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.

<table>
<thead>
<tr>
<th>Infection risk after joint arthroplasty:</th>
<th>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]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection risk after osteosynthesis:</td>
<td>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]</td>
</tr>
<tr>
<td>Leading reason for revision:</td>
<td>Peri-prosthetic hip and knee infection is among the first three reasons for joint replacement failure, according to the registers; [4]</td>
</tr>
<tr>
<td>Mortality risk:</td>
<td>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]</td>
</tr>
<tr>
<td>Additional costs:</td>
<td>the average cost of management of infection after hip fracture surgery is &gt; 30,000 Euros. [6] The cost for the management of any single case of hip or knee PJI ranges from 40,000 to &gt; 100,000 Euros. [7, 8]</td>
</tr>
</tbody>
</table>

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 POLYMERS
- 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 deesterification 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]
IN VIVO DATA

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.

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]

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.

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) (I-V ANC), 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-V ANC).

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-V ANC groups, respectively, demonstrating a clear protective effect of the coating on bone healing. [15]

<table>
<thead>
<tr>
<th></th>
<th>Bony bridging &gt; 75% fracture healing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>0 %</td>
</tr>
<tr>
<td>s-V ANC</td>
<td>33 %</td>
</tr>
<tr>
<td>l-V ANC</td>
<td>50 %</td>
</tr>
</tbody>
</table>

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

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 cefazidime 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.

<table>
<thead>
<tr>
<th></th>
<th>Controls (N=184)</th>
<th>Treated (N=189)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delayed wound healing</td>
<td>7 (3.8%)</td>
<td>2 (1.2%)</td>
<td>0.1</td>
</tr>
<tr>
<td>Other complications</td>
<td>5 (2.7%)</td>
<td>4 (2.1%)</td>
<td>0.7</td>
</tr>
<tr>
<td>Peri-prosthetic infection</td>
<td>11 (6.0%)</td>
<td>1 (0.6%)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

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

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

Kostantinos Malizos¹ · Michael Blauth² · Adrian Danita³ · Nicola Capusano³ · Riccardo Mezzoprete⁴ · Nicola Logoluso⁵ · Lorenzo Drago⁶ · Carlo Luca Romano⁷

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 antibioticloaded 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.

<table>
<thead>
<tr>
<th></th>
<th>Controls (N=127)</th>
<th>Treated (N=126)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delayed wound healing</td>
<td>7 (5.5%)</td>
<td>5 (3.9%)</td>
<td>0.76</td>
</tr>
<tr>
<td>Delayed union</td>
<td>5 (3.9%)</td>
<td>2 (1.6%)</td>
<td>0.44</td>
</tr>
<tr>
<td>Other complications</td>
<td>6 (4.7%)</td>
<td>4 (3.2%)</td>
<td>0.77</td>
</tr>
<tr>
<td>Infection</td>
<td>6 (4.7%)</td>
<td>0 (0.0%)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

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

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]

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

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

Level of evidence III.
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.

<table>
<thead>
<tr>
<th></th>
<th>DAC (N=27)</th>
<th>Controls (N=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harris Hip Score</td>
<td>84.6 ± 15.8</td>
<td>81.6 ± 15.2</td>
</tr>
<tr>
<td>Hospital stay incl. rehabilitation (days)</td>
<td>28.2 ± 3.9</td>
<td>33.8 ± 5.4</td>
</tr>
<tr>
<td>Hip dislocation</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Delayed wound healing</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Infection</td>
<td>0</td>
<td>4 (14.8%)</td>
</tr>
</tbody>
</table>

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

Abstract

Antibacterial Hydrogel Coating in the Prevention of Periprosthetic Joint Infection After Bone Reconstruction with Megaprosthesi: a Consecutive Case Series
C. Zoccali 1, R. Biagini 1, P.A. Daolio 2, D.A. Campanacci 3

Oncological Orthopedics, Regina Elena National Cancer Institute, Rome, Italy. 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.

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

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, Israel, 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).

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

<table>
<thead>
<tr>
<th>Australia</th>
<th>Italy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Czech Republic</td>
<td>New Zealand</td>
</tr>
<tr>
<td>Denmark</td>
<td>Norway</td>
</tr>
<tr>
<td>Finland</td>
<td>Poland</td>
</tr>
<tr>
<td>France</td>
<td>South Africa</td>
</tr>
<tr>
<td>Germany</td>
<td>Spain</td>
</tr>
<tr>
<td>Greece</td>
<td>Switzerland</td>
</tr>
<tr>
<td>Holland</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>Israel</td>
<td></td>
</tr>
</tbody>
</table>
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  
COMPRESSORIO 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. C.LI. HUMANITAS  
IST. ORTOPEDICO GALEAZZI - MILANO  
IST. CODIVILLA-PUTTI - CORTINA  
MARK MEDICAL SPA - GORIZIA  
OSP. PRI ACCR NIGRISOLI - BOLOGNA  
OSP. S. MARIA DEL CARMINE -ROVERETO  
OSP. TREVIGLIO / CARAV AGGIO - 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 VVIPITENO  
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  
POLICLÍNICO UNIV. A.GEMELLI - ROMA  
OSP. RIEI  
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  
POLICLÍNICO PALERMO  
CLINICA NOTO PALERMO  
IOR RIZZOLI BAGHERIA  
OSP. Vallo della Lucania  
OSP.le Fatebenefratelli Benevento  
OSP.le Eboli  
Policlinico Napoli  
OSP.le civile Salerno
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<td>Nuffield Orthopaedic Centre, Oxford</td>
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<td>St Vincent’s Private Hospitals Ltd</td>
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<td>Argentina</td>
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</table>
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.

<table>
<thead>
<tr>
<th>Author and date of publication</th>
<th>Treated Patients</th>
<th>Mean Follow-Up (Months)</th>
<th>Number of Adverse Events</th>
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<tr>
<td>Romanò et al. (2016)</td>
<td>189</td>
<td>14.5</td>
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<td>Malizos et al. (2017)</td>
<td>126</td>
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<td>Capuano et al. (2018)</td>
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<td>Zagra et al. (2019)</td>
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<tr>
<td>Zoccali et al. (2019)</td>
<td>47</td>
<td>18</td>
<td>0</td>
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<tr>
<td><strong>Total</strong></td>
<td><strong>411</strong></td>
<td><strong>22 ± 7</strong></td>
<td><strong>0</strong></td>
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</table>

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.

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.

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]
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

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

List of reference websites

English

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


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.dac-coating.com/dac/dac-barrier-effect/
References


