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INFECTION

Antibacterial coating of implants: are we missing something?

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Implant-related infection is one of the leading reasons for failure in orthopaedics and trauma, and results in high social and economic costs. Various antibacterial coating technologies have proven to be safe and effective both in preclinical and clinical studies, with post-surgical implant-related infections reduced by 90% in some cases, depending on the type of coating and experimental setup used. Economic assessment may enable the cost-to-benefit profile of any given antibacterial coating to be defined, based on the expected infection rate with and without the coating, the cost of the infection management, and the cost of the coating. After reviewing the latest evidence on the available antibacterial coatings, we quantified the impact caused by delaying their large-scale application. Considering only joint arthroplasties, our calculations indicated that for an antibacterial coating, with a final user's cost price of €600 and able to reduce post-surgical infection by 80%, each year of delay to its large-scale application would cause an estimated 35 200 new cases of post-surgical infection in Europe, equating to additional hospital costs of approximately €440 million per year. An adequate reimbursement policy for antibacterial coatings may benefit patients, healthcare systems, and related research, as could faster and more affordable regulatory pathways for the technologies still in the pipeline. This could significantly reduce the social and economic burden of implant-related infections in orthopaedics and trauma.

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The impact of implant-related infections in orthopaedics and trauma

The biomaterials and medical devices industry has experienced rapid growth in recent decades, thanks to technological advances and a sustained clinical demand. The industry is projected to maintain a compound annual growth rate of approximately 10% over the next ten years, with orthopaedics and cardiovascular surgery continuing to lead the market worldwide.[1,2]

According to a recent report, approximately 1.5 million joint arthroplasties are performed annually in Europe,[3] while the prevalence of individuals with a hip or knee prosthesis in the United States is around seven million.[4] Osteosynthesis for long bone fractures shows a similar impact, with around 270 000 new implants inserted each year in France, or 403 per 100 000 people.[5] This is comparable to the 395 joint arthroplasties performed each year per 100 000 people in the same country.[3]

Although the application of implanting biomaterials is becoming more common, their long-term durability is not guaranteed, and infection remains one of the main reasons for early failure in orthopaedics and trauma. Despite the introduction of routine systemic antibiotic prophylaxis administration, as well as improved surgical facilities and procedures, prosthetic joint infection (PJI) affects between 0.5% and 15% of patients undergoing primary or revision joint arthroplasty, when considering high-risk and oncological cases;[6,7] these figures may be underestimated.[8] Surgical site infection (SSI) after internal osteosynthesis for closed fracture has a reported incidence ranging from 0.5% to 10%,[9-12] and up to 50% after open fractures.[13] Post-surgical infection following spine surgery occurs in 1% to 14% of patients, depending on the pre-operative diagnosis and type of surgery;[14,15] similar figures are reported for a variety of surgical procedures involving implantable devices in orthopaedics and trauma.[16-18]

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Table I. Economic impact of prosthetic joint infection (PJI). Different values for similar pathological conditions reflect the variability of the costs across countries, the heterogeneous methodologies used for calculation, and the different strategies adopted for infection management

Author	Country	Condition	Economic analysis performed	Cost
Klouche et al[23] (2010)	France	Hip PJI	Hospital costs for revision surgery	€23 757
Haenle et al[24] (2012)	Germany	Knee PJI	Hospital costs for revision surgery	€25 195
Lieb et al[25] (2015)	Germany	Knee PJI	Hospital costs for revision surgery	€19 946
Romanò et al[29] (2010)	Italy	Hip PJI	Hospital costs for revision surgery	€60 394
Alp et al[27] (2016)	Turkey	Hip and knee PJI	Hospital costs for revision surgery	$16 999
Vanhegan et al[26] (2012)	United Kingdom	Hip PJI	Hospital costs for revision surgery	£21 937
Kamath et al[28] (2015)	United States	Hip PJI	Hospital costs for revision surgery	$31 753
		Knee PJI	Hospital costs for revision surgery	$25 692
Kurtz et al[20] (2012)	United States	Hip PJI	Hospital costs for revision surgery	$30 300
			Total hospital charges for revision surgery	$93 600
		Knee PJI	Hospital costs for revision surgery	$24 200
			Total hospital charges for revision surgery	$74 900
Parisi et al[30] (2017)	United States	Hip PJI	Long-term economic effect as per Markov utility model	$390 806
Brochin et al[31] (2018)	United States	Hip PJI	Hospital costs for revision surgery	$31 312

Table II. Classification of antibacterial implant protection strategies[40]

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

The economic and social costs of implant-related infections are significant,[19-22] with high morbidity and a possible increase in mortality.[10] In particular, direct hospital costs, related to the management of PJI, range from approximately €20 000 to €60 000 (Table I),[23-31] while the long-term economic effect of post-surgical infection after joint arthroplasty has been calculated to exceed $390 000 per case.

Antibacterial coating in orthopaedics and trauma

Every time a biomaterial is implanted, a competition between the host and the bacteria occurs for surface colonization. In the event of bacterial adhesion to an implant, immediate biofilm formation starts, making the bacteria extremely resistant to the host's defence mechanisms and antimicrobials.[32-34] In fact, fully formed biofilms are found a few hours after the first bacterial adhesion on a substrate,[35,36] thus, importantly, the destiny of an implant is decided at the time of surgery. Hence, all efforts should be directed to create, at the time of surgery and implant application, a local environment favourable to the host and hostile to the microorganisms.

This observation explains why short-term systemic antibiotic prophylaxis is equally as effective as long-term prophylaxis,[37] and forms the basis for local protection of biomaterials through suitable antibacterial coating or finishing technologies.[38,39] Based on their mechanism of action, antibacterial coatings have been classified as follows (Table II).[40]

Passive surface finishing/modification: this strategy is aimed at preventing or reducing bacterial adhesion to implants through surface chemistry and/or structure modifications, without the use of any pharmacologically active substance. Examples of this approach include modified titanium dioxide surface or polymer coatings.

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

Perioperative antibacterial local carriers or coatings: this strategy employs local antibacterial carriers, or coatings, that are not built into the device, but rather are applied during surgery, immediately prior to the insertion of the implant. They may have direct or synergistic antibacterial/

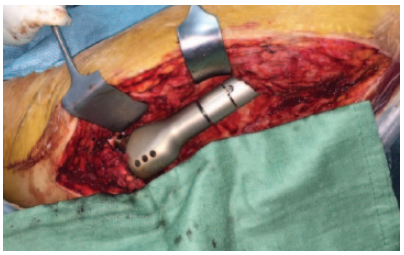

Fig. 1a

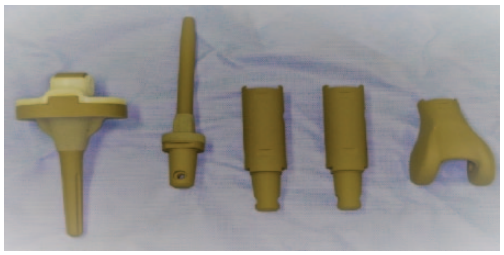

Fig. 1b

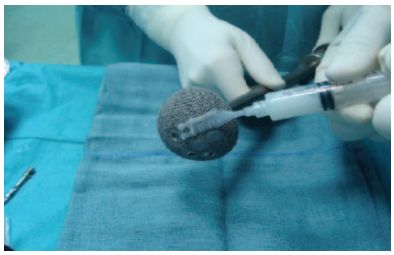

Fig. 1c

Examples of antibacterial coating of joint prosthesis: a) silver-coated hip tumour prosthesis; b) iodine-coated tumour prosthesis; c) vancomycin-loaded Defensive Antibacterial Coating (DAC) hydrogel, applied at surgery on an acetabular titanium component.

anti-adhesive activity or may deliver high local concentrations of loaded antibiotics or antibacterials.

Translating preclinical research to clinical application is particularly challenging, time-consuming, and expensive. As a result, many promising coating technologies that show clear efficacy and safety in the preclinical setting fail to reach the market.[41] Besides local antibiotic carriers such as antibiotic-loaded poly(methyl methacrylate) (PMMA), bone grafts, and bone substitutes that were not specifically designed to act as antimicrobial coatings of implants, only four technologies are currently available in orthopaedics and trauma for clinical use, or at least with reported clinical results.[42] These are silver and iodine coatings, gentamicin poly(D, L-lactide) (PLLA) coating, and a fast-resorbable hydrogel coating composed of covalently linked hyaluronan and PLLA (Defensive Antibacterial Coating (DAC); Novagenit Srl, Mezzolombardo, Italy) (Fig. 1) (Table III).

Silver coatings. Silver antibacterial activity is well known, and mostly depends on the ability of dissolved cations to interfere with bacterial cell membrane permeability and cellular metabolism. Moreover, when released in an aqueous medium, silver cations also contribute to the formation of reactive oxygen species and other mechanisms that potentially influence prokaryotic cells.[43] Different technologies are currently used to apply the silver coating to metallic orthopaedic implants.[42,44] Comparative and prospective studies are lacking; only retrospective case series have been published, with coating application restricted to tumour prostheses.[45,46]

A retrospective case-control study was recently published by Wafa et al[47] that reported the results of silver-coated tumour prostheses in 85 patients compared with 85 matched control patients treated between 2006 and 2011. Indications included 50 primary reconstructions (29.4%), 79 one-stage revisions (46.5%), and 41 two-stage revisions for infection (24.1%). At a minimum follow-up of 12 months, comparing the matched silver-free control group with the silver-coated mega-endoprosthesis group, there was a significant reduction in the overall postoperative infection rate from 22.4% to 11.8% ($p = 0.03$) in favour of the silver-coated implant group, with a mean reduction of approximately 48% in infection rate.

Despite these results, the routine use of silver-coated implants remains rather limited for several reasons. The main concerns have been about the toxicity of silver ions; the same activity that interferes with prokaryotic cells could also interfere with eukaryotic cells, exerting cytotoxicity on bone cells, while the silver ions released could accumulate and cause harm in distant locations within the body.[48] Another limitation is the incomplete protection of the implant, since the intramedullary part of the prosthesis and some modular components of the implant (including the acetabular component and the polyethylene insert) cannot be coated. Moreover, only a few implant designs are offered with silver coating protection, while the cost of the technology remains quite high when considering applications outside oncology.[49]

Iodine coating. Povidone-iodine can be used as an electrolyte, resulting in the formation of an adhesive, porous anodic oxide with the antiseptic properties of iodine.[50] Besides extensive preclinical studies,[50-52] excellent clinical efficacy was reported for iodine coating of titanium alloys in a continuous, non-comparative series of 222 patients.[53] Preoperative diagnoses included tumour in 95 cases (42.8%), 34 limb deformities (15.3%), 29 cases of degenerative disease (13.1%), 27 cases of osteomyelitis (12.2%), 24 non-unions (10.8%), and 16 fractures (7.2%). A variety of implants were used: 82 spinal instrumentations, 55 plates for osteosynthesis, 36 external fixations (pins and wires), 32 tumour prostheses, ten hip prostheses, four knee prostheses, two nails, and one cannulated screw. At a mean follow-up of 18.4 months (3 to 44), acute infection developed in three tumour cases (1.9%).

Two more recent non-comparative studies – one investigating iodine coating and megaprosthesis,[54] the other investigating total hip arthroplasty (THA)[55] – confirmed the safety and efficacy of the technology at longer follow-ups. Based on these findings, clinical trials are currently ongoing to meet the regulatory requirements for market approval. While no adverse event has been reported to date, the longer-term effects of local application of iodine coating and the application to materials other than titanium are yet to be assessed.

Gentamicin PLLA coating. Approximately a decade ago, the gentamicin PLLA matrix coating for tibial nails was

Table III. Comparison of clinically available antimicrobial coating technologies specifically designed for orthopaedics and trauma implants

Factor	Silver	Iodine	Gentamicin poly(D, L-lactide) matrix	Hyaluronic acid and poly(D, L-lactide) hydrogel
Regulatory phase	Market	Clinical trials	Market	Market
Trademark and manufacture company	Agluna (Accentus Medical Ltd, Didcot, United Kingdom); Mutars (Implantcast GmbH, Buxtehude, Germany); PorAg (Waldemar Link GmbH & Co. KG, Hamburg, Germany)	Not applicable	UTN PROtect Tibial Nail (DePuy Synthes, Bettlach, Switzerland); Expert Tibial Nail (ETN) PROtect (DePuy Synthes, Johnson & Johnson, New Brunswick, New Jersey)	Defensive Antibacterial Coating (DAC) (Novagenit Srl, Mezzolombardo, Italy)
Mechanism of action	Silver ion release	Iodine release	Gentamicin release	Antifouling activity with ancillary antibiotic release
Main applications	Tumour mega-prosthesis	Titanium implants including spine instrumentation, hip and knee joint arthroplasties, plates and screws	Tibial nail for the treatment of tibial fractures and nonunions	Orthopaedics, traumatology, dentistry, and maxillofacial implants
Main limitations	Only available for some tumour prostheses; lack of prospective, comparative studies; incomplete implant protection (may only be applied to the extramedullary part of the implant and may only be applied to metallic substrate); possible ion toxicity	Not available on the market; lack of comparative studies; incomplete implant protection (lack of data on the application to materials other than titanium); lack of data on long-term safety	Only available for one specific application; lack of prospective, comparative studies; incomplete implant protection (fixation screws and screw holes not protected; may not work against gentamicin-resistant strains)	Clinical trials only available for primary and revision joint arthroplasty and internal osteosynthesis for closed fractures; lack of long-term studies; may not prevent late haematogenous infection

first introduced into clinical use in Europe. The coating, based on a fully resorbable PLLA matrix with gentamicin sulphate, provides 80% release of the antibiotic within the first 48 hours.[56] In the first published clinical report, Fuchs et al[57] observed no deep infections at six months' follow-up in 21 patients treated with a UTN PROtect Tibial Nail (DePuy Synthes, Bettlach, Switzerland) for closed or open tibial fractures, as well as for revisions. Furthermore, Metsemakers et al[58] reported a retrospective analysis, including nine patients with a Gustilo and Anderson grade II or grade III open tibial fracture, four infected nonunions, two acute tibial shaft fractures pretreated with external fixation, and one aseptic nonunion with a soft-tissue defect. At 18 months' follow-up, no implant-associated deep infection was reported. Finally, the most recent and largest study, using data from four centres, analyzed the outcome of 99 patients with fresh open or closed tibial fractures or undergoing nonunion revision surgery.[59] At 18 months' follow-up, deep surgical site infection or osteomyelitis was noted in 4/55 patients (7.2%) after fresh fracture and in 2/26 patients (7.7%) after revision surgery. The heterogeneous material and the lack of a comparator makes the interpretation of these results particularly difficult.

A limit of this technology is the fact that it is only available for the tibia and for one specific nail design. Furthermore, screws and fixation holes are not protected by the coating, while gentamicin resistance, ranging from 2% to 50% in Europe,[60] may reduce the efficacy of the coating in some cases.

DAC hydrogel. DAC hydrogel is the first antimicrobial coating specifically designed to protect implanted biomaterials in orthopaedics, traumatology, dentistry, and maxillofacial surgery.[61,62] The device is based on previous observations of the ability of hyaluronic-based compounds to reduce bacterial adhesion and biofilm formation, and to protect against various infectious agents.[63-68] In line with these observations, significant reductions of adhering bacteria on sterile titanium discs, coated with DAC hydrogel, were observed after 15, 30, 60, and 120 minutes of incubation.[62]

Although designed as a stand-alone product, the DAC hydrogel has demonstrated itself to be capable of entrapping several antibacterial agents at concentrations ranging from 2% to 10%, released locally for up to 72 hours, with an amount of drug released that is hundreds or thousands of times higher than the minimum inhibitory concentration (MIC), in a time- and dose-dependent manner.[61]

The safety and efficacy of DAC hydrogel have been investigated in animal studies that showed the ability of the antibiotic-loaded hydrogel to prevent implant-related infection significantly with[69] and without[70] systemic antibiotic prophylaxis. In a further study, focusing on the impact on bone healing and implant osteointegration, no detrimental effects were noted in vancomycin-loaded DAC-coated implants.[71]

In the first large multicentre randomized prospective clinical trial, a total of 380 patients were included who were scheduled to undergo primary (n = 270), revision (n = 110), total hip (n = 298), or total knee (n = 82) joint arthroplasty with a cementless or a hybrid (partially cemented) implant.[72] The patients were randomly assigned, in six European orthopaedic centres, to receive an implant with the DAC coating, intraoperatively loaded with antibiotics, or without the coating (control group). Overall, 373 patients were available at a mean follow-up of 14.5 months (SD 5.5). A total of 11 SSIs were observed in the control group, with only one observed in the treatment group (6% *vs* 0.6%; p = 0.003). No local or systemic side effects related to the DAC hydrogel coating were

Table IV. Main effects of preventing post-surgical infection after joint arthroplasty according to various simulations

Authors (year)	Baseline post-surgical infection rate in target population, %	Expected infection reduction rate, %	Estimated reduction in deep infections, n (cases per 100 000 procedures)	Estimated annual cost savings per index procedure
Shearer et al[77] (2015)	*0.3*	*10.0*	30	$98
Graves et al[76] (2016)	*2.4*	*87.0*	1915	£108
Trentinaglia et al[49] (2018)	*2.0*	*80.0*	1600	€200

reported, and no detectable interference with implant osteointegration was noted.

In another multicentre prospective study, 256 patients undergoing osteosynthesis for a closed fracture were randomly assigned, in five European orthopaedic centres, to receive the antibiotic-loaded DAC coating or to a control group without coating. At a mean follow-up of 18.1 months (SD 4.5), six SSIs (4.6%) were observed in the control group compared with none in the treated group ($p < 0.02$). No local or systemic side effects related to DAC hydrogel coating were observed, and no detectable interference with bone healing was reported.[73] However, it should be noted that, although the mean follow-up period was over 1.5 years, this is relatively short from the point of view of osseointegration and implant survival.

More recently, DAC hydrogel-coated cementless one-stage exchange for infected prosthesis showed similar results when compared with a retrospective series of matched controls treated with two-stage revision without the coating. No difference in the rate of infection recurrence was observed at a minimum follow-up of two years.[74] In line with these findings, in another case-control study, at a mean follow-up of 2.7 years (2.1 to 3.5), cementless two-stage hip revision for infected cases showed no evidence of infection recurrence, implant loosening, or adverse events in the DAC-treated group, compared with four cases of infection recurrence in the control group.[75] However, as previously noted,[72] longer-term data are required to examine delayed or late prosthetic joint infections. In fact, while the quick resorption of the hydrogel makes long-term side effects quite unlikely, this same feature may limit or prevent the ability of this technology to protect the implant from late, haematogenous infections.

Effects of delaying the routine use of antibacterial coatings. Graves et al[76] have demonstrated that implementing measures against post-surgical infection after joint arthroplasty results in a measurable reduction of PJI, with considerable cost-saving and improved quality of life. According to their simulation, considering a cohort of 77 321 patients undergoing primary THA, a combined treatment strategy able to reduce post-surgical infection (odds ratio (OR) 0.13) may prevent 1481 cases of deep infection, leading to annual cost savings of £8 325 277 when compared with a baseline strategy (plain cement, conventional ventilation, and no systemic antibiotics).

Shearer et al[77] calculated that the net monetary benefit resulting from a 10% reduction in PJIs was $278 per index procedure, and concluded that strategies aimed at reducing PJI may have a greater effect on cost and long-term effectiveness of THA than further enhancements in implant longevity.

Our group recently described an algorithm to calculate the cost-effectiveness of different antibacterial coating strategies applied to joint prostheses, taking both direct and indirect hospital costs into account.[49] According to this model, an antibacterial coating technology able to reduce post-surgical infection by 80%, at a cost per patient of €600, would provide a reduction in hospital costs of €200 per patient if routinely applied in a population that would otherwise have an expected post-surgical infection rate of 2% (Table IV). Projecting these figures at a European level, with approximately 2.2 million joint arthroplasties performed per year,[3] we may speculate that a year of delay in the routine use of such a coating would result in 35 200 additional PJI cases per year with additional annual costs of approximately €440 million per year. These calculations do not include any costs that might result from an increased mortality rate, permanent disability deriving from post-surgical infection, or potential medicolegal claims.

In conclusion, implant-related infections have a pronounced social and economic impact,[78] with increased rates of morbidity and mortality.[79] Unless novel, effective measures are taken to reduce the incidence of SSIs, these complications will become a growing burden to healthcare systems over the coming decades.[80,81] Despite the recognized need for implant-related infection containment and the demonstrated efficacy of some antibacterial coatings notwithstanding, only a few technologies are currently available in orthopaedics and trauma. In fact, while some potentially effective solutions are found not suitable for orthopaedic implants, due to cytotoxicity, immunoreactivity, or interference with bone healing and osteointegration, those successfully tested *in vitro* and *in vivo* may still be unable to reach large scale clinical application, due to biotechnological, economic, and regulatory issues. In particular, while economic calculations do allow to predict a positive cost-benefit ratio – at least in some applications, as shown here – to the best of our knowledge, no specific reimbursement for coated implants is currently foreseen in European countries. On the other hand, a number of technologies are struggling in the pipeline, awaiting the long and expensively attained approval of regulatory bodies. While adverse events resulting from a new technology are promptly

and widely reported, the opportunity cost following the delayed or denied introduction of potentially useful new products remains largely unknown to the public. This imbalance has led to an increasingly strict vision from policymakers and regulatory bodies concerning new medical device approval.

Given the potential benefits that can be anticipated scientifically by a wider application of antibacterial implant-coating technologies, in our opinion, effort should be made to increase the awareness of healthcare providers and their patients concerning the existing technologies and their possible contribution to mitigate septic complication. Furthermore, specific reimbursements for the currently available coatings should be introduced, with faster and more affordable regulatory pathways for the most promising technologies in the pipeline. At the same time, an efficient and independent post-marketing surveillance system needs to be set at national or international level, in order to monitor the clinical results and promptly report on any possible side effect or long-term complication of such new technologies.

Supplementary Material

The antibacterial coating cost impact calculation spreadsheet used to calculate the costs given in this study.

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- C. L. Romanò: Wrote the manuscript.
- H. Tsuchiya: Edited the manuscript.
- I. Morelli: Reviewed the literature, Edited the manuscript.
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