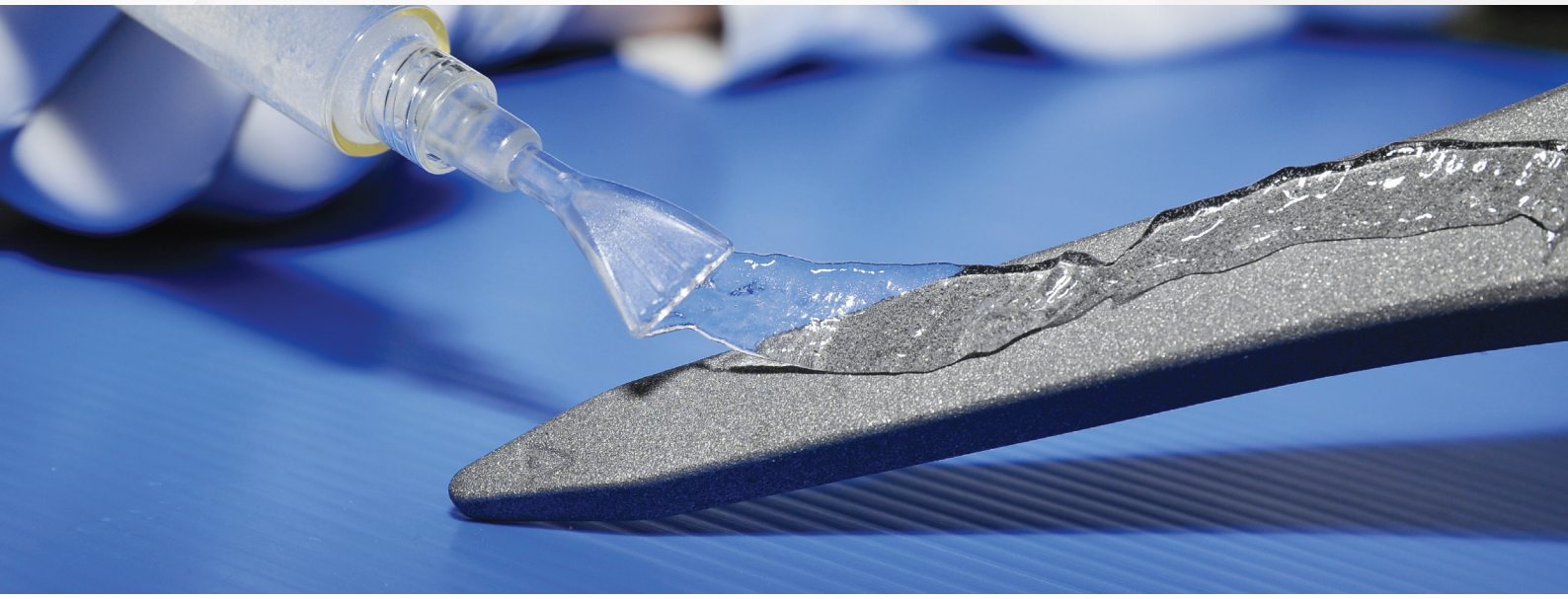
DAC®

DEFENSIVE ANTIBACTERIAL COATING



WHITE PAPER 2019

INDEX

RATIONALE AND INTENDED USE

In spite of systemic antibiotic prophylaxis, **implant-related infection remains one of the leading reasons for failure of joint replacements and of internal osteosynthesis**, with extremely high social and economic associated costs (cf. **Table 1**). [1]

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

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% [2]. The incidence of SSI after open fractures of the long bones is more than 20%; [3]
Leading reason for revision: Peri-prosthetic hip and knee infection is among the first three reasons for joint replacement failure, according to the registers; [4]
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 [5]. The RR for patients undergoing hip revision for PJI, compared with aseptic hip revision, ranges from 1.87 to 3.10; [6]
Additional costs: the average cost of management of infection after hip fracture surgery is > 30,000 Euros. [6] The cost for the management of any single case of hip or knee PJI ranges from 40,000 to > 100,000 Euros. [7, 8]

All implant-associated infections share complex diagnostic and treatment procedures, due to the presence of bacterial biofilm(s) and slow-growing, persistent microorganisms, able to even survive into the host's cells and often resistant to most or all of the available antibiotics.

Given its challenging treatment, prevention is pivotal in reducing the burden of the disease.

To this aim, providing implanted biomaterials with an antibacterial coating or finishing has been advocated by experts and respected institutions as one of the most promising solutions, in order to mitigate the impact of septic complications. [9]

In line with this vision, **the "Defensive Antibacterial Coating" (DAC®, Novagenit Srl, Mezzolombardo, Italy) has been specifically designed to protect from bacterial colonization and biofilm formation a wide variety of implantable biomaterials used in orthopaedics, traumatology, dentistry and maxillofacial surgery**.

The biodegradable hydrogel is intended to serve as **a temporary physical barrier against the bacterial adhesion and the formation of microbial biofilms**.

DAC® represents an additional measure of infection prevention, which is not intended to replace or to substitute the asepsis measures and the usual protocols of antibiotic prophylaxis recommended in orthopedic surgery.

Five years after the very first introduction of the Defensive Antibacterial Coating in the clinical setting, this "White Paper" is aimed at providing a comprehensive review of the evidence related to the preclinical and clinical results in orthopaedics and trauma *.

In particular, evidence will be provided concerning the following statements:

- **DAC IS MADE OF HIGHLY BIOCOMPATIBLE POLIMERS**
- **DAC IS SAFE ACCORDING TO *IN VITRO* RESULTS**
- **DAC HAS A PROVEN ANTIBIOFILM ACTIVITY**
- **DAC IS EFFECTIVE AND SAFE *IN VIVO***
- **DAC PROVIDES AN AVERAGE 8 TIMES REDUCTION OF POST-SURGICAL IMPLANT-RELATED INFECTIONS IN ORTHO-TRAUMA**
- **NO SIDE EFFECTS REPORTED**
- **DAC IS ASSOCIATED WITH A FAVORABLE COST-BENEFIT-RATIO**

For more information, you may also visit:

www.dac-coating.com

www.coatingdac.com

www.novagenit.com

* Not all available studies on DAC technology are included in this White Paper.

IN VITRO DATA

Chemical structure

Composed of covalently linked hyaluronan (HA) and poly-d,l-lactide PLA) (**Fig. 1**), the "Defensive Antibacterial Coating" (DAC®, Novagenit Srl, Mezzolombardo, Italy) has been specifically developed in order to protect implanted biomaterials used in orthopaedics, traumatology, dentistry and maxillofacial surgery from bacterial colonization. [10,11]

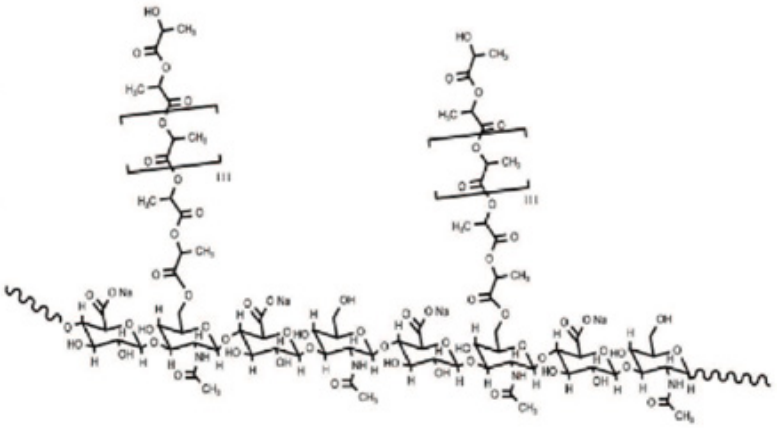


Fig. 1. Chemical structure of the HA-g-PLA copolymer

As a medical device, DAC® is in the form of a kit, composed of a sterile, double-sealed syringe, containing a powder, intended to be mixed at the time of surgery with a water-based solution to form the hydrogel; also provided are accessories, suitable to apply the hydrogel coating on the surface of the implants.

DAC IS COMPOSED BY HIGHLY BIOCOMPATIBLE AND FULLY RESORBABLE BIOPOLIMERS

Cell compatibility assay

In vitro cell compatibility of DAC® HA-g-PLA hydrogel (polymer concentration 6%, w/v) was evaluated using human dermal fibroblasts. The viability of cells cultured in direct or indirect contact with HA-g-PLA hydrogel was comparable with that of the control well, showing that the hydrogel does not release in the culture medium substances that interfere with cell viability and they do not cause a decrease in the cell viability after direct contact with them. [10]

Further *in vitro* and *in vivo* biocompatibility studies were performed on the DAC® hydrogel and on the DAC® kit, in accordance to ISO standards, all showing no cytotoxicity, genotoxicity, sensitization, irritation or intracutaneous reactivity, systemic toxicity (acute), subchronic toxicity or interference with bone or peri-implant tissues (Novagent Srl, data on file).

Furthermore, as degradation of DAC® HA-g-PLA hydrogel occurs via deesteriication of hyaluronic acid and polylactic acid, it gives raise exclusively to the starting macromolecules, whose degradation pathways in the human body are widely known and whose use as implantable class III medical devices is largely accepted and tested safe.

DAC SHOWED FULL *IN VITRO* BIOCOMPATIBILITY

IN THE HUMAN BODY THE DAC HYDROGEL GIVES RISE ONLY TO TESTED SAFE MACROMOLECULES

Antiadhesive and antibiofilm activity

The mechanism of action is related to the antifouling and antiadhesive properties of hyaluronic acid.

Both the ability of the DAC® HA-g-PLA hydrogel to reduce bacterial adhesion and biofilm formation were extensively studied *in vitro*.

Reductions of adhered bacteria on sterile titanium discs, coated with DAC® hydrogel, equal to 86.8, 80.4, 74.6 and 66.7% vs. untreated discs were observed after 15, 30, 60 and 120 min of incubation, respectively [12] (Fig. 2).

In another experiment, the ability to dislodge previously adhered bacteria was investigated.

Once again, the results showed that **DAC® hydrogel treatment of discs reduced the amount of adhered bacteria in respect to control discs after 15, 30, 60 and 120 min by 84.0, 72.8, 72.3 and 64.3%, respectively** (**Figg. 2-5**). [12]

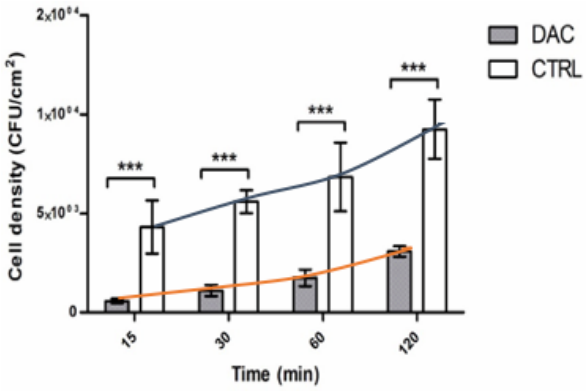


Figure 2. Adhesion densities of *S. aureus* (mean CFU/cm2 ± standard deviation) to discs pre-treated with DAC® ("Defensive Antibacterial Coating", Novagenit Srl, Mezzolombardo, Italy) and controls at 15, 30, 60 and 120 min; *** P < 0.001 (two-way ANOVA followed by Bonferroni post hoc test). [12]

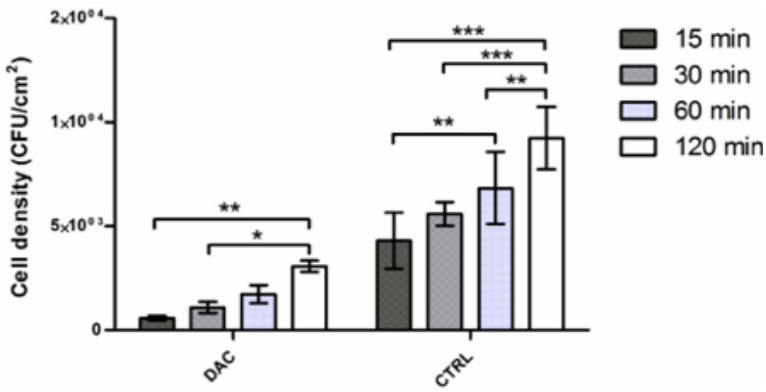


Figure 3. Adhesion densities of *S. aureus* (mean CFU/cm2 ± standard deviation) over time in pre-treated with DAC® and control discs at 15, 30, 60, 120 min; * 0.01 < P <0.05, ** 0.001 < P < 0.01, *** P < 0.001 (two-way ANOVA followed by Bonferroni post hoc test). [12]

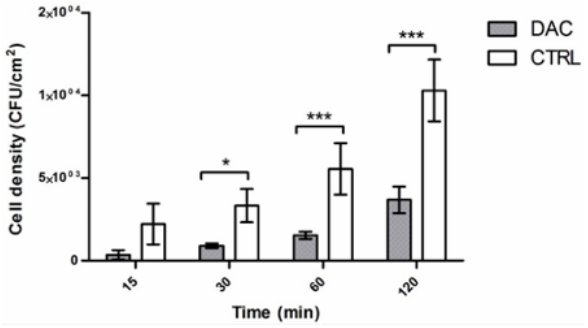


Figure 4. Adhesion densities on discs with of *S. aureus* (mean CFU/cm2 ± standard deviation) applied before DAC treatment and controls at 15, 30, 60, 120 min; * 0.01 < P <0.05, *** P < 0.001 (two-way ANOVA followed by Bonferroni post hoc test). [12]

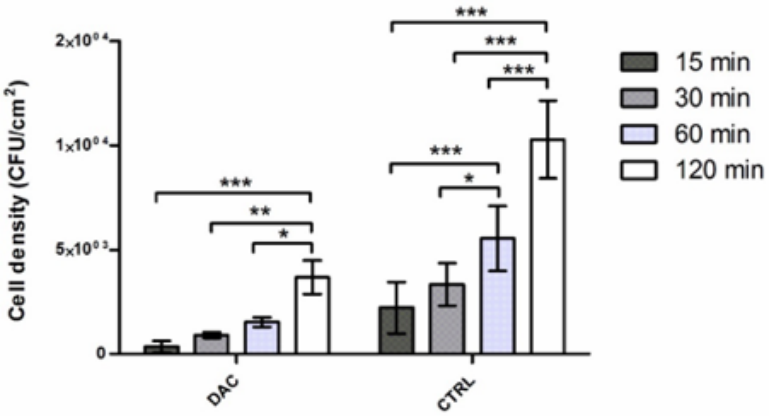


Figure 5. Adhesion densities over time on discs with of *S. aureus* (mean CFU/cm2 ± standard deviation) applied before DAC treatment and controls at 15, 30, 60, 120 min; * 0.01 < P <0.05, ** 0.001 < P < 0.01, *** P < 0.001 (two-way ANOVA followed by Bonferroni post hoc test). [12]

Concerning more specifically the antibiofilm activity, **DAC® hydrogel showed similar or superior *in vitro* activity, compared to various antibacterials and a synergistic activity when used in combination.** [11]

In one experimental setting, *S. epidermidis* and *S. aureus* were grown on chrome-cobalt devices in 6-wells polystyrene plates containing TSB for 24 h at 37°C. The plates were incubated at 37°C in ambient air, until a visible biofilm was obtained. Gentamycin and vancomycin were tested at a final concentration of 20 mg/mL. Similarly, when mixed with the hydrogel, 60 mg of gel powder was reconstituted with 1 mL of water for injections containing gentamicin or vancomycin at 20 mg/mL concentration. The amount of biofilm at each time was determined before hydrogel and antibiotic agents' addition and after 0.5, 1, 2, 4, 6, 24 and 48 h of incubation by a spectrophotometric assay.

At each time point, both gentamicin and vancomycin showed only a partial inhibition of biofilm formation (ca. 30–40% for gentamicin; ca. 40–50% for vancomycin), with minor difference between the two studied microorganisms.

On the other side, **the hydrogel alone resulted in a significant reduction of biofilm of ca. 50%, in comparison to the untreated controls, while a combination of the hydrogel with either antibacterial coating resulted in a larger reduction of biofilm formation (approximately 75–80% in comparison with untreated controls)** (**Fig. 6**). [12]

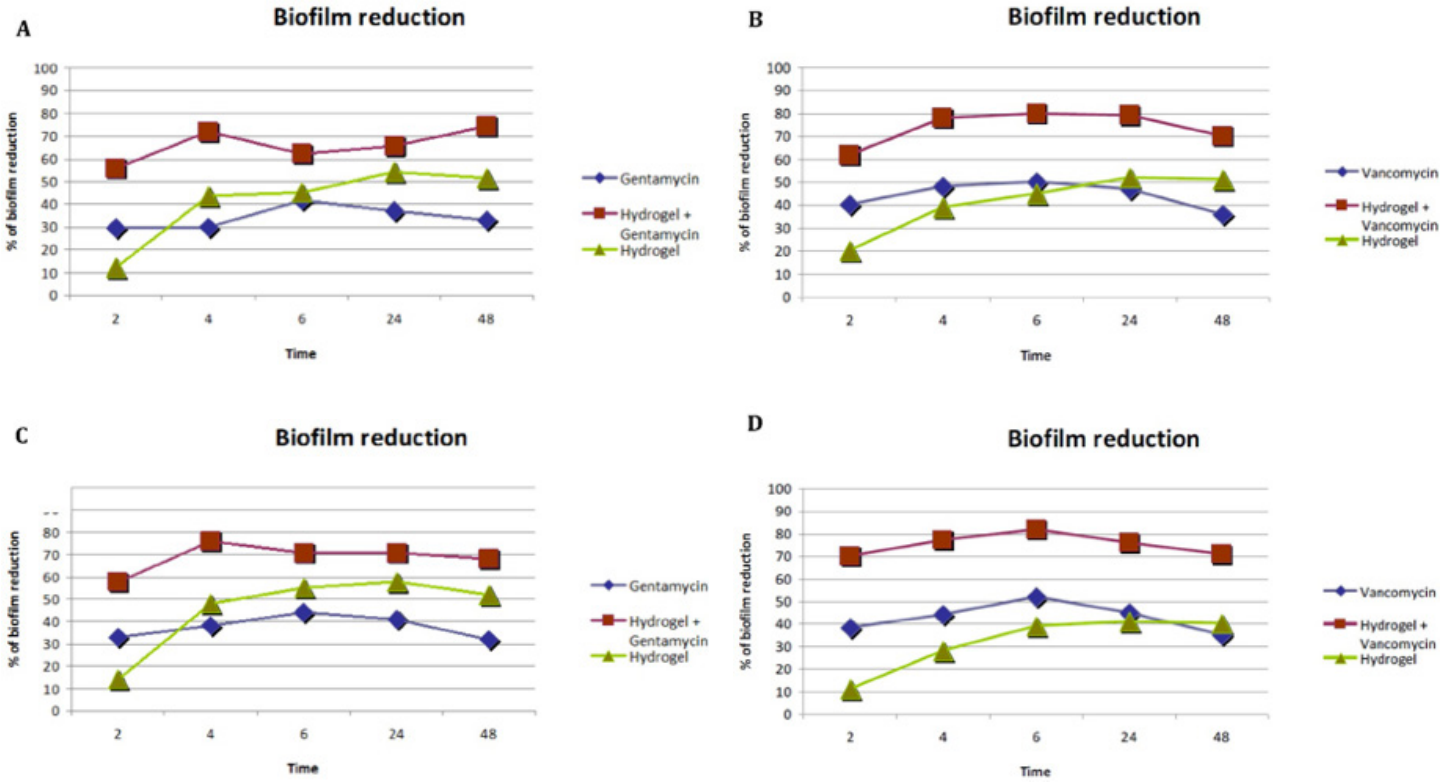


Figure 6. Comparison of the efficacy of DAC hydrogel, gentamicin, vancomycin or a combination thereof, on biofilm formation reduction of *Staphylococcus aureus* (A. and B.) and *Staphylococcus epidermidis* (C. and D.) over time (hours). Note that **the hydrogel alone is able to provide an equal or superior biofilm reduction compared to commonly used antibiotics**, while a synergistic effect is observed using a combination of the hyaluronic acid based hydrogel and the antibiotic compounds. [12]

DAC HYDROGEL COATING HAS A PROVEN ANTIADHESIVE AND ANTIBIOFILM ACTIVITY

WHEN COMBINED WITH VACOMYCIN OR GENTAMYCIN, THE DAC HYDROGEL SHOWS A SYNERGISTIC ANTIBIOFILM ACTIVITY

Rationale for the intra-operative DAC® hydrogel antibiotic loading

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.

According to this model, 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 the bacterial 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,** it may be anticipated that, **whenever the immune system should fail to destroy the planktonic microorganisms, these may still have the chance to colonize 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 coating of the implant at a later stage, once the coating hydrolysis proceeds (**Fig. 7**). [13]

Furthermore, several studies have shown i. the ability of the hydrogel to be loaded and to completely release all the tested antibiotics in less than 72 hours; ii. The synergistic effect of the hydrogel + antibiotic, compared to either component alone [11]; iii. The absence of any measurable side effects of the antibiotic-loaded **DAC® hydrogel coating both in preclinical [14,15] and in all available clinical studies [cf. Clinical Data - Safety].**

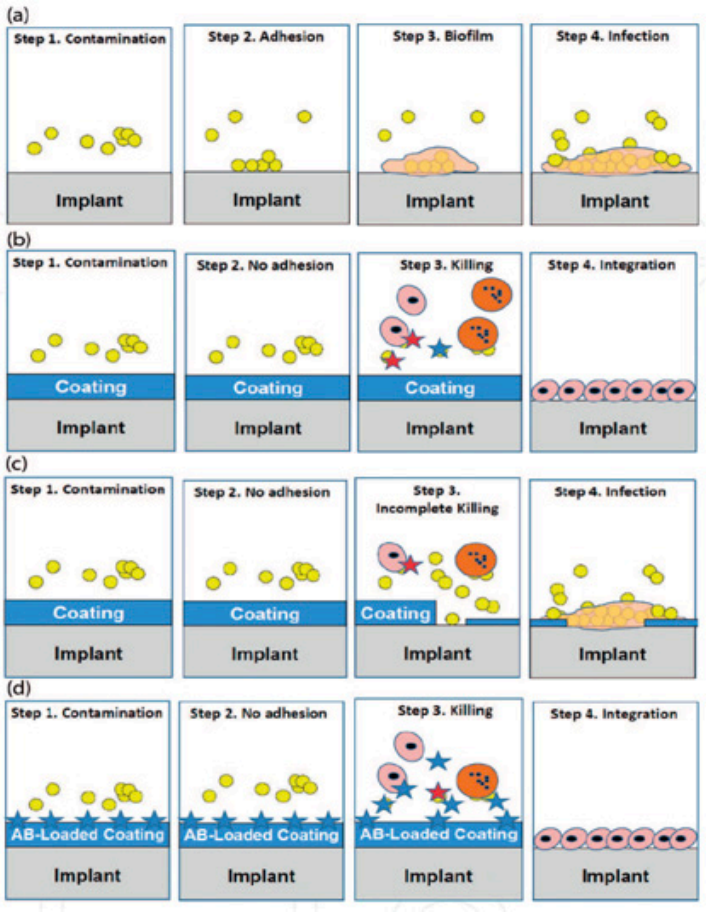


Figure 7. Rationale for intra-operative mixing of DAC® hydrogel coating with antibacterial agents. Schematic representation of different scenarios. (a) Noncoated implants may get colonized by biofilm-forming bacteria (yellow circles) and infection will develop. (b) Antiadhesive coating may reduce/prevent bacterial adhesion, while the immune system (orange circles and red stars) and the systemically administered antibiotics (blue star) kill planktonic microorganisms. (c) However, if bacterial load is large enough, or if immune response and local antibiotic levels are inadequate, surviving bacteria may eventually colonize the implant, once the coating has been hydrolyzed or covered by host's proteins. (d) To prevent this, the antibacterial hydrogel may be loaded, at the time of surgery, with antibiotic agents (blue stars) that may be locally released, contributing to eliminate all remaining planktonic bacteria. [13]

INTRA-OPERATIVE MIXING THE DAC HYDROGEL WITH ANTIBIOTICS MAY BE HELPFUL TO KILL PLANKTONIC BACTERIA

FEASIBILITY AND SAFETY OF THE DAC COMBINATION WITH SEVERAL ANTIBACTEIRAL AGENTS HAS BEEN SUCCESSFULLY TESTED

Antibiotic-loaded DAC® hydrogel is able to significantly reduce bacterial colonization in a highly contaminated rabbit model of implant-related infection, with no local or systemic side effects.

International Orthopaedics (SICOT)
DOI 10.1007/s00264-013-2237-2

ORIGINAL PAPER

Efficacy of antibacterial-loaded coating in an in vivo model of acutely highly contaminated implant

Gianluca Giavaresi · Enzo Meani · Maria Sartori · Andrea Ferrari · Davide Bellini · Anna C. Sacchetta · Joachim Meraner · Andrea Sambri · Caterina Vocale · Vittorio Sambri · Milena Fini · Carlo L. Romanò

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Methods A histocompatibility study was performed in 10 adult New Zealand rabbits. Then, methicillin-resistant Staph. aureus were inoculated in the femur of 30 adult New Zealand rabbits at the time of intra-medullary nailing; vancomycin-loaded DAC® coated nails were compared to controls regarding local and systemic infection development.

Results Histocompatibility study showed **no detrimental effect of DAC® hydrogel on bone tissue after 12 weeks from implant**.
After seven days from implant, none of the rabbits receiving vancomycin-loaded DAC® nail showed positive blood cultures, compared to all the controls; **vancomycin-loaded DAC® coating was associated with local bacterial load reduction ranging from 72 to 99 %, compared to controls**.

Conclusions Vancomycin-loaded DAC® coating is able to **significantly reduce bacterial colonization in an animal model of an intra-operatively highly contaminated implant, without local or general side effect**. [14]

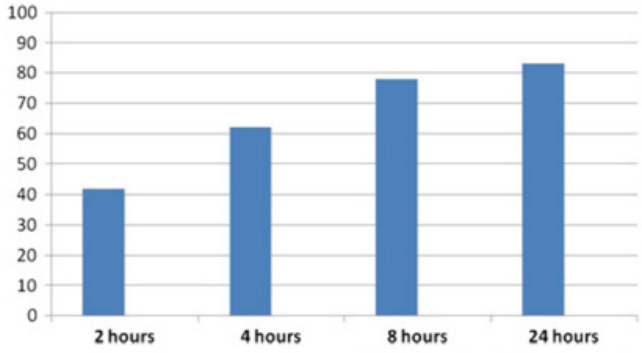

Fig. 1 Release of vancomycin from DAC® hydrogel at defined intervals during incubation at 37 °C. Release expressed as percentage of total antibiotic quantity loaded

More than 80% of the antibiotic is released in the first 24 hours from the **DAC® hydrogel.**

This observation is in line with that observed in *in vitro* studies, showing complete antibiotic release within 72 hours.

The fast and complete antibiotic release provides the best antibacterial activity, minimizing the risk of antibiotic resistance induction.

Antibiotic-loaded DAC® hydrogel has a protective effect on bone healing in a contaminated rat model of non-union.

Hindawi Publishing Corporation
Mediators of Inflammation
Volume 2016, Article ID 9595706, 12 pages
http://dx.doi.org/10.1155/2016/9595706

Hindawi

Research Article

Systemic and Local Administration of Antimicrobial and Cell Therapies to Prevent Methicillin-Resistant *Staphylococcus epidermidis*-Induced Femoral Nonunions in a Rat Model

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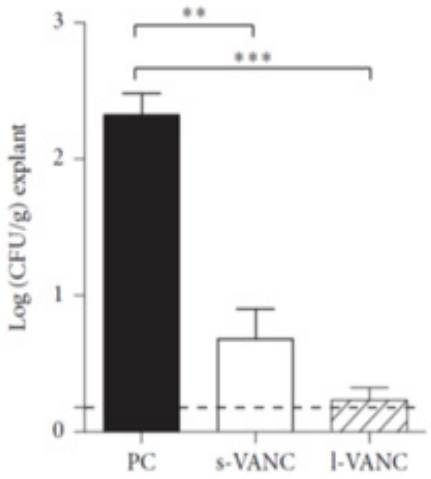

Microbiological detection of bacterial growth on the explanted specimens.
Comparisons among groups were analyzed with one-way ANOVA corrected with Bonferroni's *post hoc* test. Statistical significance was $p < 0.01$ (**), and $p < 0.001$ (***); $n = 6$. At 42 days from surgery, **DAC® hydrogel** enriched with vancomycin at 5% (v/w) (l-VANC), distributed on plates and screws during the osteosynthesis, shows nearly undetectable bacterial growth, which is significantly lower that that observed in controls without the coating (PC) and even lower than that observed in systemically administered vancomycin (s-VANC).

Forty-two days after surgery, 50% of the **DAC® hydrogel** coated osteosynthesis showed bone healing at the fracture site, compared to 0 % and 33 % in the control and s-VANC groups, respectively, demonstrating a clear **protective effect of the coating on bone healing**. [15]

	Bony bridging > 75% fracture healing
Controls	0 %
s-VANC	33 %
l-VANC	50 %

DAC HYDROGEL COATING IS SAFE AND EFFECTIVE IN PREVENTING IMPLANT-RELATED POST-SURGICAL INFECTION

DAC HYDROGEL COATING APPLIED TO INTERNAL OSTEOSYNTHESIS PROTECTS AGAINST INFECTED NON-UNION IN THE ANIMAL MODEL

Prevention of peri-prosthetic joint infection

J. Bone Joint Infect. 2016, Vol. 1 34

IVYSPRING INTERNATIONAL PUBLISHER

Journal of Bone and Joint Infection
2016; 1: 34-41. doi: 10.7150/jbji.15986

Research Paper

Does an Antibiotic-Loaded Hydrogel Coating Reduce Early Post-Surgical Infection After Joint Arthroplasty?

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Methods: In this multicenter, randomized prospective study, a total of **380 patients**, scheduled to undergo primary (n=270) or revision (n=110) total **hip (N=298) or knee (N=82) joint replacement with a cementless or a hybrid implant**, were randomly assigned, in six European orthopedic centers, to receive an implant either with the antibiotic-loaded DAC coating (treatment group) or without coating (control group). Pre- and postoperative assessment of clinical scores, wound healing, laboratory tests, and x-ray exams were performed at fixed time intervals.

Results: Overall, **373 patients were available at a mean follow-up of 14.5 ± 5.5 months (range 6 to 24)**. On average, a volume of 8.3 mL hydrogel was used to coat an implant. The most often used antibiotics were vancomycin and gentamicin at a concentration of 5% and 3.2%, respectively.
Fifteen patients received an implant with a combined vancomycin and meropenem antibiotic coating; 4 patients received an implant coated with teicoplanin 5% or ceftazidime 5% or amphotericin B 5%, all in a second-stage procedure for previous infection.
Wound healing, laboratory and radiographic findings showed no significant difference between the two groups. **Eleven early surgical site infections were observed in the control group and only one in the treatment group (6% vs. 0.6%; p=0.003).** No local or systemic side effects related to the DAC hydrogel coating were observed, and **no detectable interference with implant osteointegration was noted**.

	Controls (N=184)	Treated (N=189)	P
Delayed wound healing	7 (3.8%)	2 (1.2%)	0.1
Other complications	5 (2.7%)	4 (2.1%)	0.7
Peri-prosthetic infection	11 (6.0%)	1 (0.6%)	0.003

Conclusions: The use of a fast-resorbable, antibiotic-loaded hydrogel implant coating can **reduce the rate of early surgical site infections, without any detectable adverse events or side effects after hip or knee joint replacement with a cementless or hybrid implant**. [16]

Prevention of infection after osteosynthesis

J Orthop Traumatol (2017) 18:159–169
DOI 10.1007/s10195-017-0442-2

ORIGINAL ARTICLE

Fast-resorbable antibiotic-loaded hydrogel coating to reduce post-surgical infection after internal osteosynthesis: a multicenter randomized controlled trial

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Materials and methods In this multicenter randomized controlled prospective study, a total of **256 patients in five European orthopedic centers** who were scheduled to receive osteosynthesis for a closed fracture, were randomly assigned to receive antibiotic-loaded DAC or to a control group (without coating). Pre- and postoperative assessment of laboratory tests, wound healing, clinical scores and X-rays were performed at fixed time intervals.

Results Overall, **253 patients were available with a mean follow-up of 18.1 ± 4.5 months (range 12–30).** On average, 5.7 mL (range: 1 to 10 mL) of DAC® hydrogel were needed to coat the implant. Gentamicin and vancomycin were the most used antibiotics, at concentration of, respectively 4% or 2%. Wound healing, clinical scores, laboratory tests and radiographic findings did not show any significant difference between the two groups. **Six surgical site infections (4.6%) were observed in the control group compared to none in the treated group (P\0.03). No local or systemic side-effects related to the DAC hydrogel product were observed and no detectable interference with bone healing was noted.**

	Controls (N=127)	Treated (N=126)	P
Delayed wound healing	7 (5.5%)	5 (3.9%)	0.76
Delayed union	5 (3.9%)	2 (1.6%)	0.44
Other complications	6 (4.7%)	4 (3.2%)	0.77
Infection	6 (4.7%)	0 (0.0%)	0.03

Conclusions The use of a fast-resorbable antibiotic-loaded hydrogel implant coating provides a **reduced rate of postsurgical site infections after internal osteosynthesis for closed fractures, without any detectable adverse event or side-effects**. [17]

Level of evidence 2.

One-stage revision surgery for the treatment of peri-prosthetic infection

Knee Surgery, Sports Traumatology, Arthroscopy
https://doi.org/10.1007/s00167-018-4896-4

KNEE

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

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Methods In this two-center case–control, study, **22 patients**, treated with a one-stage procedure, using implants coated with an antibiotic-loaded hydrogel [defensive antibacterial coating (DAC)], were compared with **22 retrospective matched controls**, treated with a two-stage revision procedure, without the coating.

Results At a **mean follow-up of 29.3 ± 5.0 months**, **two patients (9.1%) in the DAC group showed an infection recurrence, compared to three patients (13.6%) in the two-stage group**. Clinical scores were similar between groups, while **average hospital stay and antibiotic treatment duration were significantly reduced after one-stage, compared to two-stage (18.9 ± 2.9 versus 35.8 ± 3.4 and 23.5 ± 3.3 versus 53.7 ± 5.6 days, respectively).**

Conclusions Although in a relatively limited series of patients, our data shows **similar infection recurrence rate after one-stage exchange with DAC-coated implants, compared to two-stage revision without coating, with reduced overall hospitalization time and antibiotic treatment duration.** These findings warrant further studies in the possible applications of antibacterial coating technologies to treat implant-related infections. [18]

Level of evidence III.

Two-stage revision surgery for the treatment of peri-prosthetic infection

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ORIGINAL PAPER

Two-stage cementless hip revision for peri-prosthetic infection with an antibacterial hydrogel coating: results of a comparative series

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Methods In this case-control study, **27 patients**, treated with a two-stage procedure, using cementless implants coated with an antibiotic-loaded hydrogel (DAC®, "Defensive Antibacterial Coating"), were **compared with 27 matched controls**, treated with a two-stage cementless revision procedure, without the coating.

Results At a **mean follow-up of 2.7 (minimum 2.1–maximum 3.5) years, no evidence of infection, implant loosening, or adverse events were observed in the DAC-treated group**, **compared to four cases of infection recurrence in the control group**.

	DAC (N=27)	Controls (N=27)
Harris Hip Score	84.6 ± 15.8	81.6 ± 15.2
Hospital stay incl. rehabilitation (days)	28.2 ± 3.9	33.8 ± 5.4
Hip dislocation	1	1
Delayed wound healing	0	1
Infection	0	4 (14.8%)

Conclusions Although in a relatively limited series of patients our data show that cementless two-stage hip revision, performed with an antibacterial hydrogel coating, may provide **better infection control than two-stage without the coating, with reduced hospitalization time**, these findings warrant further studies in the possible applications of antibacterial coating technologies to treat implant-related infections. [19]

Prevention of infection after megaimplants in oncological patients

32nd annual Meeting of the EUROPEAN MUSCULO SKELETAL ONCOLOGY SOCIETY EMSOS 2019

Abstract

Antibacterial Hydrogel Coating in the Prevention of Periprosthetic Joint Infection After Bone Reconstruction with Megaprosthesis: a Consecutive Case Series

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Orthopaedic Oncology Unit, Istituto Ortopedico "G. Pini", Milan, Italy
Dept. Trauma and General Orthopedics, Azienda Ospedaliera Universitaria Careggi, Florence, Italy

47 consecutive patients in three Centers

Osteosarcoma (n=12), chondrosarcoma (n=7), Ewing's sarcoma and other sarcomas (n=8) giant cells tumor (n=7), other neoplasia (n=9), other pathologies (n=4).
Distal femur (n=17), proximal femur (19), distal/proximal femur (1), proximal tibia (1), pelvis (6), scapula (1), proximal humerus (n=4), proximal/distal humerus (1), tarsal bone (1).

Average length of surgeries: 5.6 ± 2.9 hours (range, 2 - 15).

One patients died during the **follow-up (18 months)** due to their underlying malignancy.

Infection rate: 1 / 47 (2.1%) (treated without implant removal)

No complications related to the use of ALHBG were reported at follow-up.

Implant-related infection prevention in orthopaedics and trauma

Summary of comparative clinical studies

Overall, DAC® HA-g-PLA hydrogel coating has been shown to be associated with an 8 times reduction of post-surgical infection rate of orthopaedic and trauma implants or from 6.7% to 0.8% in a total of 724 patients, followed for an average of 23 months post-operatively.

The Table summarizes the data available from published comparative studies, concerning DAC® hydrogel efficacy.

Author and date of publication	Mean Follow-Up (Months)	Controls	Post-surgical infections	Treated	Post-surgical infections
Romanò et al. (2016)	14.5	184	11	189	1
Malizos et al. (2017)	18.1	127	6	126	0
Capuano et al. (2018)	29.3	22	3	22	2
Zagra et al. (2019)	30	27	4	27	0
Total	23 ± 7.8	360	24 (6.7%)	364	3 (0.8%)

DAC HYDROGEL COATING HAS BEEN SHOWN TO BE ASSOCIATED WITH AN AVERAGE 8 TIMES REDUCTION OF POST-SURGICAL IMPLANT-RELATED INFECTIONS IN ORTHOPAEDICS AND TRAUMA

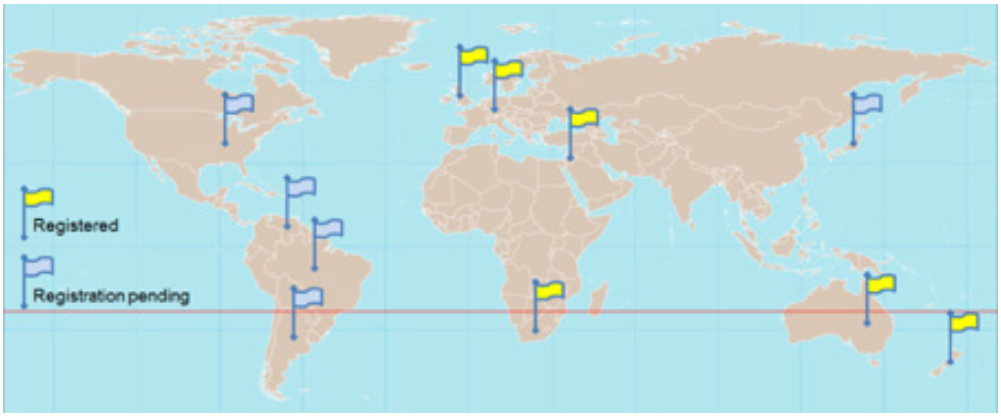
Post-marketing surveillance report

As of March 2019, the DAC® HA-g-PLA hydrogel is registered for clinical use in all the European Countries, Switzerland, United Kingdom, lsrael, South Africa, Australia, New Zealand.

The product is currently sold in **17 Countries** (Table 1.) and **routinely used in several large volume and university hospitals** (Table 2.)

Post-marketing surveillance confirms the high biocompatibility of DAC® HA-g-PLA hydrogel for use as a coating of orthopaedic and trauma implants:

in approximately 4,000 implants performed **from the end of 2013 to the first trimester of 2019** there have been **no reports of adverse events** (Novagent Srl, data on file).



Approx 4,000 Implants

Reported Adverse Events: 0

Table 1. Countries were DAC® HA-g-PLA hydrogel coating is sold, as per March 2019.

Australia	Italy
Czech Republic	New Zealand
Denmark	Norway
Finland	Poland
France	South Africa
Germany	Spain
Greece	Switzerland
Holland	United Kingdom
Israel	

Table 2. List of some of the main clinical centres where the DAC® HA-g-PLA hydrogel coating is used, as per March 2019.

Northern Italy

A. SAN. ULSS N. 3 - BASSANO D/ G
A.O. G. PINI - MILANO
AZ. OSP. S. ANTONIO E BIAGIO - AL
CDC PRI. S. FRANCESCO - VERONA
COMPRENSORIO SANITARIO BRESSANONE
IOR - CHIR. VERT/ONCOLOGICA
IOR - DR DALLARI - COTI - BOLOGNA
IOR - ONCOLOGICO III°CLINICA - BO
IOR - PROF. ZAFFAGNINI- 1CLI - BO
IOR - SPORT - BOLOGNA
IS. CLI. HUMANITAS
IST. ORTOPEDICO GALEAZZI - MILANO
IST. CODIVILLA-PUTTI - CORTINA
MARK MEDICAL SPA - GORIZIA
OSP S.PELLEGRINO - CASTIGLIONE STIV
OSP. PRI ACCR NIGRISOLI - BOLOGNA
OSP. S. MARIA DEL CARMINE -ROVERETO
OSP. TREVIGLIO / CARAVAGGIO - BG
OSPEDALE DELL'ANGELO - MESTRE
OSPEDALE DI FIEMME - CAVALESE
OSPEDALE DI MONTECCHIO - VICENZA
OSPEDALE S. BORTOLO - VICENZA
REG. PIEMONTE A.S.L. 21 CASALE
Osp.le VIPITENO
Osp.le Vercelli
Osp.le C.T.O. Torino
Osp.le Sondalo
IRCCS Osp.le S.Raffaele Milano
Ospedale C.T.O. Torino
Osp.le Maggiore Novara
Osp.le Garbagnate Milanese
Osp.le Luigi Sacco Milano
IST CLINICO S. ANNA Brescia
DIP. RIZZOLI - CDC VILLA CHIARA Bologna
Osp.le Santa Maria della Misericordia Uine
Osp.le Santa Maria degli Angeli Pordenone
Osp.le San Paolo Savona
Osp.le Villa Aprica Como
CDC VILLA BIANCA SPA - TRENTO
OSPEDALE DI GORIZIA
AZ. SAN. DI BOLZANO - BOLZANO
COMPR. SANITARIO DI BRUNICO
AZ. OSP. C. POMA - MANTOVA

Central Italy

AZ. U.S.L. DI RAVENNA - LUGO
ESTAR - AREA SE SIENA
OSP. S. MARIA GRUCCIA - MONTEVARCHI
OSP. SAN DONATO - AREZZO
OSPEALE CECCARINI DI RICCIONE
OSPEDALE "D. CERVESI" - CATTOLICA
PRIV - VILLA MARGHERITA- Roma
UNI CAMPUS BIO MEDICO ROMA
PRIV - CDC MERCEDE - ROMA
VILLA VERDE CDC ROMA
POLICLINICO UNIV. A.GEMELLI - ROMA
OSP. RIETI
OSPEDALE DI PALESTRINA
OSPEDALE DI SUBIACO
IFO CENTRO TUMORI ROMA
OSPEDALE DI FROSINONE
OSPEDALE MATER DEI ROMA
POL. UMBERTO I ROMA
POLICLINICO GEMELLI ROMA
AZIENDA OSP. SAN CAMILLO FORLANINI ROMA
OSPEDALE ALBANO LAZIALE
OSPEDALE S.FILIPPO NERI ROMA
Osp.le C.T.O. Firenze
CDC PAIDEIA SPA - ROMA
CDC VILLA CHIARA - CASALECCHIO RENO
AZIENDA OSP. RIUNITI ANCONA

Southern Italy

OSPEDALE DI ASCOLI PICENO
OSPEDALE DI PESCARA
OSPEDALE DI CIVITANOVA MARCHE
C.CURA BUCCHERI LA FERLA PALERMO
POLICLINICO PALERMO
CLINICA NOTO PALERMO
IOR RIZZOLI BAGHERIA
Osp. Vallo della Lucania
Osp.le Fatebenefratelli Benevento
Osp.le Eboli
Policlinico Napoli
Osp.le civile Salerno

Europe

Switzerland
Osp.le Civile Lugano

Spain
Hospital Mutua Universal Barcellona

Hospital de Viladecans

Centro Medico Teknon Barcellona

Vall d'Hebron University Hospital Barcellona
Hospital Arnau de Vilanova Lérida
Hospital Clinico Valladolid

Denmark
Rigshospitalet, Copenhagen
Regionshospitalet Holstebro, Holstebro
Sydvestjysk Sygehus, Esbjerg

Greece
UNIVERSITY HOSPITAL OF LARISA -
ARESTOTELE UNI GREECE

Germany
HELIOS KLINIK BERLIN/BUCH
SCHÖN-KLINIK LORSCH
EV. KLINIKUM BIELEFELD
UNIVERSITÄTSKLINK HOMBURG/SAAR
KLINIKEN NOROBERPFALZ TIRSCHENREUTH
UNIVERSITÄTSKLINIK FRANKFURT/MAIN
ALTONAER KINDERKRANKENHAUS HAMBURG
ROBER-KOCH-KRANKENHAUS APOLDA
ASKLEPIOS KLINIK BIRKENWERDER
KRANKENHAUS ST. ELISABETH DAMME
ATOS KLINIK HEIDELBERG
UNIVERSITATSKLINIK - INNSBRUCK (AT)
STEIERM. KRANKENHAUS BAD RADKERSBURG
STEIERM. KRANKENHAUS STOLZALPE (AT)
UNFALLKRANKENHAUS KLAGENFURT (AT)
EV. KRANKENHAUS WIEN (AT)
ENDOKLINIK HAMBURG Dr. Jonen Dr. Zahar

Poland
Orthopedist Clinic Poznan Rehasport

Norway

Holland
University Medical Center Utrecht Dr. Charles Vogely

Finland
Helsinki University Hospital trauma centers
Turku University
Tampere University
Oulu University
Kuopio University
Keski-Suomen Keskussairaala
Etelä- Savon keskussairaala
Etelä-Pohjanmaan keskussairaala
Päijät- Häme keskussairaala

France

Rep. di San Marino

International

United Kingdom
Nuffield Orthopaedic Centre, Oxford

Royal National Orthopaedic Hospital, Stanmore

Royal Orthopaedic Hospital, Birmingham

New Zealand
Simon McMahon, osp. pubblico di Dunedin, Dunedin,

Israel
Telaviv Medical Center

Australia
Princess Alexandra Hospital Brisbane
SJOG Bendigo
The Royal Children's Hospital MELBOURNE
St Vincent's Private Hospitals Ltd

South Africa

Pending registrations

U.S.A.

Colombia
Brasile
Argentina

Summary of clinical studies

Since its very first introduction in the market in 2013, no adverse events had ever been reported concerning the clinical use of the DAC® HA-g-PLA hydrogel either used alone or in combination with antibacterial agents.

In particular, all published studies did report the absence of any side effect or adverse event attributable to the DAC® HA-g-PLA hydrogel.

The Table summarizes the data available from published studies, concerning DAC® hydrogel safety.

Author and date of publication	Treated Patients	Mean Follow-Up (Months)	Number of Adverse Events
Romanò et al. (2016)	189	14.5	0
Malizos et al. (2017)	126	18.1	0
Capuano et al. (2018)	22	29.3	0
Zagra et al. (2019)	27	30	0
Zoccali et al. (2019)	47	18	0
Total	411	22 ± 7	0

DAC HYDROGEL COATING HAS NO KNOWN SIDE EFFECTS

THE COMBINATION OF THE DAC HYDROGEL COATING WITH VARIOUS ANTIBIOTICS DID NOT SHOW ANY SIDE EFFECT

COST-BENEFIT ANALYSIS

Positive cost-benefit balance of the large scale use of the DAC® hydrogel coating, applied to joint replacement.

The Journal of Arthroplasty 33 (2018) 1656–1662

Contents lists available at ScienceDirect

The Journal of Arthroplasty

journal homepage: www.arthroplastyjournal.org

Health Policy & Economics

Economic Evaluation of Antibacterial Coatings on Healthcare Costs in First Year Following Total Joint Arthroplasty

Maria Teresa Trentinaglia, PhD [a, b], Catherine Van Der Straeten, MD [c], Ilaria Morelli, MD [d], Nicola Logoluso, MD [e], Lorenzo Drago, MD, PhD [f], Carlo L. Romanò, MD [e, *]

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[b] Department of Environmental Science and Policy, Università degli Studi di Milano, Milan, Italy
[c] Musculoskeletal Sciences and Technology Lab, Department of Surgery and Cancer, Imperial College London, London, UK
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[e] Centre for Reconstructive Surgery and Osteo-Articular Infections C.R.I.O. Unit, IRCCS Galeazzi Institute, Milan, Italy
[f] Laboratory of Clinical-Chemistry and Microbiology, IRCCS Galeazzi Institute, and SCIBIS Department, University of Milan, Milan, Italy

Methods: The variables included in the algorithm were average cost and number of primary joint arthroplasties; average cost per patient of the **Antibacterial coatings (ABCs);** incidence of periprosthetic joint infections and expected reduction using the ABCs; average cost of infection treatment and expected number of cases.

Results: The point of economic balance for COPAL G þ C, DAC, and Agluna in the first year after surgery was reached in patient populations with an expected postsurgical infection rate of 1.5%, 2.6%, and 19.2%, respectively.

Table 5
Economic Impact in the First Year After Surgery of the 3 Coatings Under Study, Applied in a Selected Population With an Average Risk of Surgical Site Infection of 5.0%.

Variable	No Coating	COPAL G + V	DAC	Agluna
Number of joint arthroplasties per year	40,000			
Joint arthroplasty, average cost per patient	€8000			
ABC, cost per patient	€0	€480	€1170	€4600
Total direct cost per year (Equation 1)	€320,000,000	€339,200,000	€366,800,000	€504,000,000
Percent of expected PJI	5%			
Percent reduction in PJI with ABC	0	68.0%	90.0%	48.0%
Expected number of infections	2000	640	200	1040
Cost of septic revision, per patient	€50,000			
Expected indirect cost per year (Equation 2)	€100,000,000	€32,000,000	€10,000,000	€52,000,000
Total costs per year (Equation 3)	€,420,000,000	€,371,200,000	€,376,800,000	€,556,000,000
Balance		€48,800,000	€43,200,000	-€136,000,000
% Balance		113.15%	111.46%	75.54%

ABC, antibacterial coating; PJI, periprosthetic joint infection.

If applied on a national scale, in a moderately high-risk population of patients with a 5% expected postsurgical infection rate, COPAL G C and **DAC hydrogel would provide annual direct cost savings of approximately** € 48,800,000 and **€ 43,200,000** (€ 1220 and € 1080 per patient), respectively, while the silver coating would be associated with an economic loss of approximately € 136,000,000.

Conclusion: This economic evaluation shows that **ABC technologies have the potential to decrease healthcare costs primarily by decreasing the incidence of surgical site infections**, provided that the technology is used in the appropriate risk class of patients. [20]

DAC® hydrogel coating is already cost-effective in a population of patients undergoing primary hip or knee joint replacement with an expected incidence of post-surgical infection of 0.5%. [21]

Date: 2018-10-12
Session: Infections Free Papers (I)
Time: 08:00 - 10:00
Room: Room 522a+b+c

Abstract no.: 51076
ECONOMIC IMPACT OF AN ANTIBACTERIAL HYDROGEL COATING IN PRIMARY JOINT ARTHROPLASTY: A MARKOV EXPECTED UTILITY ANALYSIS

Carlo ROMANO[1], Nicola LOGOLUSO[2], Maria Teresa TRENTINAGLIA[3], Emanuela ROMANO[4]
[1]IRCCS R.Galeazzi, Milan (ITALY), [2]IRCCS R.Galeazzi, MILAN (ITALY), [3]University of Milan, Milan (ITALY), [4]Bocconi University, Milan (ITALY)

Little is known about cost-effectiveness of technologies that provide local antibacterial protection of implanted biomaterials in case of a widespread adoption to prevent postsurgical infection in orthopaedics. This study models the use of an antibacterial hydrogel coating (DAC®, Defensive Antibacterial Coating) in primary total hip or knee arthroplasty, to determine whether the use of this device is cost-effective, when compared with implants without coating. We used a Markov decision model to tabulate costs and quality-adjusted life years (QALYs) accumulated over time. Infection revision rates were used to determine the probability of undergoing a revision arthroplasty because of infection or infection recurrence. Other relevant data, such as medical costs, utilities and mortality rates, were estimated from the arthroplasty literature or from in-hospital resource. The analysis shows that DAC reduces cumulated costs by 45% and increases effectiveness, in terms of QALYs, by 5.1%. The cost of one additional QALY with DAC is equal to €1,581.94, 47% less than the unitary cost obtained without DAC. In a population with a 2.0% revision rate, DAC is a dominant strategy that generates significant savings, amounting to € 7,905.34, for each patient undergoing a primary TJA. Last, the coating is already cost-effective in a population of patients undergoing primary hip or knee replacement with an expected incidence of infection, without the coating, of 0.5%.

DAC HYDROGEL COATING IS ASSOCIATED WITH A FAVORABLE COST-BENEFIT-RATIO

DAC® hydrogel coating is the result of a collaborative EU founded project

EU iDAC PROJECT

Project acronym: **IDAC**

Participants: Italy (Coordinator), Greece, France, Belgium, Finland, Netherlands, Germany

Project N°: 277988

Total costs: € 4 029 693

EU contribution: € 3 000 000

Duration: January 2012 - June 2015

Anti-bacterial gel fights infection in knee and hip replacements

EU-funded project develops special coating for bone implants that cuts the risk of infection and minimises the need for further surgery, potentially benefitting thousands of patients across Europe.

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Every year a fast-growing number of patients in Europe receive knee and hip replacements. While most operations are successful, implants carry a significant risk of infection, with 1-2% of all hip and knee replacements getting infected after surgery.

In Italy alone, the cost of such infections is estimated to be €90-100 million (2011 figures) per year due to the cost of prolonged hospital stays – in particular for Methicillin-Resistant Staphylococcus Aureus (MRSA) infections – and the higher costs of secondary surgery.

Aiming to cut implant infection rates, EU-funded project IDAC has developed a special coating for implanted biomaterial. It is capable of both being absorbed by the body and preventing bacteria from colonising the implant.

"Periprosthetic joint infection is a serious and challenging issue for the patient and health care systems. It can result in severe functional limitation of the joint replacement, pain and disability," says project coordinator Daniele Pressato of Novagenit in Italy.

Special antibacterial coating

IDAC researchers developed a resorbable hydrogel that carries antibiofilm and antibacterial compounds. The gel – called an implant defensive antibacterial coating, or IDAC – is highly effective and easy to use as it is available in a single-use, sterile kit.

The hydrogel works as a barrier against biofilm formation. Surgeons mix it with different active antibacterial drugs during surgery, allowing the correct dosage for each individual patient. It is spread over the orthopaedic implants, effectively winning the 'race to the surface' against bacteria which can be unintentionally introduced during surgery.

IDAC has no drug-resistance risks, and can be stored for up to two years in a refrigerator as a powder in a prefilled syringe. It can be delivered in a few minutes and doesn't require any

Page 1 of 2

Research and Innovation

specific training of a surgeon or nurse.

Successful clinical trials

The gel was tested in two randomised, controlled, single-blind clinical trials carried out in four European Centres of excellence for orthopaedic surgery. In the first trial, hip or knee replacement patients were randomly assigned to receive either IDAC gel-coated or uncoated implants.

"The clinical outcomes after 12 months show a high safety profile for the gel and a significant reduction in the incidence of infection compared to the untreated group," says Pressato. Patients treated with IDAC did not develop any infection, while 7.5% of patients not treated with IDAC developed an infection.

In a second trial, patients receiving treatment for fractures in long bones had gel-coated implants of plates, nails and screws, while another group had uncoated implants. "Even in this trial the results showed a significant reduction of infection in the gel-treated groups," says Pressato.

The project also successfully demonstrated the ability of the hydrogel to be resorbed by the body within 72 hours, helping to avoid the risk of side effects or interfering with the osteointegration of the implant.

Unique position on the global market

IDAC was awarded a patent in 2013 in the EU and US, and it is currently available on the European market (with a CE mark). It has no direct competitors in a market which is growing as the demand for orthopaedic implants increases by about 2.5-4 % a year.

Pressato expects demand to continue to rise, and he hopes that it will soon be available on markets in the Far East and the United States. In the future, the gel could also be adapted to other sectors including plastic surgery, chronic wound management, dental surgery and oncological orthopaedics.

Project details

- Project acronym: **IDAC**
- Participants: Italy (Coordinator), Greece, France, Belgium, Finland, Netherlands, Germany
- Project N°: 277988
- Total costs: € 4 029 693
- EU contribution: € 3 000 000
- Duration: January 2012 - June 2015

See also

Project website: http://www.i-dac.eu/
Project details:
http://cordis.europa.eu/project/rcn/101783_en.html

View the article online:
http://ec.europa.eu/research/infocentre/article_en.cfm?artid=44636

Page 2 of 2

Research and Innovation

DAC® hydrogel coating is internationally recognized as one of the most promising technologies to reduce the burden of post-surgical infection in orthopaedics.

THE BONE & JOINT JOURNAL

■ SPECIALTY UPDATE

The management of periprosthetic infections in the future

A REVIEW OF NEW FORMS OF TREATMENT

D. A. George,
V. Gant,
F. S. Haddad

From University College London Hospitals, London, United Kingdom

The number of arthroplasties being undertaken is expected to grow year on year, and periprosthetic joint infections will be an increasing socioeconomic burden. The challenge to prevent and eradicate these infections has resulted in the emergence of several new strategies, which are discussed in this review.

Cite this article: ***Bone Joint J*** **2015;97-B:1162–9.**

Despite many initiatives to reduce it over the years, the rate of periprosthetic joint infection

times[12] due to their shedding pathogens from their skin, respiratory particles, hair and

DAC® hydrogel coating is **mentioned among the most promising technologies to mitigate the impact of peri-prosthetic infections in a Specialty Update paper published in 2015 by Prof. Haddad and co-workers from the University College London Hospitals, London, United Kingdom. [22]**

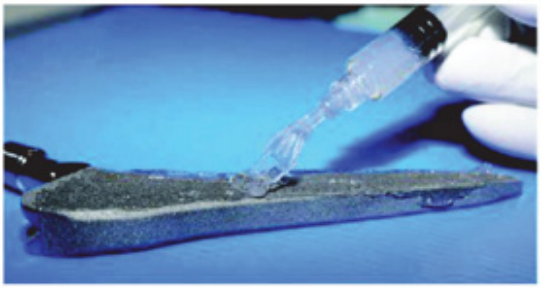

Fig. 3a

Fig. 3b

Photographs showing a disposable antibacterial coating (DAC) hydrogel; (a) hydrogel spread on a titanium prosthesis using a syringe, (b) layers of the hydrogel on the prosthesis (reproduced from Drago L, Boot W, Dimas K, et al. Does implant coating with antibacterial-loaded hydrogel reduce bacterial colonization and biofilm formation in vitro? Clin Orthop Relat Res 2014;472:3311-3323)[107]

List of refence websites

English
www.novagenit.com
www.dac-coating.com
www.coatingdac.com

Brochure: http://www.oudshoornbv.com/beheer/file.php?file=DAC-Gel_brochure.pdf

Thesis: https://dspace.library.uu.nl/bitstream/handle/1874/371375/Boot.pdf?sequence=1&isAllowed=y

French
https://en.calameo.com/read/00490786713e9cabc8a77

Italian
https://core.ac.uk/download/pdf/81802372.pdf

List of reference videos

http://www.dac-coating.com/dac/video/
http://www.novagenit.com.au/dac/dac-videos
http://www.novagenit.com.au/dac/what-is-dac
http://www.dac-coating.com/dac/dac-barrier-effect/

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