are yet to be assessed.

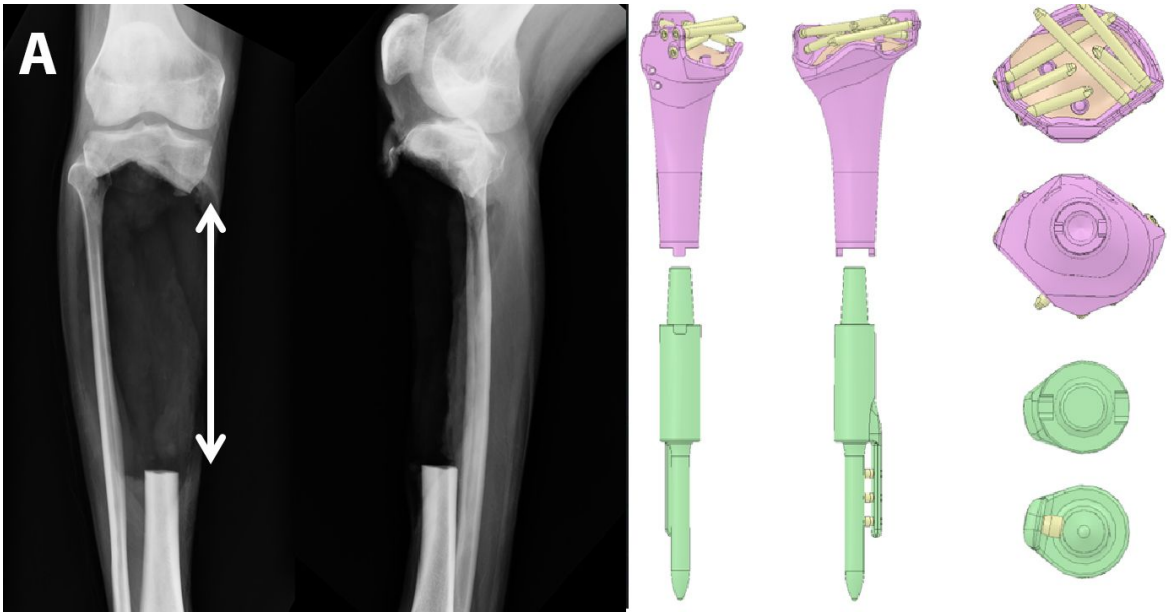
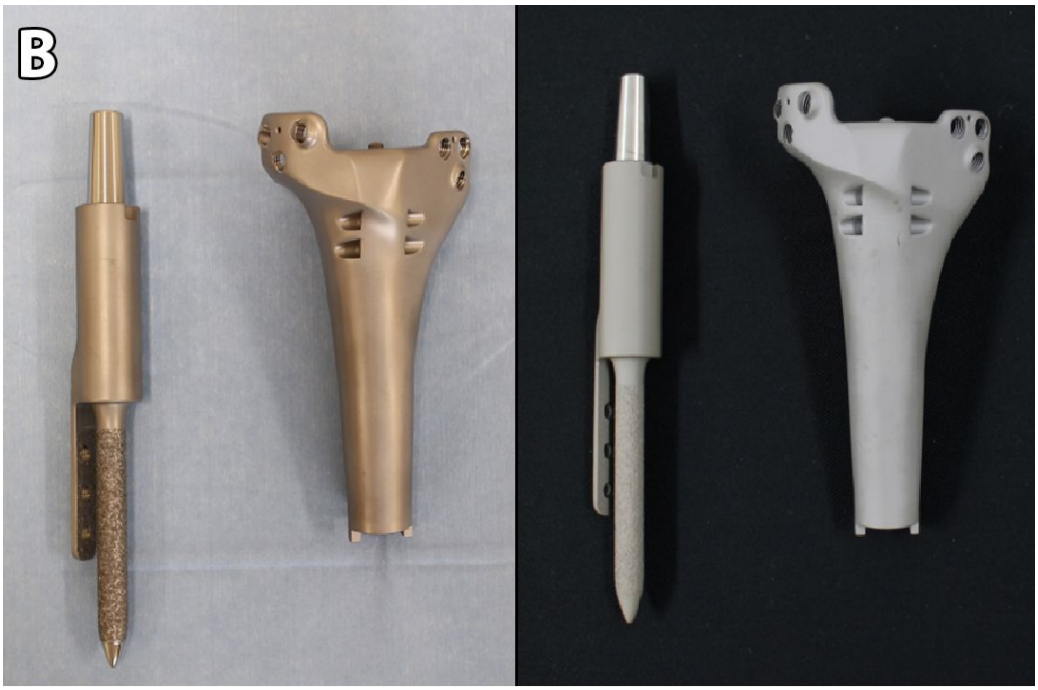


Figure 1 A to C. A. Left: 20 cm intercalary defect after tumor resection. Right: Custom-made implant with 3D printer. B. Left: Custom-made titanium implant with 3D printer. Right: The implant after surface modification with iodine (off-label). C. Left: intraoperative picture after reconstruction (off-label use), Center: Radiograph 1 year after operation. Right: Excellent bone ingrowth.



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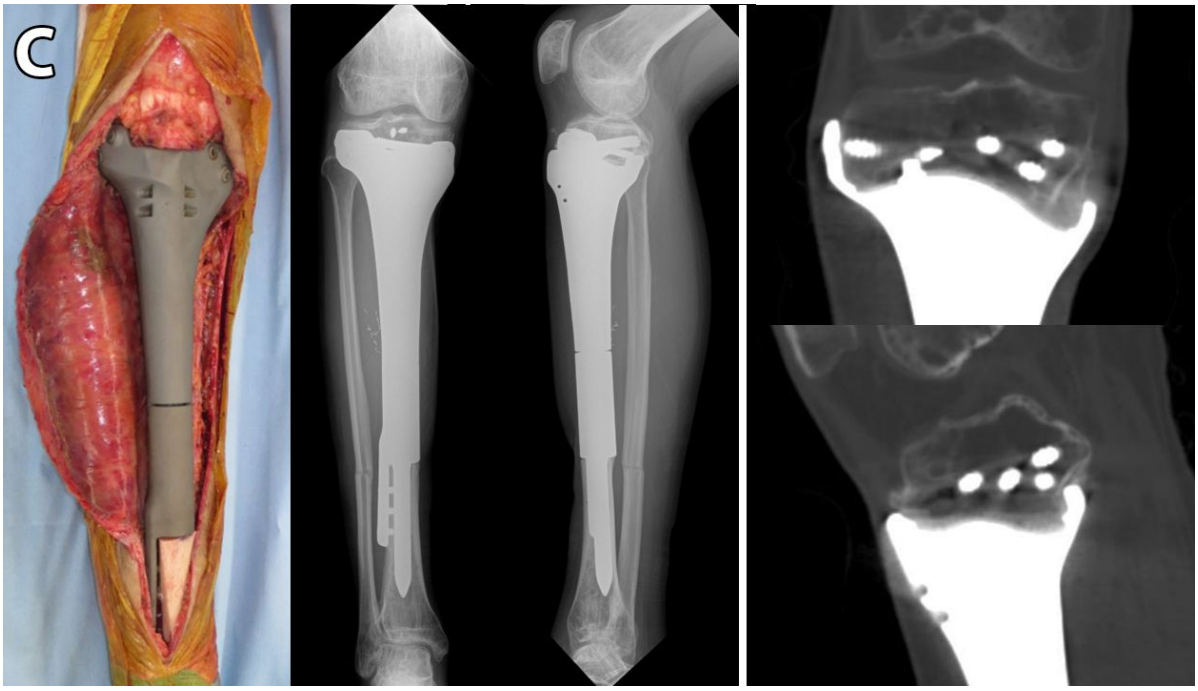

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ANTIBIOTIC-LOADED POLY-METHYLMETHACRYLATE (PMMA) BONE CEMENT

Even if antibiotic-loaded bone cement was not originally designed to act as an antibacterial coating, it is currently widely used to mitigate the risk of septic complications after joint replacement with cemented implants. Moreover, antibiotic-loaded cement spacers are often employed to deliver local antimicrobials in two-stage revision procedures for peri-prosthetic infection [31]. The most common combination of antibiotics to be added to bone cement is aminoglycosides (gentamicin or tobramycin) with vancomycin. The most recent systematic reviews and meta-analysis confirm the efficacy of antibiotic-loaded bone cement to reduce the risk of post-operative infection after primary total joint replacement by a factor ranging from 20 to 84% [32, 33].

Despite the routine clinical use of bone cement based on PMMA as a fixing coating with antimicrobial activity for implants, it has several disadvantages and limitations. The main limit is the fact that this solution may only be applied to implants requiring bone cement fixation and this excludes, by definition, all cementless implants. Moreover, even in cemented prosthesis, several parts of the implants remain unprotected by the antibiotic-loaded cement mantle, as for example the polyethylene insert, the locking mechanisms and all the extra-medullary surfaces. A further limit consists of the limited number and concentration of antibiotic(s) that can be loaded to polymethylmethacrylate and the limited capability of bone cement to release the antibiotics. In particular, only antibiotics with sufficient thermal stability and water solubility can be used, at a concentration that should not exceed 0.5 to 2 g/40 g PMMA [34]. Research has been underway to develop methods to increase the antimicrobial activity of bone cement, for example, by adding silver-containing substances [35, 36].

GENTAMICIN PLLA COATING

A coating for tibial nails, composed of a poly-l-lactic acid (PLLA) matrix, loaded with gentamicin, was first introduced into clinical use in Europe approximately fifteen years ago. The coating provides 80% release of the antibiotic within the first 48 hours [37]. In the first published clinical report, Fuchs et al [38] observed no deep infections at six months' follow-up in 21 patients treated with a UTN PROtect Tibial Nail (DePuy Synthes, Bettlach, Switzerland) for closed or open tibial fractures, as well as for revisions. Metsemakers et al [39] reported a retrospective analysis, including nine patients with a Gustilo and Anderson grade II or grade III open tibial fracture, four infected nonunions, two acute tibial shaft fractures pretreated with external fixation, and one aseptic nonunion with a soft tissue defect. At 18 months' follow-up, no implant-associated deep infection was reported. Finally, in the most recent and largest study, data from four centres, analyzed the outcome of 99 patients with fresh open or closed tibial fractures or undergoing nonunion revision surgery [40]. At 18 months' follow-up, deep surgical site infection or osteomyelitis was noted in 4/55 patients (7.2%) after fresh fracture and in 2/26 patients (7.7%) after revision surgery. The heterogeneous material and the lack of a comparator makes the interpretation of these results particularly difficult.

Apart from the absence of comparative trials, a limit of this technology is the fact that it is only available for the tibia and for one specific nail design. Furthermore, screws and fixation holes are not protected by the coating, while gentamicin resistance, ranging from 2% to 50% in Europe [41], may reduce the efficacy of the coating in some cases.

THE DAC® HYDROGEL COATING

The "Defensive Antibacterial Coating" is the first antibacterial hydrogel coating specifically designed for orthopedic and trauma and maxilla-facial implants. Based on hyaluronic acid (HA), grafted to polylactic acid (PLA), it is applied at surgery directly on the implant or on the tissues to be protected from bacterial adhesion. Hyaluronic acid is a mucopolysaccharide, naturally occurring in all mammal organisms. Due to its high biocompatibility, and non-immunogenicity, HA is considered as an ideal biomaterial for medical and pharmaceutical use [42] and has several clinical applications in dermatology, aesthetic surgery, dentistry, urology, orthopedics and ophthalmology [43]. Local application of hyaluronic-based compounds has been demonstrated to be protective against various infectious agents, depending on HA concentration and molecular weight, while the ability of HA to reduce bacterial adhesion and biofilm formation has been recently reported [44]. High biocompatibility, safety profile and anti-adhesive properties make HA and its composites an attractive option to design a resorbable coating, aimed at reducing the impact of biofilm-related infections in various clinical settings.

In line with these premises and to design a sufficiently stable HA-based antibacterial coating for use in orthopedics, a combination of HA with polylactic acid was investigated [45]. In fact, PLA is a synthetic polyester, widely used for orthopedic implants [46]. The patented combination of the two biocompatible and biodegradable polymers did finally allow to obtain a chemical-physical stability of the coating that was considered optimal for implant protection, without any risk of side effects [47].

The sterile, bioabsorbable, implantable DAC® hydrogel is intended to be applied, at the time of surgery, as a protective barrier over the surface of an implantable device (e.g., orthopaedic prosthesis or fracture fixation devices), to prevent bacterial adhesion, colonization, and biofilm formation through physical means. The device may also be intra-operatively loaded with one or more antimicrobial agents to further enhance the killing of planktonic bacteria that may be eventually present.

The kit for orthopedics and trauma applications includes a prefilled syringe, containing the sterile DAC® powder, one complete set of sterile components (connector, backstop and spreader) and one empty graduated syringe (Fig. 2).

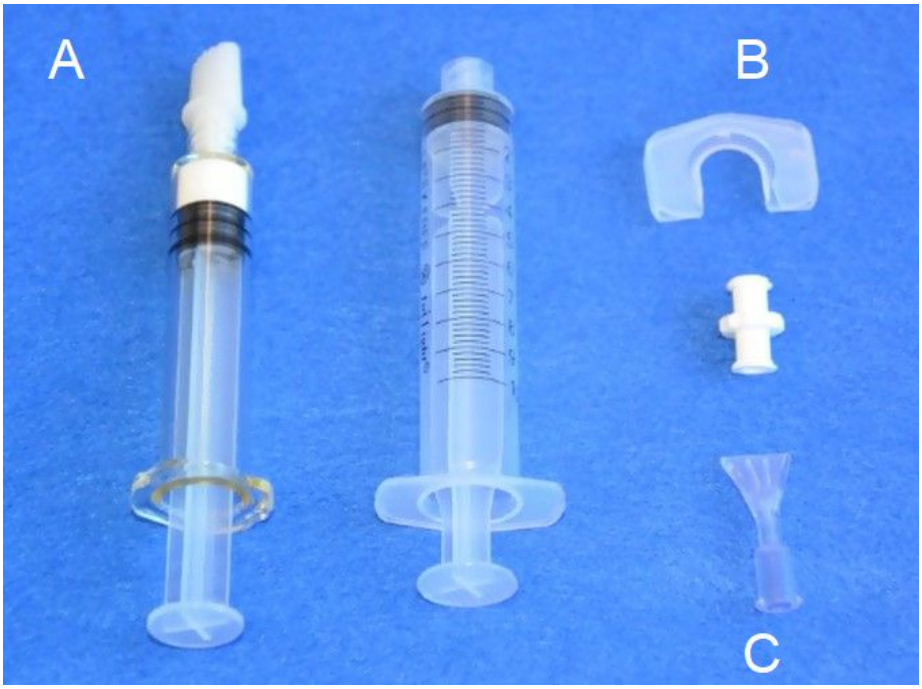

Figure 2 A to C. The DAC® kit includes a prefilled syringe containing the DAC® powder (A), a backstop and a connecting system for the hydrogel preparation (B) and a spreader to facilitate the hydrogel application on the implant surface (C), at the time of surgery.

At variance with all other existing antibacterial coating technologies, the DAC® hydrogel has been designed to offer an "ALL IMPLANT(S)" coating ability and can be used to protect various surfaces, including titanium alloys, nickel-chrome, cobalt-chrome, stainless steel, hydroxyapatite, polyethylene or other polymeric biomaterials (Fig. 3).

The hydrogel is not designed and should not be mixed with bone cement or its components (polymethylmethacrylate, PMMA) until they have finished their exothermal reaction and have completely hardened. The ability of DAC® hydrogel to completely cover even sand-blasted titanium surface and resist scraping has been confirmed by scanning electron microscopy (SEM) analysis [48]. Moreover, the DAC® coated implants can be press-fit inserted with the usual surgical technique. The resistance to scraping and de-clothing has been tested in the animal models and in human femurs, simulating a press-fit insertion of a cementless implant [49]. Both studies demonstrated the ability of the hydrogel coating to resist insertion, with approximately 60% to 80% of the hydrogel remaining adherent to all the implant surface, while the remainder being retrieved along the inner surface of the medullary canal.

In line with the concept of "ALL IMPLANT" coating, primary or revision cementless or hybrid joint prostheses and all internal osteosynthesis, including plates, screws and intramedullary nails, the surface in contact with the bone and all the modular parts, the polyethylene insert, the screws, sleeves, pegs, etc. and the respective locking mechanisms, should be protected with the hydrogel coating (Fig. 3).

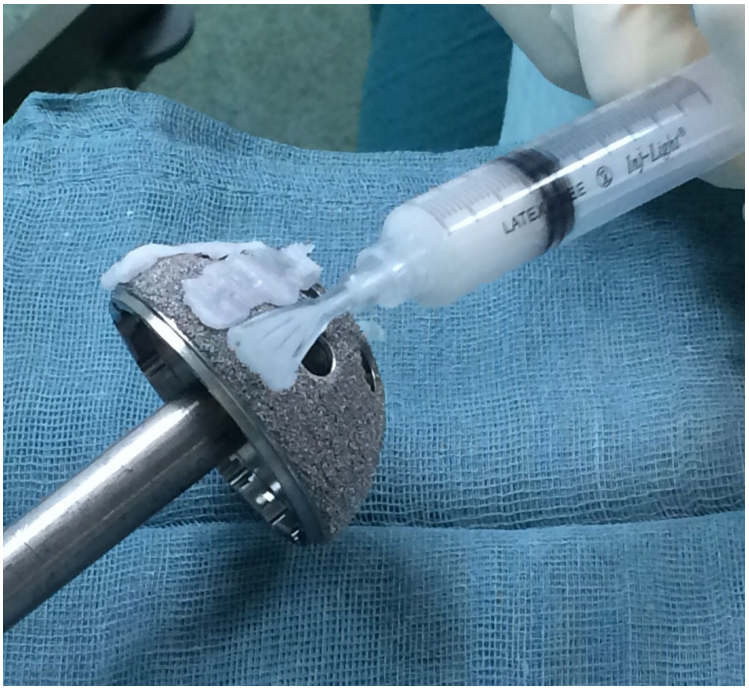

Figure 3 A to D. Examples of DAC® application on different implants: on a titanium acetabular cup (A), on a hydroxyapatite surface of a femoral stem implant (B), on a polyethylene insert of a revision knee prosthesis (C), and to the interlocking parts of a modular hip mega-implant (D).

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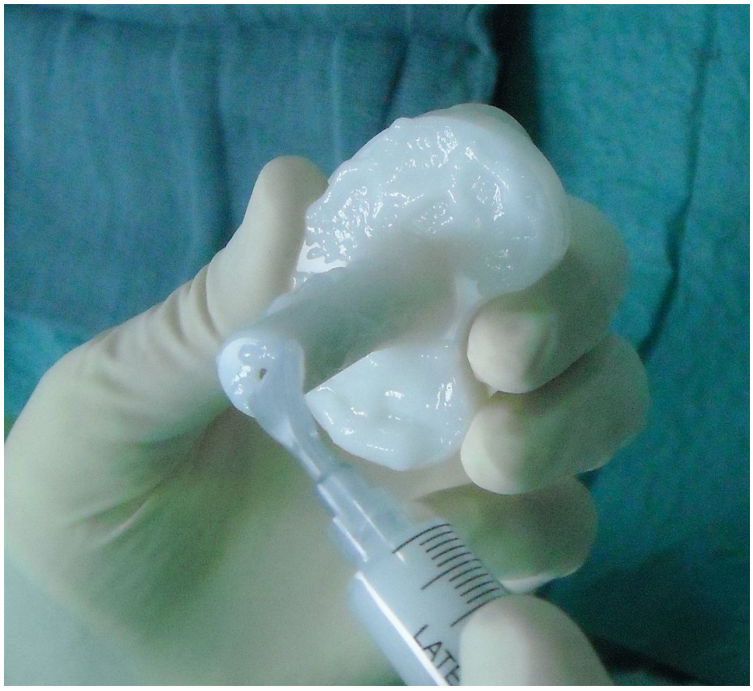

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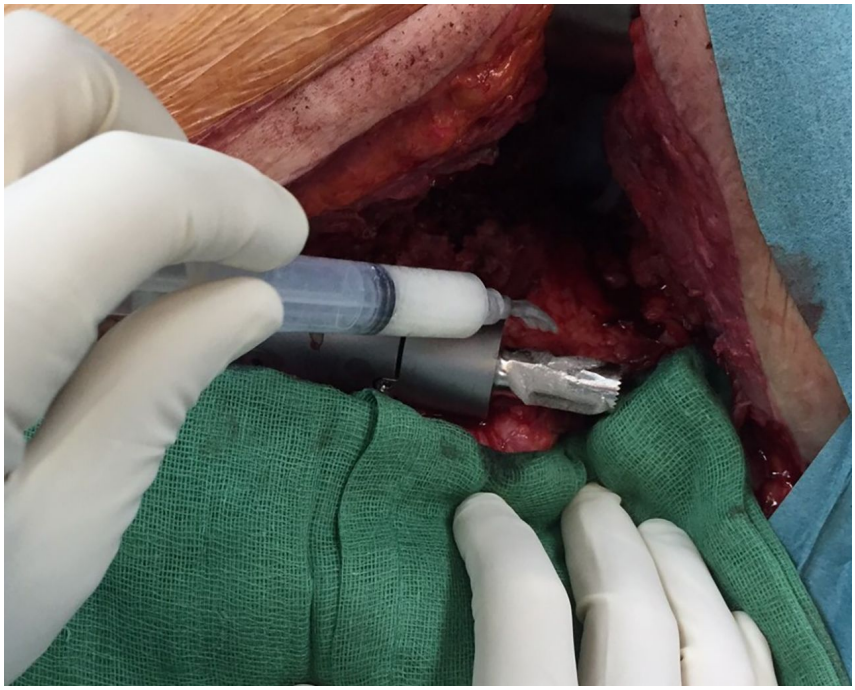

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Although the protection of the intra-medullary parts of an implant is pivotal, in order to prevent bacterial adhesion and proliferation at the implant-bone interface, defending the extra-medullary parts of the implant may be equally beneficial to reduce the chance of bacterial adherence and progressive colonization.

Furthermore, the antibiotic-loaded DAC® hydrogel coating can be successfully used in one-stage exchange procedure in peri-prosthetic infections [50]. However, in these cases, performing through debridement removing all infected and contaminated material remains paramount.

Preclinical studies have demonstrated the ability of the DAC® hydrogel to significantly reduce bacterial adhesion and biofilm formation of common bacterial pathogens, thus providing an effective protection of the implant [47, 48]. According to this finding, the antiadhesive hydrogel coating acts as a tool to reduce and delay bacterial adhesion and biofilm formation to a variable degree, depending on the local environment, the bacterial species and load. This activity of the coating may represent a key additional advantage to the host's cells to win the competition with the microorganisms that may eventually be present. Reducing the ability of bacteria to adhere to the implant will decrease the chance of bacterial colonization and infection, provided that the immune system and eventually the systemically administered antibiotic are able to kill the microorganisms in their planktonic state. Several studies have shown the effective antibiotic concentration in hydrogel ranges from 20 mg/mL to 50 mg/mL (2-5%), which is completely released within 72 hours of implantation [49]. (Table 4).

Antibiotic in powder form	Volume of sterile water for injection to be added	Volume of solution to be taken to reconstitute the DAC hydrogel
Vancomycin 500 mg	10 mL	5 mL
Vancomycin 1000 mg	20 mL	5 mL
Rifampicin 600 mg	15 mL	5 mL
Teicoplanin 200 mg	5 mL	5 mL
Teicoplanin 400 mg	10 mL	5 mL
Meropenem 500 mg	10 mL	5 mL
Meropenem 1000 mg	20 mL	5 mL
Cephazolin 1000 mg	20 mL	5 mL
Daptomycin 350 mg	10 mL	5 mL
Daptomycin 500 mg	10 mL	5 mL

Antibiotic in liquid form	Antibiotic vials	Volume of sterile water for injection to be added	Volume of solution to be taken to reconstitute the DAC hydrogel
Gentamicin 80mg / 2 mL	2 (= 4 mL)	1 mL	5 mL
Tobramicin 100mg / 2 mL	2 (= 4 mL)	1 mL	5 mL
Tobramicin 150mg / 2 mL	1 (= 2 mL)	3 mL	5 mL
Ciprofloxacin 200mg / 100 mL	1 (= 100 mL)	0 mL	5 mL
Ciprofloxacin 400mg / 100 mL	1 (= 200 mL)	0 mL	5 mL
Clindamicin 300mg / 2 mL	1 (= 2 mL)	3 mL	5 mL
Clindamicin 600mg / 4 mL	1 (= 2 mL)	1 mL	5 mL

Moreover, microbiological analysis has demonstrated a synergistic antibacterial effect of the hydrogel-antibiotic combination, compared to either component alone [48. 49], while both preclinical [51, 52] and clinical studies do not report any adverse event or any detrimental effect on bone healing or implant osteointegration. In 842

patients, at an average follow-up of 21.4 months, the DAC® hydrogel coating has been shown to be associated with approximately 10 times reduction in post-surgical implant-related infections (Table 5).

	Average Follow-Up	CONTROLS		TREATED	
Author and date of publication	Months	Patients	Post-surgical infections	Patients	Post-surgical infections
Romanò et al. (2016) [53]	14.5	184	11	189	1
Malizos et al. (2017) [54]	18.1	127	6	126	0
Capuano et al. (2018) [50]	29.3	22	3	22	2
Zagra et al. (2019) [55]	30	27	4	27	0
De Meo et al. (2020) [56]	12	17	6	17	0
Zoccali et al. 2021) [57]	24	42	6	42	0
Total	21.4 ± 7.5	419	36 (8.6%)	423	3 (0.7%)

CONCLUSIONS

Implant-related infections are projected to grow over the next decade. These are associated with increased rates of morbidity and mortality and have a significant social and economic impact on the society and health care systems. Despite the recognized need to curtail implant-related infection, only a few clinically applicable technologies are currently available in orthopaedics and trauma. Given the potential benefits that can be anticipated scientifically by a wider application of antibacterial implant coating technologies, with a well demonstrated positive cost-benefit ratio [58, 59], all effort should be made to increase the awareness of health care providers and implement the technology in health care systems to potentially mitigate the septic complication.

Furthermore, specific reimbursements for the currently available coatings should be introduced, with faster and more affordable regulatory pathways for the most promising technologies in the pipeline. At the same time, an efficient and independent post-marketing surveillance system need to be set at national or international level, to monitor the clinical results and promptly report on any possible side effect or long-term complication of such new technologies.

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