MENTORS IN ORTHOPEDICS

ANTIBACTERIAL HYDROGEL COATING OF IMPLANTS IN ORTHOPEDICS AND TRAUMA: SURGICAL TECHNIQUE AND CLINICAL APPLICATIONS

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SUMMARY

Background: Implant-associated infections and subsequent biofilm formation remain primary causes of orthopedic surgery failure, affecting up to 80% of bacterial infections and resulting in significant socioeconomic burdens. Bacterial colonization typically occurs within hours of implantation, creating a protective intercellular matrix that resists systemic antimicrobial therapy and host immune responses.

Objective: This article describes the surgical application, technical specifications, and clinical outcomes of a fast-resorbable, hyaluronic acid-based hydrogel coating designed to prevent bacterial adhesion on orthopedic and trauma implants.

Key Points: The Defensive Antibacterial Coating (DAC®) consists of hyaluronic acid grafted to polylactic acid. This biocompatible hydrogel acts as a physical barrier against microbial colonization and can be intraoperatively loaded with antibiotics, such as vancomycin or meropenem, at concentrations of 2% to 5%. The coating is compatible with various biomaterials, including titanium, cobalt-chrome, and polyethylene, and retains 60% to 80% adherence following press-fit insertion. Clinical data from 724 patients indicate an eightfold reduction in early post-surgical infections compared to uncoated controls. No adverse effects on bone healing, osseointegration, or systemic laboratory markers have been reported. The hydrogel undergoes complete resorption within 72 hours, coinciding with the window of maximum infection risk.

Conclusion: The application of a resorbable, antibiotic-loaded hydrogel provides a versatile and safe method for reducing peri-prosthetic and fracture-related infections. This technology effectively bridges the gap between initial implantation and host tissue integration by inhibiting early biofilm formation without compromising long-term implant stability.

KEYWORDS

Arthroplasty, Replacement; Biofilms; Hyaluronic Acid; Prosthesis-Related Infections; Fracture Fixation, Internal

INTRODUCTION

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 ranges 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 numbers.

Whenever a biomaterial is implanted, a competition between the host's and the bacterial cells takes place 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 (Fig.1) [13].

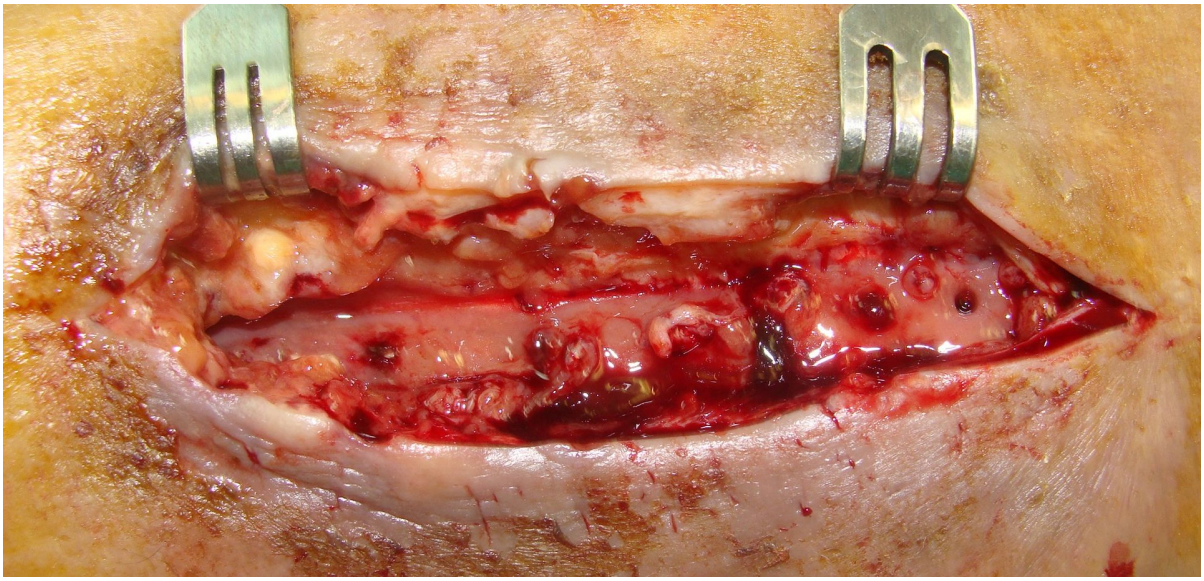


Figure 1. Naked eye visible bacterial biofilm in a septic non-union of the distal third of the fibula, after the infected metallic plate and screws had been removed.

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 (Fig. 2). Once established, the biofilms efficiently protect the microorganisms both from the host's immune system and from the systemically administered antibiotics.

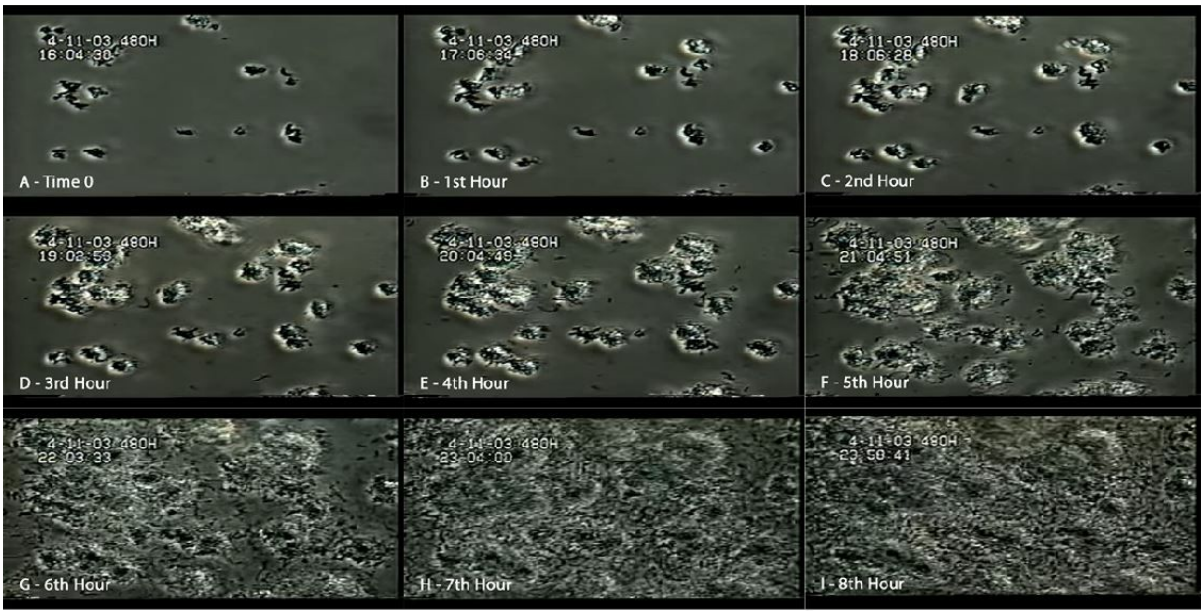


Figure 2. Time course of bacterial colonization and biofilm formation on a dental surface. In less than 10 hours the biofilm is fully formed and the bacteria may survive and replicate, protected from local environment assaults, including most of the immunological, chemical or physical factors (redrawn from https://www.youtube.com/watch?v=hAodAX_xjpY)

The colonization of the implant from the bacteria is then decided at the very time of surgery and takes place within few hours 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]. In spite of 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.

Recently, a fast-resorbable, hyaluronic-based hydrogel coating - DAC®, "Defensive Antibacterial Coating" (Novagenit Srl, Mezzolombardo, TN - Italy). was developed to protect implanted biomaterials in orthopedics, trauma and maxillo-facial surgery. Currently this is the first and the only antibacterial coating solution specifically designed to be applied to all cementless and hybrid (partially cemented) implants and to protect all the implant surfaces. Preclinical and clinical testing did show the safety and the efficacy of the device, that acts as a physical barrier to bacterial adhesion and is able to reduce biofilm formation. Moreover, the hydrogel, which is directly applied by the surgeon at the time of surgery, can be intra-operatively mixed with one or more antibacterial agents, in order to enhance the killing of planktonic bacteria that may remain in the local environment.

In this paper we present the surgical technique, including the preparation, application and tips and tricks related to the use of this technology in orthopedics and trauma, with a short summary of the most relevant clinical outcomes concerning safety and efficacy.

THE DAC® HYDROGEL COATING

The "Defensive Antibacterial Coating" is the first hydrogel coating of orthopedic and trauma implants, based on hyaluronic acid (HA), grafted to polylactic acid (PLA). 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 [17] and has several clinical applications in dermatology, aesthetic surgery, dentistry, urology, orthopedics and ophthalmology [18]. 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 [19]. 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 in order to design a sufficiently stable HA-based antibacterial coating for use in orthopedics, a combination of HA with polylactic acid was investigated [20]. In fact, PLA is a synthetic polyester, widely used for orthopedic implants [21]. 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. [22]

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.

PREPARATION AND SURGICAL TECHNIQUE

The DAC® hydrogel received the CE mark at the end of year 2013 and, as of March 2019, it is available in all European Countries, Australia, Israel, New Zealand, South Africa, Switzerland and United Kingdom. Pending registrations are in Argentina, Brazil, Colombia, Japan and the U.S.A. Currently, the available kits for orthopedics and trauma (www.dac-coating.com or www.coatingdac.com) include a prefilled syringe, containing the sterile DAC® powder, one complete set of sterile components (connector, backstop and spreader) and one empty graduated syringe (Fig. 3). The DAC® kit should be stored in a refrigerator at a temperature between 2 and 8 °C. Do not freeze.

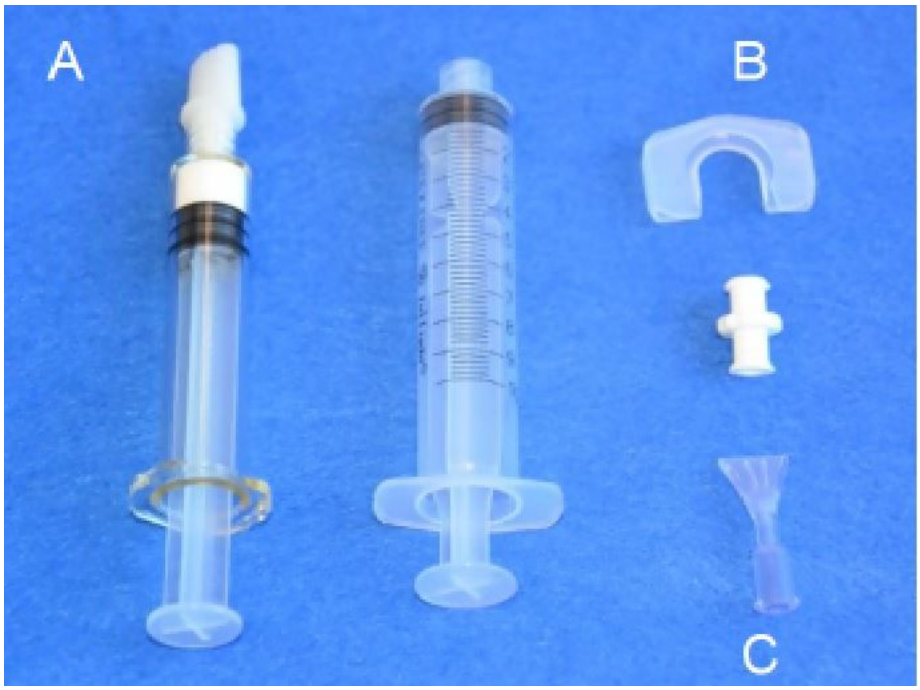
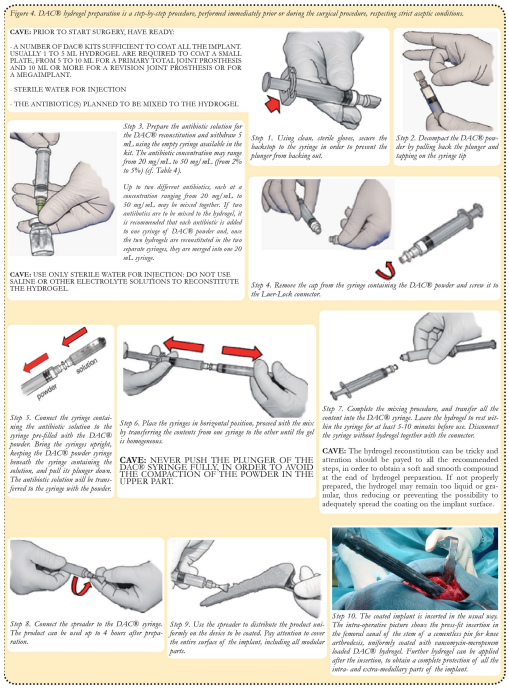


Figure 3. The DAC® kit includes a prefilled syringe containing the DAC® powder (A), a backstop and a connecting system for the hydrogel preparation (B) and a spreader to facilitate the hydrogel application on the implant surface, at the time of surgery.

The main element of DAC® kit is the substance powder contained in the prefilled syringe. This powder, to be reconstituted before use with water for injection, forms a hydrogel with appropriate physical-chemical properties to be distributed evenly on the surfaces to be protected. The different kits contain material to prepare 2 to 15 mL of hydrogel. Five millilitres of hydrogel cover approximately 110 cm2 surface, with a 0.45 mm thick layer. Then, the choice of one kit rather than the other essentially depends on the size of the surface that is intended to be covered.

The preparation of the DAC® hydrogel is performed at surgery, respecting strict aseptic conditions. The hydrogel preparation takes approximately 3 to 5 minutes and can be performed immediately prior or during the surgical procedure. From a practical point of view, whenever possible it is recommended to prepare the hydrogel some minutes prior or at skin incision. This will allow the hydrogel to rest and will save time at the moment of the implant insertion. Once prepared, the hydrogel may remain at ambient temperature in a safe place on the surgical

table for up to 4 hours, without any notable change in its chemo-physical properties. The DAC® hydrogel preparation is a step-by-step procedure (Fig. 4), that can be easily performed by one of the surgeons or, more often, by a trained nurse.



THE "ALL IMPLANT(S) CONCEPT" AND CURRENT CLINICAL APPLICATIONS

At variance with all other existing antibacterial coating technologies, the DAC® hydrogel has been designed to offer an "ALL IMPLANT(S)" coating ability. In fact, the hydrogel can be used to protect various surfaces, including titanium alloys, nickel-chrome, cobalt-chrome, stainless steel, hydroxyapatite (Fig. 5), polyethylene or other polymeric biomaterials.

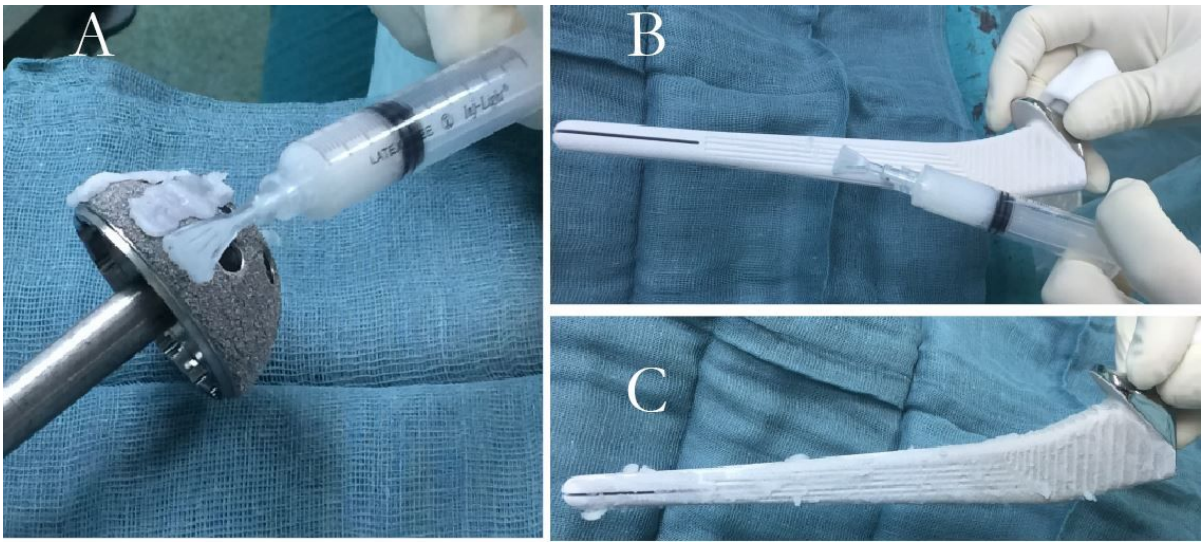


Figure 5. According to the concept of "ALL IMPLANT – ALL IMPLANTS" coating protection, the DAC® hydrogel has been used to protect different metallic and non-metallic implants, without any notable side effect or interference with osteointegration. Here is shown its application on a titanium acetabular cup (A) and on a hydroxyapatite surface of a femoral stem implant (B and C).

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 [23]. Moreover, the DAC® coated implants can be press-fit inserted with the usual surgical technique. In fact, 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 [24]. 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, not only all the surface in contact with the bone needs to be coated, but also 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. 6).

Figure 6. Application of the DAC® hydrogel to a polyethylene insert of a revision knee prosthesis (A) and to the interlocking parts of a modular hip megaimplant (B and C).

In fact, while 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 also the extra-medullary parts of the implant may be equally beneficial to reduce the chance of bacterial adherence and progressive colonization of the intra-medullary aspect of a device (Fig. 7).

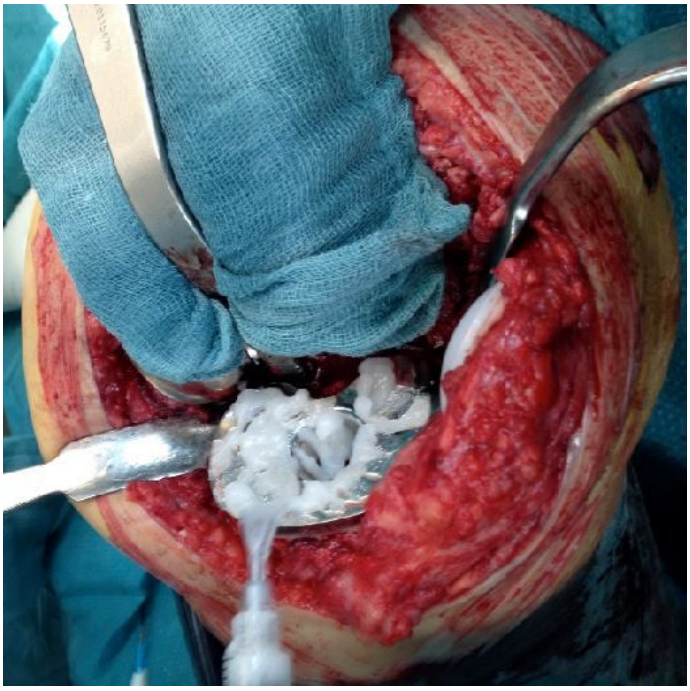


Figure 7. The DAC® coating is applied to the extra-medullary part of the tibial component of a revision knee prosthesis.

On the other hand, according to the concept of "ALL IMPLANTS" coating, the hydrogel can be applied to virtually all types of primary or revision cementless or hybrid joint prostheses, thus allowing the surgeon to choose the most suitable implant in any given case (Fig. 8).

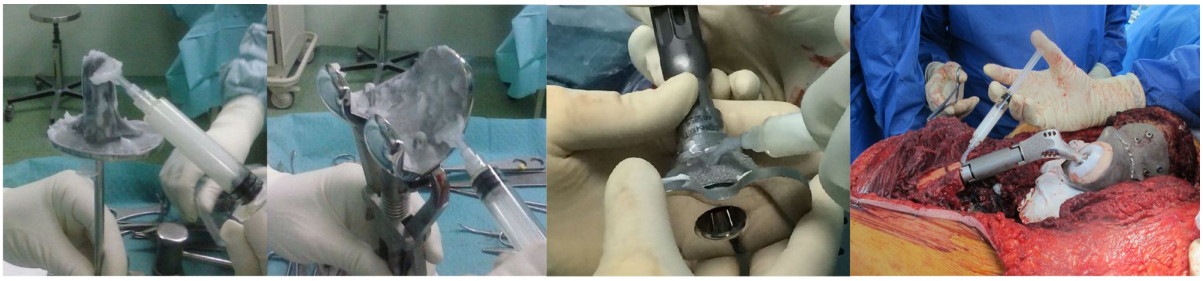


Figure 8. Application of the DAC® coating to a cementless knee primary implant (A), or to a knee revision prosthesis (B). In (C) the application to a femoral megaprosthesis is shown, after the custom-made acetabular component has been already completely coated with the hydrogel. Generally, to coat a primary hip or knee prosthesis, approximately 5 to 10 mL of hydrogel are needed, while for a revision prosthesis or a megaimplant, more than 10 mL may be required, depending on the size and the design of the prosthesis.

Similarly, for trauma patients, the coating can be used to protect all internal osteosynthesis, including plates, screws and intramedullary nails (Fig. 9).

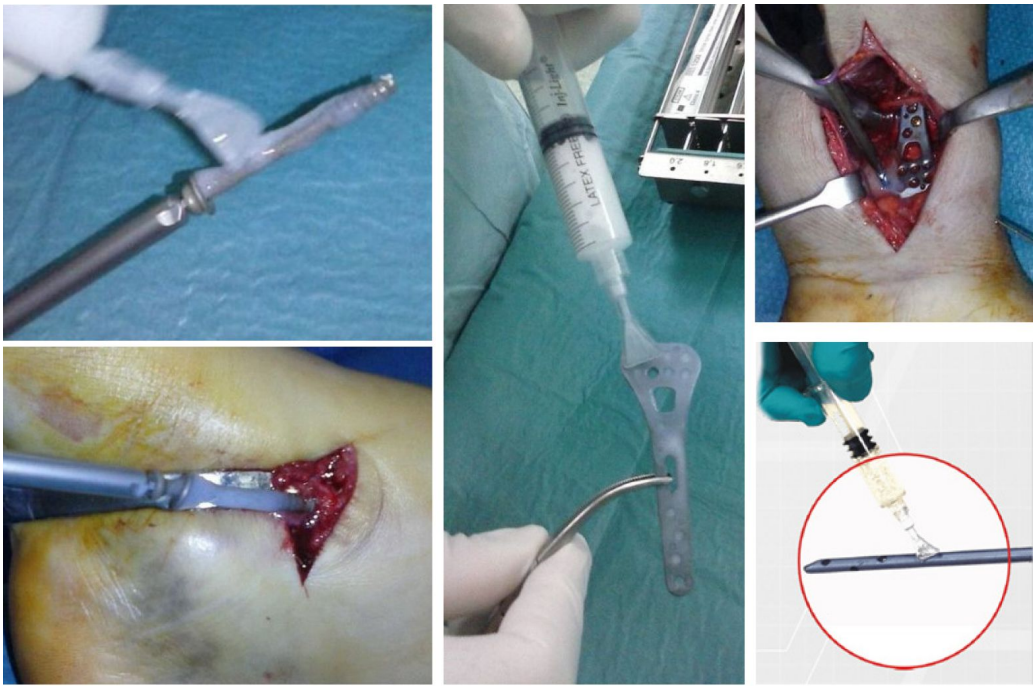


Figure 9. Examples of application of the DAC® coating to a screw, used to fix a medial malleolus fracture (A and B) and to metallic plates, used to fix a wrist fracture (C and D). Intramedullary nails may also be coated with the hydrogel prior to their insertion (E).

Furthermore, the antibiotic-loaded DAC® hydrogel coating can be used successfully in infected cases, for one-stage exchange procedure in peri-prosthetic infection [25] (Fig. 10).

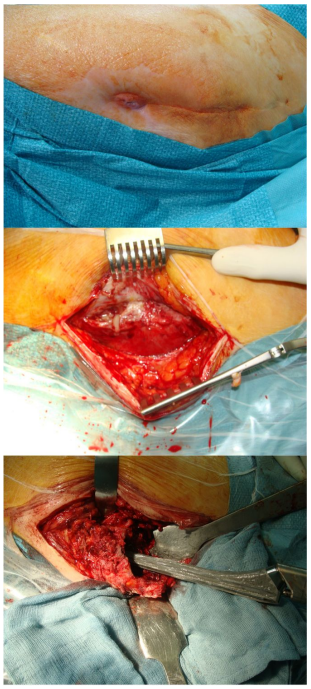


Figure 10. One-stage exchange with DAC® coated cementless hip prosthesis for the management of a peri-prosthetic hip infection. (A) Pre-operative clinical aspect, with draining sinus; (B) at surgery, subfascial purulent fluid collection; (C) one-stage joint revision with a cementless, coated implant.

In these cases, it still remains crucial, however, that an accurate surgical debridement is performed and that all infected tissues and contaminated foreign materials are removed.

RATIONALE FOR INTRA-OPERATIVE MIXING OF DAC® HYDROGEL COATING WITH ANTIBACTERIAL AGENTS

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 [22, 23]. 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.

However, since the hydrogel coating has no bactericidal activity in itself, it may be anticipated that, whenever the immune system should fail to destroy the planktonic microorganisms, these may still have the chance to recolonize the implant and the surrounding tissues at a later stage, when the coating will be hydrolyzed or covered by the host's proteins. This observation supports the ancillary function exerted by the antibiotic(s), that may be loaded intra-operatively to the DAC® hydrogel, in order to minimize the possibility for planktonic bacteria, which may eventually remain in the local environment, to overcome the anti-fouling ability of the coating at a later stage, once the coating hydrolysis proceeds (Fig. 11) [22]. Several studies have shown the ability of the hydrogel to be loaded and to completely release all the tested antibiotics (Table 2) in less than 72 hours [24].

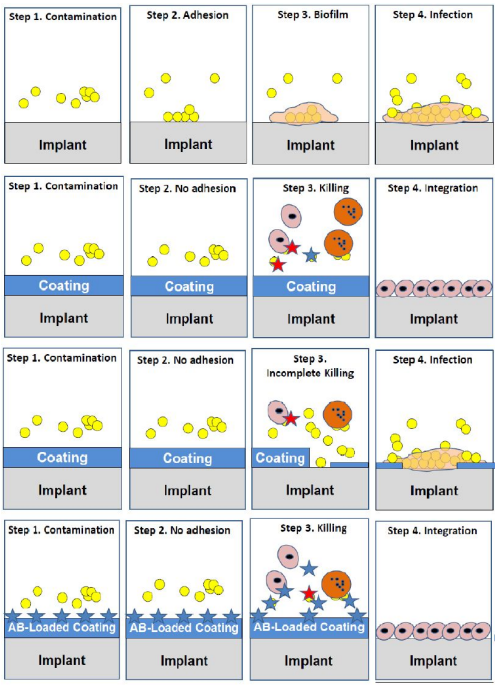


Figure 11. DAC® hydrogel coating: rationale for antibiotic loading, according to various possible scenarios.

Antibiotic/Antifungal
Amphotericin
Cephazolin
Ciprofloxacin
Daptomycin
Gentamicin
Meropenem
Rifampicin
Teicoplanin
Tigeciclin
Vancomycin

Table 2. A selection of some antibiotics that have been tested safe to be loaded intra-operatively with the DAC® hydrogel.

Moreover, microbiological analysis has demonstrated a synergistic antibacterial effect of the hydrogel-antibiotic combination, compared to either component alone [23. 24], while both preclinical [26, 27] and clinical studies (see below) have confirmed the absence of any measurable side effect of the antibiotic-loaded DAC® hydrogel coating.

From a practical point of view, antibiotic loading of the hydrogel can be easily performed at surgery, at the same time as the hydrogel is reconstituted (cf. Fig. 4).

To this aim, the water for injection is first used to dilute the antibiotic(s) chosen by the surgeon and then to reconstitute the hydrogel. The antibiotic concentration may range from 20 mg/mL to 50 mg/mL (or from 2% to 5%) (Table 3). It should be noted, in this regard, that, according to an in vivo model of implant-related infection in the rabbit, vancomycin 2% appears equally effective as 5% [26].

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 80 mg / 2 mL	2 (= 4 mL)	1 mL	5 mL
Tobramicin 100 mg / 2 mL	2 (= 4 mL)	1 mL	5 mL
Tobramicin 150 mg / 2 mL	1 (= 2 mL)	3 mL	5 mL
Ciprofloxacin 200 mg / 100 mL	1 (= 100 mL)	0 mL	5 mL
Ciprofloxacin 400 mg / 100 mL	1 (= 100 mL)	0 mL	5 mL
Clindamicin 300 mg / 2 mL	1 (= 2 mL)	3 mL	5 mL
Clindamicin 600 mg / 4 mL	1 (= 2 mL)	1 mL	5 mL

Table 3. Charts showing the proportion of antibiotic and water for injection needed to intra-operatively reconstitute the DAC® hydrogel in order to load it with some antibiotics currently available in powder or liquid form.

Up to two different antibiotics, each at a concentration ranging from 20 mg/mL to 50 mg/mL, may also be mixed together. The most often used combination has been vancomycin 5% and meropenem 5%, however other combinations are possible.

In case two antibiotics are to be loaded, it is recommended to add each antibiotic in one separate syringe of DAC® powder. Once the two hydrogels are reconstituted, the content of the two syringes can be merged into one 20 mL syringe.

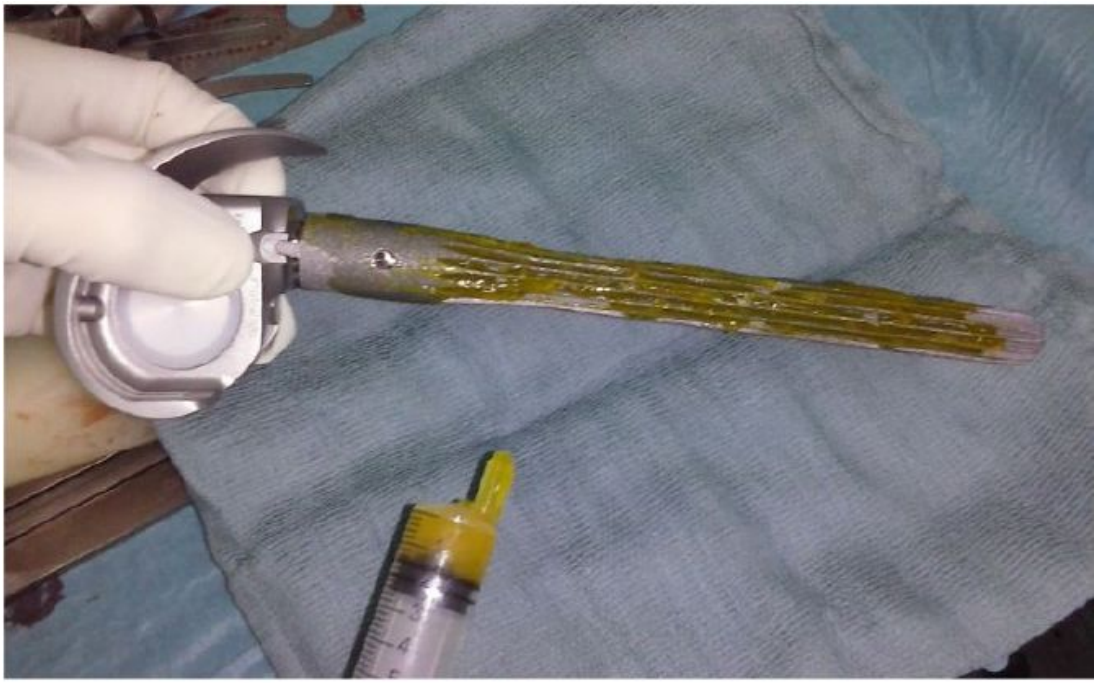


Figure 12. Tigeciclin-loaded DAC® hydrogel coating, applied at surgery on a knee revision prosthesis. The hydrogel may change its color, according to the type of the antibiotic that is loaded.

SUMMARY OF SAFETY AND CLINICAL RESULTS

Since its very first introduction in the market in 2013, no adverse events had ever been reported concerning the clinical use of the DAC® hydrogel either used alone or in combination with antibacterial agents (Novagenit Srl, data on file).

In particular, all published studies did report the absence of any side effect or adverse event attributable to the DAC® hydrogel and no detrimental effect on bone healing or implant osteointegration (Table 4).

Author and date of publication	Mean Follow-Up (Months)	Treated Patients	Number of Adverse Events Related to the DAC Hydrogel
Romanò et al. (2016) [43]	14.5	189	0
Malizos et al. (2017) [44]	18.1	126	0
Capuano et al. (2018) [40]	29.3	22	0
Zagra et al. (2019) [45]	30	27	0
Zoccali et al. (2019) [46]	18	47	0
Total	24 ± 8	411	0

Table 4. Summary of data available from published clinical studies, concerning DAC® hydrogel safety.

Concerning efficacy, overall, at an average follow-up of 25.8 months post-operatively, the DAC® hydrogel coating has been shown to be associated with approximately an 8 times reduction of post-surgical implant-related infections, in a total of 724 patients, (Table 5).

Author and date of publication	Mean Follow-Up (Months)	Controls	Post-surgical infections	Treated Patients	Post-surgical Infections
Romanò et al. (2016) [43]	14.5	184	11	189	1
Malizos et al. (2017) [44]	18.1	127	6	126	0
Capuano et al. (2018) [40]	29.3	22	3	22	2
Zagra et al. (2019) [45]	30	27	4	27	0
Total	25.8 ± 6.7	360	24 (6,7%)	364	3 (0.8%)

Table 5. Summary of data available from published comparative clinical studies, concerning DAC® hydrogel efficacy.

CONCLUSIONS

Biofilm- and implant-related infections represent a dramatic and increasing burden worldwide. Available data show that hyaluronic acid has a proven in vitro antiadhesive/antibiofilm effect against some of the most common pathogens and HA has been used safely, alone or in combination with other polymers, with satisfactory results in different conditions associated with biofilm-related chronic infections. Clinical data in various applications, including dentistry, urology, wound management, dermatology and orthopedics paved the way to the possible use of HA as a protective coating barrier of implants. The chemical derivatization of hyaluronic acid with polylactic acid, allows the formation of graft copolymers which, when contacted with an aqueous medium, can be used to produce hydrogels, like the recent CE marked DAC®, with appropriate characteristics of stability, ease-of-use and safety for a coating device.

The resulting medicated hydrogel is transparent, easily spreadable over a surface, like a titanium prosthesis and has a specifically designed duration. Moreover, it has proven, peculiar, anti-adhesive and anti-biofilm capabilities. If required, it may also be easily loaded, at surgery, with antibacterial agents, that will be released over the following hours or few days in effective high local concentrations.

Clinical results point out the efficacy of the DAC® coating to significantly reduce early post-surgical infection after joint replacement or internal osteosynthesis, without any detectable local side effect both concerning wound and bone healing. Moreover, no changes in organ-specific serum markers or systemic unwanted effects were noted. The high biocompatibility of its basic constituents and the short time (less than three days) needed for a complete hydrogel resorption, make the occurrence of long-term side effects quite unlikely. The versatility of the device and its safety profile may open the way to a larger scale application in orthopedics and trauma and in all other surgeries that share the use of implantable biomaterials.

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