

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

Romanò CL<sup>1,2</sup>, Battaglia A<sup>3</sup>, Suardi V<sup>3</sup>, Romanò D<sup>4</sup>, Baldi A<sup>5</sup>, Zoccali C<sup>5</sup>

1- Studio Medico Cecca-Romano - Milano, Italy

2- Romano Institute - Tirane, Albania - [mail@romano.institute](mailto:mail@romano.institute)

3- Università degli Studi - Scuola di specializzazione Ortopedia, Milano, Italy

4- Department of Reconstructive Surgery of Osteo-articular Infections C.R.I.O. Unit, I.R.C.C.S. Galeazzi Orthopaedic Institute - Milano, Italy

5- Oncological Orthopedics, Regina Elena National Cancer Institute, Rome, Italy

## INTRODUCTION

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

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)<sup>[13]</sup>. 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. 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<sup>[14]</sup>, 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.<sup>[15]</sup> 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.<sup>[16]</sup>

In fact, while antibacterial coating of implants is advocated by many as a possible solution to reduce the burden

- **Leading reason for revision:** Peri-prosthetic hip and knee infection is among the first three reasons for joint replacement failure, according to the registers;<sup>[6]</sup>

- **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<sup>[3]</sup>.

- **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%<sup>[9]</sup>. The incidence of SSI after Gustilo 2 or 3 open fractures of the long bones is > 20%<sup>[10]</sup>

- **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<sup>[7]</sup>. The RR for patients undergoing hip revision for PJI, compared with aseptic hip revision range from 1.87 to 3.10;<sup>[8]</sup>

- **Additional costs:** the average cost of management of infection after hip fracture surgery is > 30,000 Euros<sup>[8]</sup>. The cost of any single case of hip or knee PJI management ranges from 40,000 to > 100,000 Euros<sup>[11, 12]</sup>.

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



Fig. 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.

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" (No-

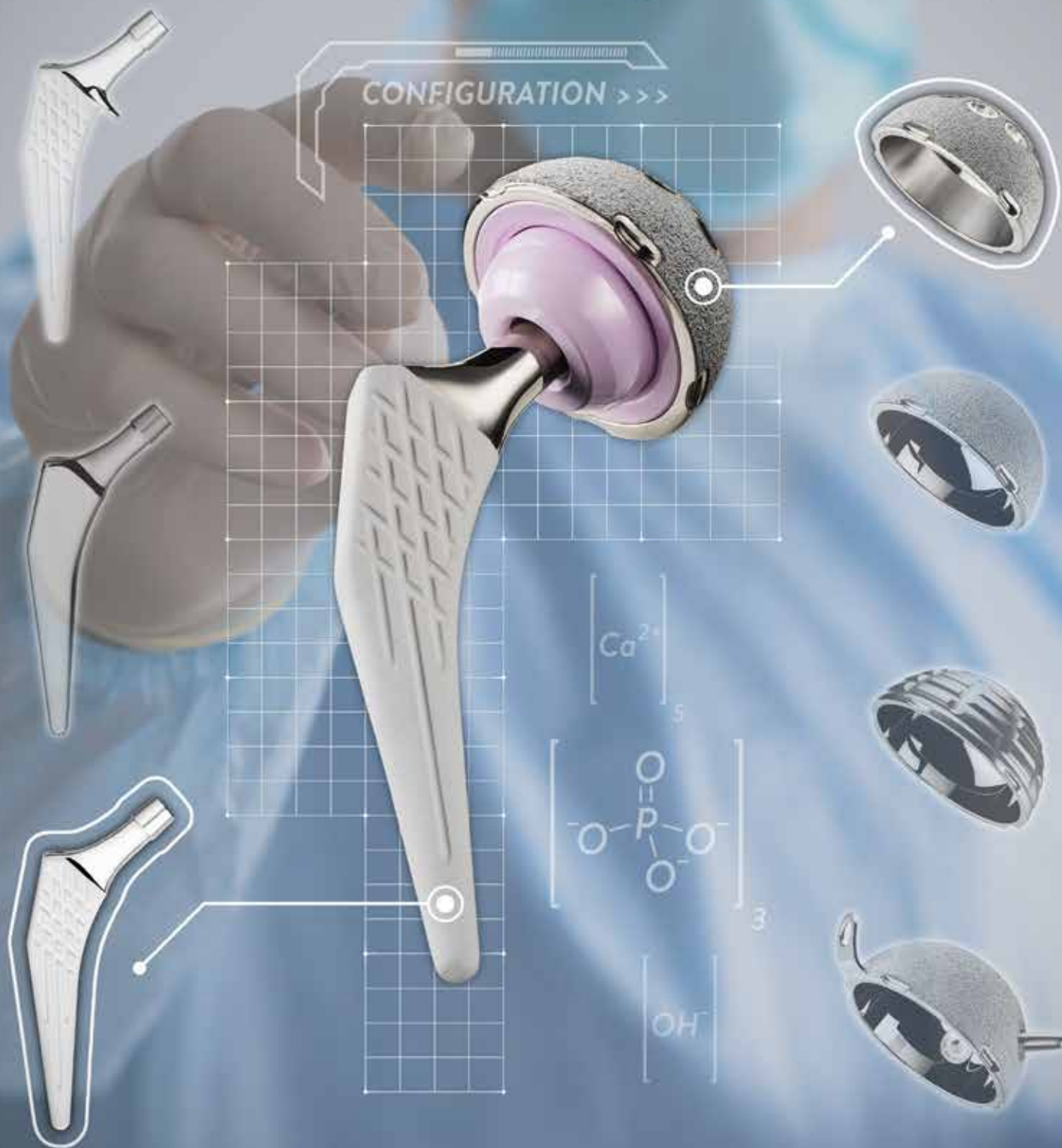
vagenit Srl, Mezzolombardo, TN - Italy). was developed to protect implanted biomaterials in orthopedics, trauma and maxillo-facial surgery. Currently this is the first and the only antibacterial coating solution specifically designed to be applied to all cementless and hybrid (partially

# SYMBOL®

## One range, One sole instrumentation set

Femoral stem, Dual mobility cup, Revision cup, Cemented, Ceramic cup

CONFIGURATION >>>



[www.dediennesante.com](http://www.dediennesante.com)

Le Mas des Cavaliers, 217 rue Nungesser - 34130 Mauguio

Tél. : +33 (0)4 66 28 06 85

**DEDIENNE SANTÉ**

Date de création : avril 2018 - Fabricant : DEDIENNE SANTÉ - Nom du produit : SYMBOL® - Destination : remplacement mécanique total de l'articulation de la hanche, Classe du DM: III - Remboursable par les organismes d'assurance maladie dans certaines situations : consulter les modalités sur le site ameli.fr - Indications et recommandations d'utilisation : il convient de lire attentivement les instructions des étiquettes et les notices d'utilisation du produit. Ce dispositif médical est marqué par le LNE/G-MED (CE 0459).



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].

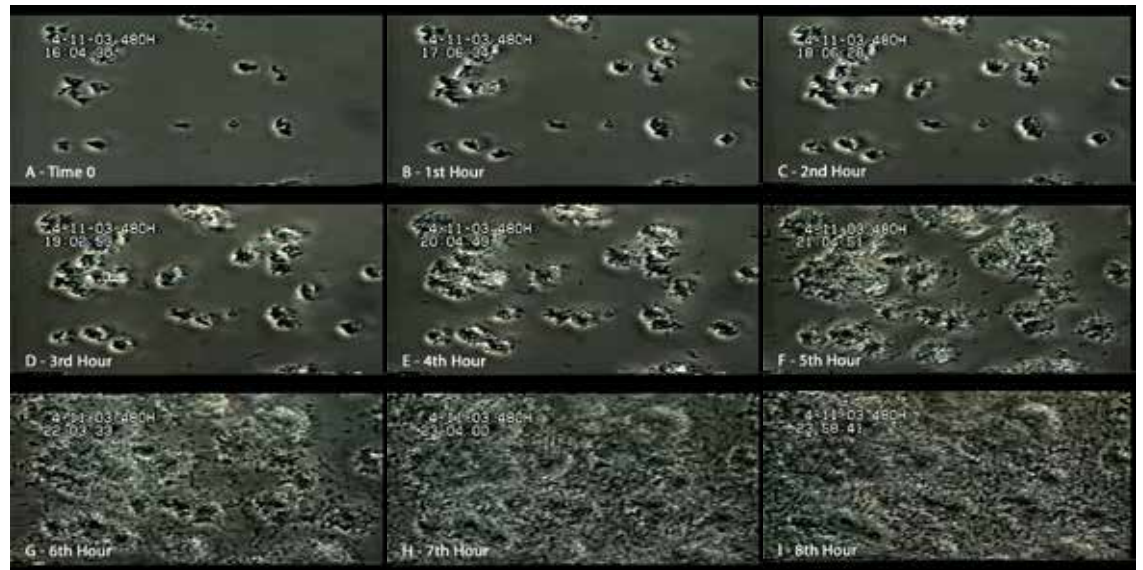


Fig. 2. Time course of bacterial colonization and biofilm formation on a dental surface. In less than 10 hours the biofilm is fully formed and the bacteria may survive and replicate, protected from local environment assaults, including most of the immunological, chemical or physical factors (redrawn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

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](http://www.dac-coating.com) or [www.coatingdac.com](http://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.

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 cm<sup>2</sup> 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



Fig. 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.

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. 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). 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).

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

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

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.



Figure 4. DAC® hydrogel preparation is a step-by-step procedure, performed immediately prior or during the surgical procedure, respecting strict aseptic conditions.

**CAVE:** PRIOR TO START SURGERY, HAVE READY:

- A NUMBER OF DAC® KITS SUFFICIENT TO COAT ALL THE IMPLANT. USUALLY 1 TO 5 ML HYDROGEL ARE REQUIRED TO COAT A SMALL PLATE, FROM 5 TO 10 ML FOR A PRIMARY TOTAL JOINT PROSTHESIS AND 10 ML OR MORE FOR A REVISION JOINT PROSTHESIS OR FOR A MEGAIMPLANT.
- STERILE WATER FOR INJECTION
- THE ANTIBIOTIC(S) PLANNED TO BE MIXED TO THE HYDROGEL.



Step 1. Using clean, sterile gloves, secure the backstop to the syringe in order to prevent the plunger from backing out.



Step 2. Decompact the DAC® powder by pulling back the plunger and tapping on the syringe tip



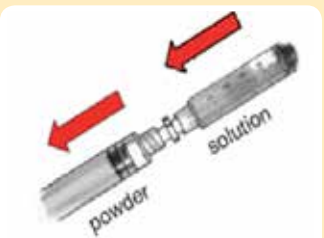
Step 3. Prepare the antibiotic solution for the DAC® reconstitution and withdraw 5 mL using the empty syringe available in the kit. The antibiotic concentration may range from 20 mg/mL to 50 mg/mL (from 2% to 5%) (cf. Table 4).

Up to two different antibiotics, each at a concentration ranging from 20 mg/mL to 50 mg/mL may be mixed together. If two antibiotics are to be mixed to the hydrogel, it is recommended that each antibiotic is added to one syringe of DAC® powder and, once the two hydrogels are reconstituted in the two separate syringes, they are merged into one 20 mL syringe.

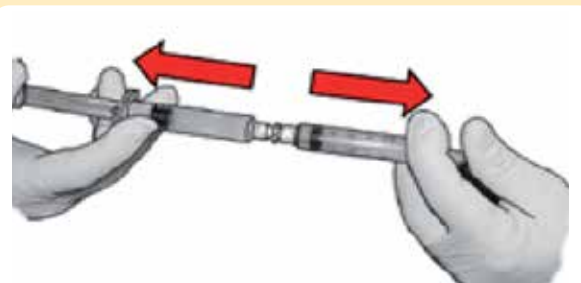
**CAVE:** USE ONLY STERILE WATER FOR INJECTION; DO NOT USE SALINE OR OTHER ELECTROLYTE SOLUTIONS TO RECONSTITUTE THE HYDROGEL.



Step 4. Remove the cap from the syringe containing the DAC® powder and screw it to the Luer-Lock connector.



Step 5. Connect the syringe containing the antibiotic solution to the syringe pre-filled with the DAC® powder. Bring the syringes upright, keeping the DAC® powder syringe beneath the syringe containing the solution, and pull its plunger down. The antibiotic solution will be transferred to the syringe with the powder.



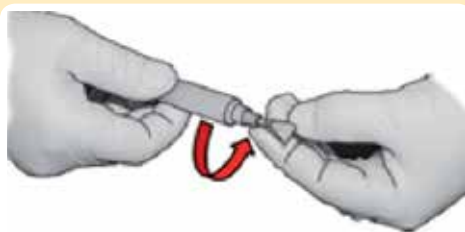
Step 6. Place the syringes in horizontal position, proceed with the mix by transferring the contents from one syringe to the other until the gel is homogeneous.

**CAVE:** NEVER PUSH THE PLUNGER OF THE DAC® SYRINGE FULLY, IN ORDER TO AVOID THE COMPACTION OF THE POWDER IN THE UPPER PART.

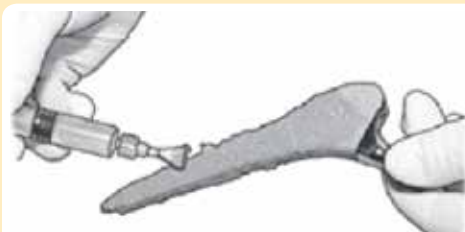


Step 7. Complete the mixing procedure, and transfer all the content into the DAC® syringe. Leave the hydrogel to rest within the syringe for at least 5-10 minutes before use. Disconnect the syringe without hydrogel together with the connector.

**CAVE:** The hydrogel reconstitution can be tricky and attention should be paid to all the recommended steps, in order to obtain a soft and smooth compound at the end of hydrogel preparation. If not properly prepared, the hydrogel may remain too liquid or granular, thus reducing or preventing the possibility to adequately spread the coating on the implant surface.



Step 8. Connect the spreader to the DAC® syringe. The product can be used up to 4 hours after preparation.



Step 9. Use the spreader to distribute the product uniformly on the device to be coated. Pay attention to cover the entire surface of the implant, including all modular parts.



Step 10. The coated implant is inserted in the usual way. The intra-operative picture shows the press-fit insertion in the femoral canal of the stem of a cementless pin for knee arthrodesis, uniformly coated with vancomycin-meropenem loaded DAC® hydrogel. Further hydrogel can be applied after the insertion, to obtain a complete protection of all the intra- and extra-medullary parts of the implant.



Each Step **We Care**

# U-Motion II™



XPE™

E-XPE™

## A FULL RANGE OF CUP PRIMARY & REVISION



Ti Plasma spray



HA/Ti Plasma spray



Ti Plasma spray



HA/Ti Plasma spray

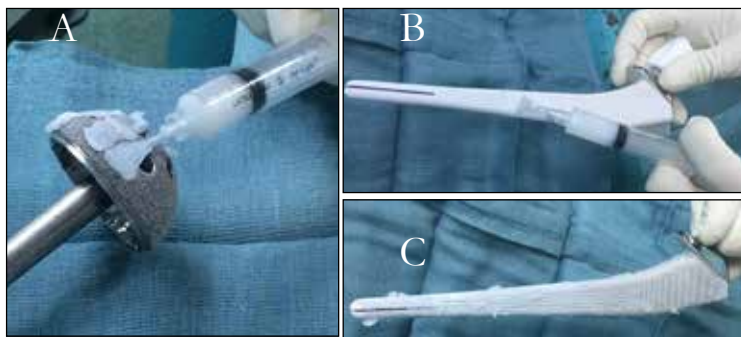


Since 1993, United Orthopedic has had the privilege of supplying world class orthopedic joint replacements, till now, had helped in 38 countries over 250 thousand suffering patients gain back their mobility and quality of life .

### UOC Europe

Avenue Général Guisan 60A, 1009 Pully, Switzerland  
Tel: +41 79 774 89 33 • [contact@uoc-europe.com](mailto:contact@uoc-europe.com)

[www.uoc-europe.com](http://www.uoc-europe.com)



**Fig. 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).

**CAVE:** The DAC® hydrogel is not designed and should not be mixed with bone cement or its components (polymethylmethacrylate, PMMA) at the time of their preparation. In fact, the hydrogel coating may only be eventually applied on the bone cement surface after its exothermal reaction is completed and the cement hardening has fully taken place.

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
Tobramycin 100 mg / 2 mL	2 (= 4 mL)	1 mL	5 mL
Tobramycin 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.

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 during 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%<sup>[26]</sup>.

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.

## 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 detri-

mental effect on bone healing or implant osteointegration (Table 4)

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).



**Fig. 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).



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





Fig. 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.

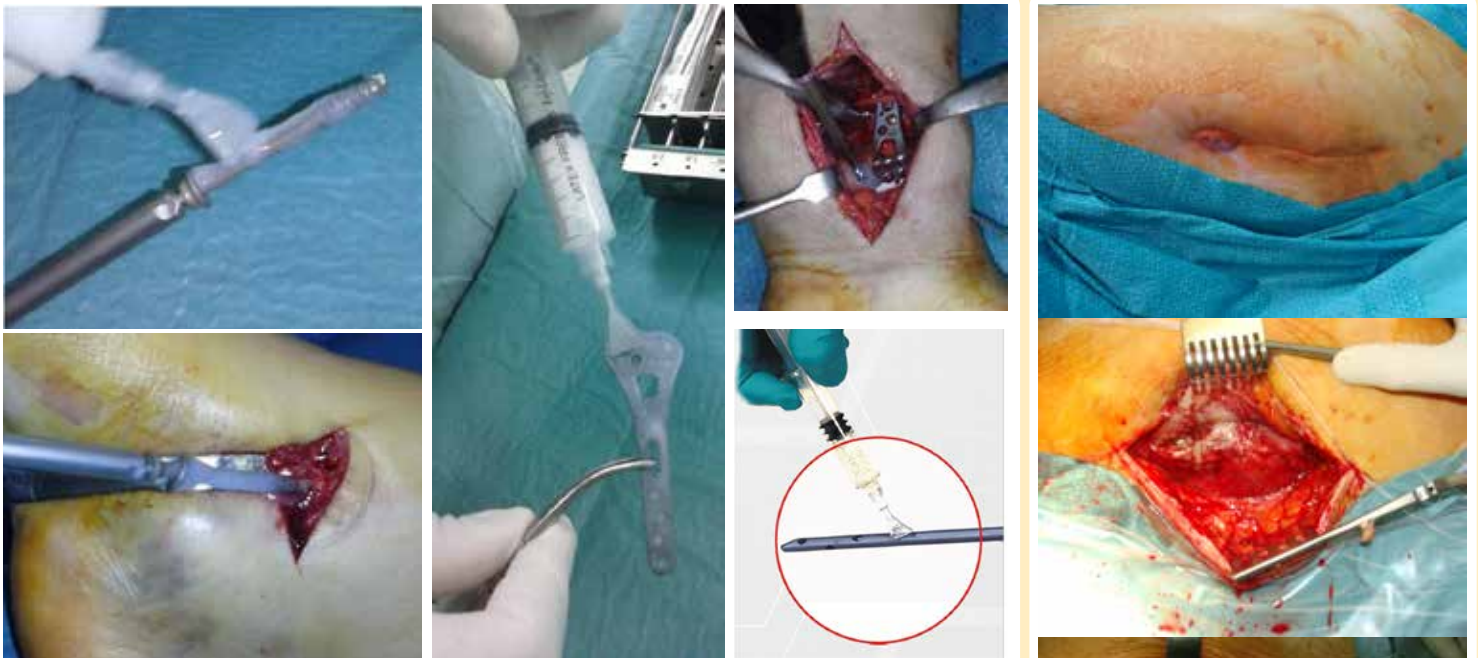


Fig. 9. Examples of application of the DAC® coating to a screw, used to fix a medial malleolus fracture (A and B) and to metallic plates, used to fix a wrist fracture (C and D). Intramedullary nails may also be coated with the hydrogel prior to their insertion (E).

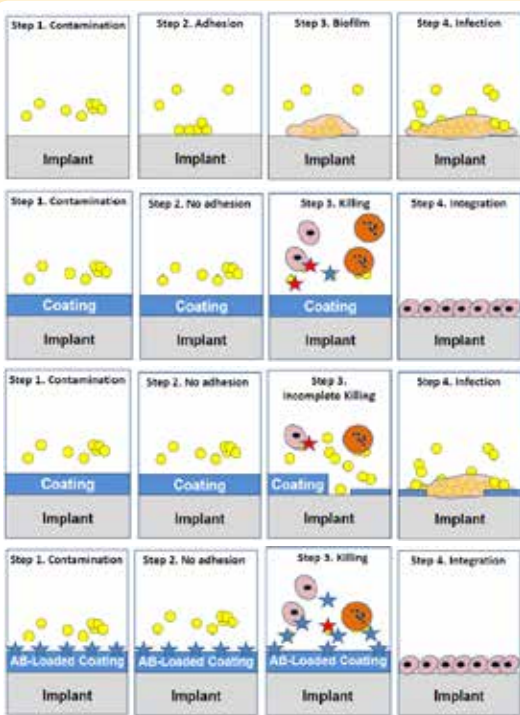


Figure 11. DAC® hydrogel coating: rationale for antibiotic loading, according to various possible scenarios.

A. Non-coated implants may get colonized by biofilm-forming bacteria (yellow circles) and infection will develop.

B. Anti-adhesive coating may reduce/prevent bacterial adhesion, while the immune system (orange circles and red stars) and the systemically administered antibiotics (blue star) kills all the planktonic microorganisms.

C. However, if bacterial load is large enough, or if the immune response and the local antibiotic levels are inadequate, surviving planktonic bacteria may eventually start colonizing the implant once the coating has been hydrolyzed or covered by the host's proteins.

D. To prevent this, the antibacterial hydrogel may be advantageously loaded, at the time of surgery, with antibiotic agents (blue stars), that are locally released by the hydrogel within 48 to 72 hours, contributing to eliminate all the remaining planktonic bacteria.

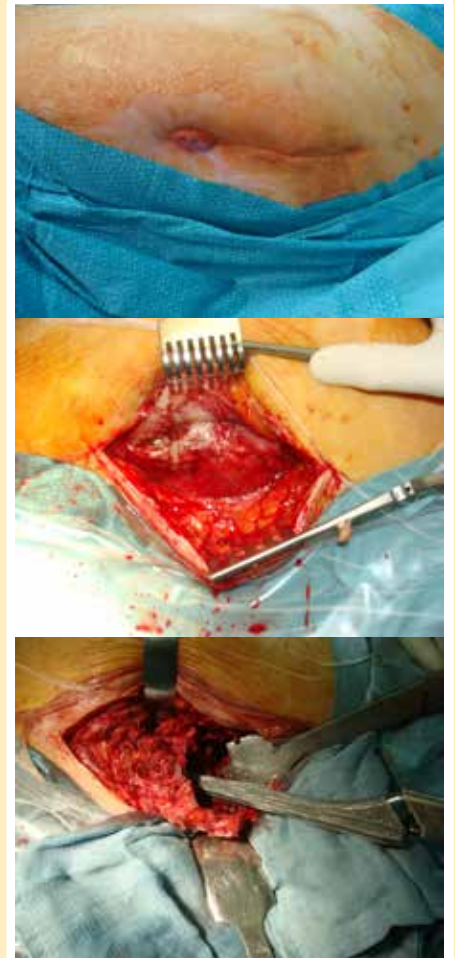


Fig. 10. One-stage exchange with DAC® coated cementless hip prosthesis for the management of a peri-prosthetic hip infection. (A) Pre-operative clinical aspect, with draining sinus; (B) at surgery, subfascial purulent fluid collection; (C) one-stage joint revision with a cementless, coated implant.



Fig. 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.



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
<b>Total</b>	<b>24 ± 8</b>	<b>411</b>	<b>0</b>

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

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
<b>Total</b>	<b>25.8 ± 6.7</b>	<b>360</b>	<b>24 (6,7%)</b>	<b>364</b>	<b>3 (0.8%)</b>

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. ■

NICE

SHOULDER COURSE

2020

June 4 - 6

Course Chairman  
PASCAL BOILEAU, MD

An Intensive 3-Day Course  
With Surgical Skills Labs and Live Surgery

Current Concepts

ARTHROSCOPY  
ARTHROPLASTY  
& FRACTURES

THE DIGITIZED  
SHOULDER

## References

- [1]. Roemling U, Balsalobre C. *Biofilm infections, their resilience to therapy and innovative treatment strategies*. J Intern Med 2012;272:541–61
- [2]. Romanò CL, Romanò D, Logoluso N, Drago L. *Bone and joint infections in adults: a comprehensive classification proposal*. European orthopaedics and traumatology. 2011;1(6):207-17
- [3]. Cats-Baril W, Gehrke T, Huff K, Kendoff D, Maltenfort M, Parvizi J. *International consensus on periprosthetic joint infection: description of the consensus process*. Clin Orthop Relat Res. 2013;471:4065–75
- [4]. Drago L, Lidgren L, Bottinelli E, Villafañe JH, Berjano P, Banfi G, Romanò CL, Sculco TP. (2016) *Mapping of microbiological procedures by the members of the International Society of Orthopaedic Centers (ISOC) for periprosthetic infections diagnosis*. J Clin Microbiol. 2016 Mar 2. pii: JCM.00155-16
- [5]. Parisi TJ, Konopka JF, Bedair HS. *What is the Long-term Economic Societal Effect of Periprosthetic Infections After THA? A Markov Analysis*. Clin Orthop Relat Res. 2017 Jul;475(7):1891-1900.
- [6]. Springer BD, Cahue S, Etkin CD, Lewallen DG, McGrory BJ. *Infection burden in total hip and knee arthroplasties: an international registry-based perspective*. Arthroplast Today. 2017;3(2):137–140. Published 2017 Jun 20. doi:10.1016/j.artd.2017.05.003.
- [7]. Gundtoft PH, Pedersen AB, Varnum C, Overgaard S. *Increased Mortality After Prosthetic Joint Infection in Primary THA*. Clin Orthop Relat Res. 2017;475(11):2623–2631. doi:10.1007/s11999-017-5289-6.
- [8]. Edwards C, Counsell A, Boulton C, Moran CG. *Early infection after hip fracture surgery: risk factors, costs and outcome*. J Bone Joint Surg Br. 2008 Jun;90(6):770-7. doi: 10.1302/0301-620X.90B6.20194.
- [9]. Bonneville P, Bonnomet F, Philippe R, Loubignac F, Rubens-Duval B, Talbi A, Le Gall C, Adam P; SOFCOT. *Early surgical site infection in adult appendicular skeleton trauma surgery: a multicenter prospective series*. Orthop Traumatol Surg Res. 2012 Oct;98(6):684-9.
- [10]. Oliveira PR, Carvalho VC, da Silva Felix C, de Paula AP, Santos-Silva J, Lima AL. *The incidence and microbiological profile of surgical site infections following internal fixation of closed and open fractures*. Rev Bras Ortop. 2016 Feb 2;51(4):396-9.
- [11]. Garrido-Gomez J, Arrabal-Polo MA, Girón-Prieto MS, Cabello-Salas J, Torres-Barroso J, Parra-Ruiz J. *Descriptive analysis of the economic costs of periprosthetic joint infection of the knee for the public health system of Andalusia*. J Arthroplasty 2013;28:1057e60.
- [12]. Kapadia BH, Johnson AJ, Issa K, Mont MA. *Economic evaluation of chlorhexidine cloths on healthcare costs due to surgical site infections following total knee arthroplasty*. J Arthroplasty 2013;28:1061e5.
- [13]. Dastgheyb S, Parvizi J, Shapiro IM, Hickok NJ, Otto M *Effect of Biofilms on Recalcitrance of Staphylococcal Joint Infection to Antibiotic Treatment*. J Inf Dis 2015;211:641–50
- [14]. Busscher HJ, van der Mei HC, Subbiahdoss G, Jutte PC, van den Dungen JJ, Zaai SA, et al. *Biomaterial-associated infection: locating the finish line in the race for the surface*. Science translational medicine. 2012;4(153):153rv10
- [15]. Romanò CL, Scarponi S, Gallazzi E, Romanò D, Drago L (2015) *Antibacterial coating of implants in orthopaedics and trauma: a classification proposal in an evolving panorama*. J Orthop Surg Res. 2015; 10: 157
- [16]. Moriarty TF, Grainger DW, Richards RG. *Challenges in linking preclinical anti-microbial research strategies with clinical outcomes for device-associated infections*. European cells & materials. 2014;28:112-28
- [17]. Volpi N, Schiller J, Stern R, Solt\_es L. *Role, metabolism, chemical modifications and applications of hyaluronan*. Curr Med Chem 2009;16:1718–45
- [18]. Leach J.B., Schmidt C.E. (2004): *Hyaluronan*. *Encyclopedia of Biomaterials and Biomedical Engineering*. Marcel Dekker, New York. 779–789
- [19]. Ardizzoni A, Neglia RG, Baschieri MC, Cermelli C, Caratozzolo M, Righi E, et al. *Influence of hyaluronic acid on bacterial and fungal species, including clinically relevant opportunistic pathogens*. J Mater Sci Mater Med 2011;22:2329–38.
- [20]. Pitarresi G, Palumbo FS, Calascibetta F, Fiorica C, Di Stefano M, Giammona G *Medicated hydrogels of hyaluronic acid derivatives for use in orthopedic field*. Int J Pharm. 2013 Jun 5;449(1-2):84-94. doi: 10.1016/j.ijpharm.2013.03.059. Epub 2013 Apr 12
- [21]. Laurencin, C., Lane, J.M., 1994. *Poly (lactic acid) and poly (glycolic acid): orthopedic surgery applications*. In: Brighton, C., Friedlaender, G., Lane, J.M. (Eds.), *Bone Formation and Repair*, Rosemont, Am. Acad. Orthop. Surg, pp. 325–339.
- [22]. Giammona G, Pitarresi G, Palumbo FS, Maraldi S, Scarponi S, Romanò CL (2018). *Hyaluronic-Based Antibacterial Hydrogel Coating for Implantable Biomaterials in Orthopedics and Trauma: From Basic Research to Clinical Applications*. 10.5772/intechopen.73203.
- [23]. Romanò CL, De Vecchi E, Bortolin M, Morelli I, Drago L. *Hyaluronic acid and its composites as a local antimicrobial/antiadhesive barrier*. Journal of Bone and Joint Infection. 2017;2(1):63-72.
- [24]. Drago L, Boot W, Dimas K, Malizos K, Hänsch GM, Stuyck J, Gawlita D, Romanò CL. *Does implant coating with antibacterial-loaded hydrogel reduce bacterial colonization and biofilm formation in vitro ? Clinical Orthopaedics and Related Research*. 2014 Nov;472(11):3311-3323.
- [25]. Capuano N, Logoluso N, Gallazzi E, Drago L, Romanò CL. *One-stage exchange with antibacterial hydrogel coated implants provides similar results to two-stage revision, without the coating, for the treatment of peri-prosthetic infection*. Knee Surg Sports Traumatol Arthrosc. 2018[ Nov;26(11):3362-3367.
- [26]. Giavaresi G, Meani E, Sartori M, Ferrari A, Bellini D, Sacchetta AC, Merauer J, Sambri A, Vocale C, Sambri V, Fini M, Romanò CL. *Efficacy of antibacterial-loaded coating in an in vivo model of acutely highly contaminated implant*. Int Orthop. 2014 Jul;38(7):1505-12.
- [27]. Boot W, Gawlita D, Nikkels PGJ, et al. *Hyaluronic Acid-Based Hydrogel Coating Does Not Affect Bone Apposition at the Implant Surface in a Rabbit Model*. Clin Orthop Relat Res. 2017;475(7):1911-1919.
- [28]. Romanò CL, Malizos K, Capuano N, Mezzoprete R, D'Arienzo M, Van Der Straeten C, Scarponi S, Drago L. *Does an Antibiotic-Loaded Hydrogel Coating Reduce Early Post-Surgical Infection After Joint Arthroplasty?* J Bone Jt Infect. 2016 Jul 19;1:34-41.
- [29]. Malizos K, Blauth M, Danita A, Capuano N, Mezzoprete R, Logoluso N, Drago L, Romanò CL. *Fast-resorbable antibiotic-loaded hydrogel coating to reduce post-surgical infection after internal osteosynthesis: a multicenter randomized controlled trial*. J Orthop Traumatol. 2017 Jun;18(2):159-169.
- [30]. Zagra L, Gallazzi E, Romanò D, Scarponi S, Romanò C. *Two-stage cementless hip revision for peri-prosthetic infection with an antibacterial hydrogel coating: results of a comparative series*. Int Orthop. 2019 Jan;43(1):111-115.
- [31]. Zoccali C, Biagini R, Daolio PA, Campanacci DA. *Antibacterial Hydrogel Coating in the Prevention of Periprosthetic Joint Infection After Bone Reconstruction with Megaprosthesis: a Consecutive Case Series*. Proceedings of the 32nd Annual Meeting of the European Musculo Skeletal Oncology Society, May 15-17, Florence, Italy.



## SPECIALITY DAYS 2019

8-9 NOVEMBER  
MADRID, SPAIN

[esska-specialitydays.org](http://esska-specialitydays.org)