Bactiguard® Technology

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Background and Clinical Need

Healthcare-associated infections (HAI) are one of the major challenges in medicine: 3.2 million people are estimated to receive an infection diagnosis every year in Europe, of whom approximately 37,000 become fatal [1]. This leads to 16 million extra-days of hospital stay, and an annual cost of approximately € 7 billion across Europe [2]. The frequency of periprosthetic infections after arthroplasty can vary broadly depending on site and type of reconstruction, ranging from 1-2 % for a primary arthroplasty [3] to as high as 36 % in the case of megaprosthesis [4]. It has been calculated that affected patients have a lower chance of survival at 5 years than people affected by three of the most common types of cancer [5], as illustrated in Figure 1.

In orthopaedic trauma, it has been estimated that up to 30 % of cases may result in infection [6]. Almost 80 % of all open fractures present some bacterial contamination [7], many of which may develop into early, delayed and/or late established infections. The risk of infection can also differ widely depending on the classification of open fracture, varying between 0-2 % for Type I fractures, between 2-10 % for Type II fractures, and between 10-50 % for Type III fractures [8, 9]. A recent linear regression analysis of the available literature published since 2000 in peer-reviewed journals and conducted by Zimmer Biomet estimated that infections following intramedullary nailing (IMN) are diagnosed, on average, in the 1.6 % of cases for closed fractures and 11.9 % of cases for open fractures, with 0.1 % and 7.5 % of deep infections in closed and open fractures, respectively [10]. A breakdown of overall and deep infection rates per surgical site is presented in Table 1.

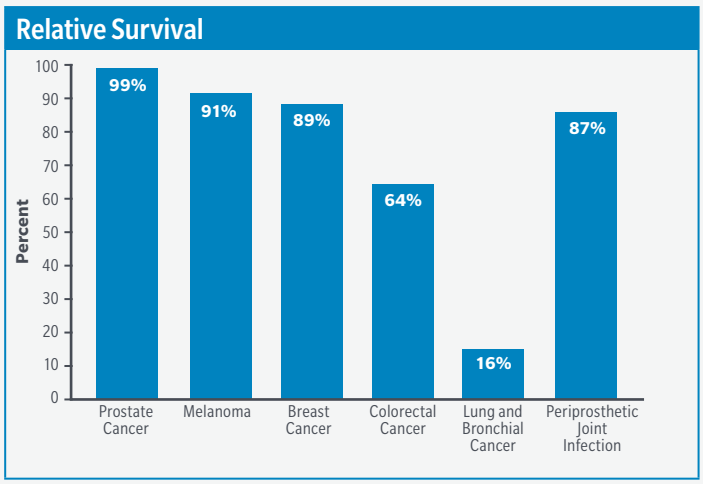

Figure 1. Five-year survival rate of patients affected by the most common forms of cancer, compared to patients affected by periprosthetic joint infection [5].

Site	Overall Infection Rate (%)	Deep Infection Rate (%)
Tibia	6.46	1.27
Distal Femur	3.92	0.94
Proximal Femur	1.53	0.09
Humerus	1.26	0.79
Ankle	7.9	5.01

Table 1. Rate of infection following IMN [10].

Socioeconomic Impact

Implant associated infections not only have a devastating impact on the quality of life of patients, but also have significant socioeconomic consequences.

These infections place a significant personal burden on healthcare professionals [11] and an economic burden on healthcare systems. It has been estimated that, in Belgium, treatment costs for deep infections following tibial fractures are approximately 6.5 times higher than uninfected cases [12]. In the UK, infections following proximal femoral fractures present a median cost of £ 24,410 with length of stay of 132.5 days, compared to uninfected cases that present a median cost of £ 7,210 and require a length of stay of 30 days [13]. In Italy, an average additional cost of € 9,560 was estimated in case of orthopaedic surgical site infections [14].

Families and wider society are also hugely impacted [15], as patients affected by implant associated infections require additional care and assistance, and their mental health is negatively affected [16]; younger patients are significantly less likely to return to work within a year from fracture [17, 18], and elderly patients have a significantly increased risk of mortality and of not returning to their own home when they require further surgery following complications after fixation of proximal femoral fractures [19].

The Role of the Biofilm

The primary challenge with treating or eradicating implant-associated infections is the ability of certain bacteria to create a protected community called a biofilm. As represented in Figure 2, shortly after planktonic or 'free floating' bacteria have come into contact with a surface, they start to proliferate and embed themselves in an organic matrix known as the extracellular polymeric substance (EPS). Inside the biofilm, aggregates of bacterial microcolonies are shielded from the surrounding environment, making them less susceptible to the attacks of the immune system or to regular dosage of antibiotics [20].

As the biofilm matures, it can release new planktonic bacteria into the environment, resulting in a new cycle of biofilm formation and spread of the infection. The entire process from the colonisation of a surface by planktonic bacteria to the creation of a mature biofilm can take place in a few days [21].

In 2001, the U.S. Centers for Disease Control (CDC) estimated that biofilms cause 65 % of infections in the developed world [22,23], and the National Institutes of Health (NIH) later referenced 80 % in a public announcement in 2007 [24].

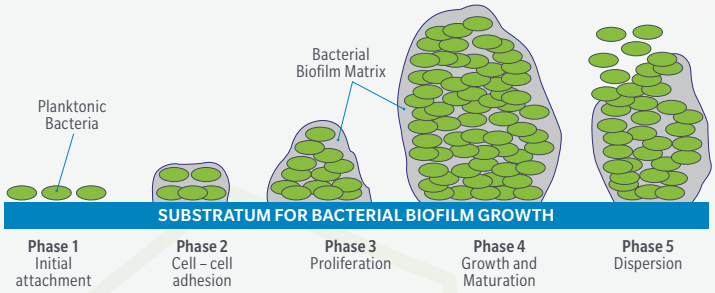

Figure 2. Biofilm formation on an implant surface.

Antibiotic Resistance

Current strategies for the control of implant associated infections rely primarily on the administration of local and systemic antibiotics. However, it is well known that bacteria develop resistance to antibiotics, even more so in healthcare facilities rather than in the community [25]. Without alternative treatments to antibiotics, it has been predicted that, by the year 2050, 10 million people worldwide will die every year due to multi-resistant microbial infections, overtaking the number of deaths caused by cancer [26].

The decreased susceptibility of bacteria grown in biofilms to antibiotics highly reduces the chances of eradicating these infections, thus further increasing the risk of triggering antibiotic resistance. Every year, more than 670,000 infections occur in the EU/EEA due to antibiotic-resistant bacteria, with the death of 33,000 people and with a cost for healthcare systems of € 1.1 billion as a direct consequence [27].

To address the growing concerns over antibiotic resistance and to ensure responsible antibiotic stewardship, Bactiguard Technology provides an alternative non antibiotic-releasing approach to tackle biofilms.

History of Bactiguard Technology [28]

The Bactiguard Technology has its origins in the work of Nobel Prize laureate Gustaf Dahlén. His apprentice Axel Bergström developed the technique of applying a thin layer of metals to non-conductive materials; Bergström's apprentice, Billy Södervall, started to apply the noble metal coating to medical devices in the 70's, filing numerous patents for the technology in the U.S.

The coating was first applied to urinary catheters through a partnership with BD (Becton, Dickinson & Company, previously C.R. Bard), with the first FDA clearance in 1994.

The Bactiguard Infection Protection (BIP) technology was then developed in the early 2000s, and in 2005 Bactiguard was founded as a standalone company, in Sweden. The first BIP urinary catheters were introduced to the European market in 2008, and the BIP central venous catheters (CVC) and BIP endotracheal tubes (ETT) in 2013.

In 2013, the technology was also licensed to Vigilenz Medical Devices to apply the noble metal coating to orthopaedic trauma products, including IM nails, which obtained the CE mark in 2018. Vigilenz was acquired by Bactiguard in 2020.

In 2019, Bactiguard and Zimmer Biomet entered into a global, exclusive licensing agreement for orthopaedic trauma implants, which led to the CE marking of the ZNN™ Bactiguard and ANN™ Bactiguard at the beginning of 2021.

The Bactiguard Technology has been applied to medical devices outside of orthopaedics for over 25 years, and to date over 200 million Bactiguard coated products have been sold worldwide (including Europe, U.S., Japan, China, Brazil, India and Mexico) [29].

1912 – Gustav Dahlén, Swedish Nobel Prize laureate in Physics. The man behind the AGA lighthouse system, from which Bactiguard Technology originates
1978 – Billy Södervall starts developing the Bactiguard Technology
1990 – Partnership with **C.R. Bard**
1994 – FDA 510k
1995 – Patent in the US
2005 – Bactiguard AB founded
2008 – Launch of **BIP Foley**
2013 – Launch of **BIP CVC & BIP ETT** License agreement with **Vigilenz**
2016 – Launch of **BIP ETT Evac**
2018 – Launch of **BIP Foley Tiemann & Female** Launch of **BIP CVC** with **Raulerson Syringe** CE mark of orthopaedic trauma implants with Bactiguard
2019 – Partnership with **Zimmer Biomet**
2020 – Acquisition of Malaysian **Vigilenz**
2021 – CE mark of **ZNN Bactiguard** and **ANN Bactiguard**

The Bactiguard Technology

Coating Characterization

The Bactiguard Technology is a stable and durable metallic coating that is firmly bound to the implant surface through strong covalent bonds [30,31].

More specifically, the Bactiguard coating is a noble metal alloy coating containing silver, gold and palladium that is applied to substrates via a wet chemistry process. The coating consists of a thin, non-continuous layer of discrete clusters, as shown by the Scanning Electron Microscope (SEM) and Time-of-Flight Secondary Ion Mass Spectrometry (ToF-SIMS) images in Figure 3 and Figure 4, respectively [32].

The amount of noble metals released by the coating has been shown to be well below the applicable tolerable intake or permitted daily exposure, thus demonstrating the toxicological safety of the Bactiguard coating [33,34]. In addition, since the coating is covalently bonded to the substrate, it does not meet the definition of a 'nanomaterial' according to the definition stated in the 2017/745/EU Medical Device Regulation [35].

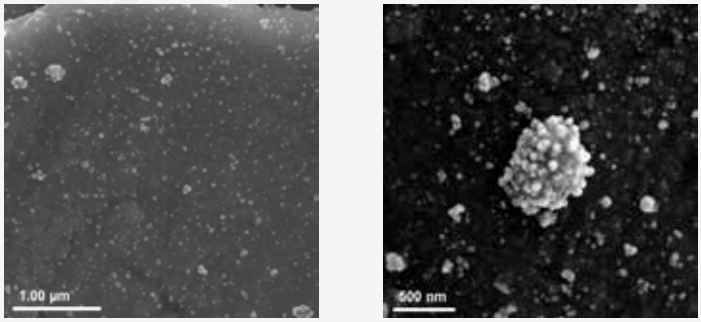

Figure 3. SEM micrographs of a titanium substrate with the Bactiguard Technology at lower (left) and higher (right) magnification. (SEM images taken internally at Zimmer Biomet)

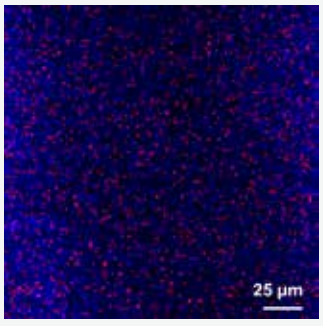

Figure 4. ToF-SIMS image showing the distribution of palladium (red) and silver (blue) on a silicone substrate [32].

Mechanism of Action

The noble metals in the Bactiguard coating have different electro-potentials and so, in combination, this results in a 'galvanic effect' that generates pico-currents (trillionth of an Ampere, 10^{-12} A) on the implant surface. These pico-currents lead to reduced adhesion of microorganisms to coated surfaces and, consequently, decreased possibility of biofilm formation, as discussed later. [36,37,38].

The electric potentials and currents that produce this galvanic effect in the coating have been measured via Electrostatic Force Microscopy (EFM) [39] and PeakForce TUNA Atomic Force Microscopy (AFM) [40], respectively (Figure 5). The current was found to vary between 0 to almost 250 pA, with an average of 71 pA compared to 0.17 pA in the uncoated control [40]. The magnitude of these currents is very small, and only detectable *in vitro* with these highly sensitive instruments.

The measured currents affect microbial adhesion by interfering with the respiratory chain, which in bacteria is located in the inter-membrane space, thus close to the surrounding environment. On the contrary, in eukaryotic (human) cells, which are about ten times larger than bacteria, the mitochondria (the respiratory organelles) are situated inside the cell membrane and are therefore more protected and less affected by electrical currents of such a small magnitude [41].

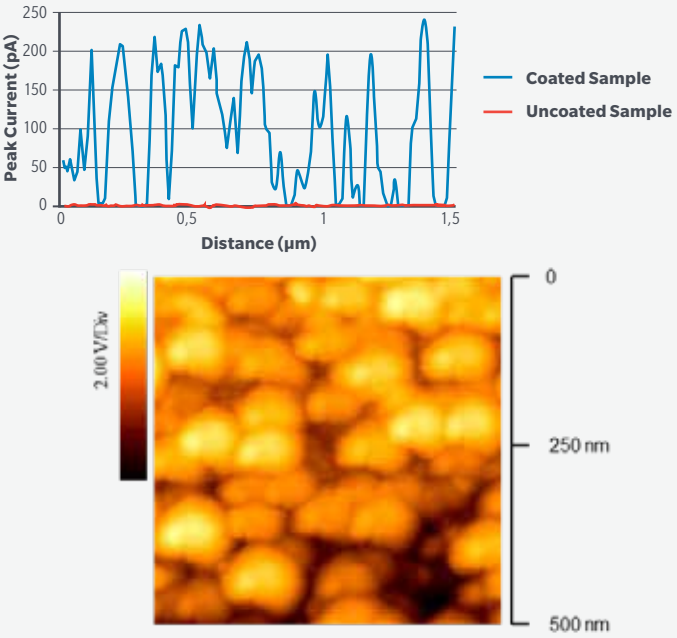

Figure 5. Top: Current distribution over a line on coated and uncoated stainless steel, measured using PeakForce TUNA AFM [40]. Bottom: EFM image showing the electric potential distribution on Bactiguard-coated glass slide [39].

While t5e galvanic effect requires the release of a very small amount of silver, the amount released during elution studies was found to be below the minimum inhibitory concentrations (MIC) reported in the literature for ionic silver [42]. The absence of inherent antibacterial properties due to this release of silver from the coating has also been confirmed with zone of inhibition tests, where none of the coated samples prevented or inhibited bacterial growth [42]. This is further evidence that the primary mechanism of action of the Bactiguard Technology is the galvanic effect.

Experimental and Clinical Evidence

In Vitro Evidence

The anti-adhesive nature of the Bactiguard coating has been demonstrated through *in vitro* microbial tests based on methods adapted from the work of Ahearn and co-workers at Georgia State University [43,44]. Numerous substrates, representing different Bactiguard-coated devices, have been tested against different microbial species; relevant results are summarised in Table 2.

	S. aureus	*P. aeruginosa*
Ti6Al4V rods	84%	99.997%
BIP Foley catheter (latex)	N.T.	85%
BIP Foley catheter (silicone)	97% (98% MRSA)	81%
BIP ETT (PVC)	91% (81% MRSA)	97%
BIP CVC (Polyurethane)	75% (79% coagulase negative *S. aureus*)	77%

Table 2. Reduction in adhesion of *Staphylococcus aureus* and *Pseudomonas aeruginosa* when the Bactiguard coating was applied to different substrates, compared to uncoated controls [45]. The Ti6Al4V rods were supplied by Zimmer Biomet. MRSA: methicillin-resistant *Staphylococcus aureus*; N.T.: Not tested.

Clinical Evidence

The reduction in bacterial adhesion observed *in vitro* has been shown to translate into reduction in infection rates in the clinical setting as well, for all Bactiguard-coated devices. Since urinary catheters were the first coated devices to enter the market, numerous studies have been published over the years reporting positive outcomes [46,47,48,49,50,51], the most recent being a randomised, prospective, multicentre study on 1,000 patients that showed a reduction in infections of 69 % compared to uncoated catheters over a mean duration of catheterization of 11 days [52]. A 52 % reduction in infection rate (median catheterization time 13 days) [53] and significantly fewer adverse events (mean catheterization time 9.2 days, range 4 to 16 days) [54] were also observed for Bactiguard coated CVC devices, whilst ETT devices showed reduced high-grade biofilm formation (median intubation time 3.6 days) [55] and a 67 % reduction in infection rates at 5 days [56].

A recent single-centre, prospective study on 148 trauma patients showed an 80 % reduction at 24 months (odds ratio 0.2, 95% confidence interval [0.07-0.55], p=0.002) in infection rates between the study group, who received Bactiguard-coated titanium alloy Orthosyn tibial and femoral IM nails (Vigilenz), and the uncoated control group, as well as some reduction in revision rates [57]. In addition, the same study also observed a 100 % rate of bony union in the study group, compared to 84 % in the control group [57]. This is in agreement with what was previously observed with Bactiguard-coated, commercially pure titanium screws, which presented comparable bone integration to that of uncoated screws in an *in vivo* animal model [58].

Durability

The durability of the coating after implantation has been observed in a retrieval study including qualitative and quantitative analysis of a nail retrieved from a patient after 8 months: all the metal elements of the coating were still detected, and were still within the coating specification [31], which suggests that the coating was still effective. This is also supported by clinical studies related to Bactiguard-coated devices, which have shown that the use of these products reduces the number of antibiotic days [47], as well as the prevalence of antibiotic resistance in the treated population [48].

Notably, no adverse event related to the Bactiguard coating has ever been recorded over more than 25 years that products have been on the market [59]. This includes CVCs, where the Bactiguard coating is in direct contact with the blood stream, and Foley urinary catheters periodically changed throughout the lifetime of some patients, thus subjecting them to the repeated exposure to the coating every time the catheter is exchanged.

Conclusion

The Bactiguard Technology consists of a thin, non-continuous layer of clusters of a silver, gold and palladium alloy, which generates galvanic currents that reduce microbial adhesion to implant surfaces, and thus decrease the possibility of biofilm formation.

The coating is non-eluting, durable, and does not contain antibiotics. This avoids challenges associated with handling of products or their shipping and storage, as it does not require controlled temperatures and conditions as seen with alternative solutions using antibiotics.

The Bactiguard Technology is well-established, with proven clinical safety and efficacy in reducing infection rates from urinary catheters, endotracheal tubes and central venous catheters.

The use of the Bactiguard Technology on titanium alloys for trauma applications has also shown effectiveness, and is expected to aid in reducing the burden of orthopaedic implant associated infections, while also supporting fracture repair.

Although the use of Bactiguard-coated intramedullary nails does not substitute for standard preventive antibiotic protocols, the availability of a non-antibiotic prophylactic solution provides an alternative approach to infection management. This is particularly timely given that the current infection control scenario is ever more challenged by antibiotic resistance.

Disclaimers

ZNN and ANN Bactiguard are intended to reduce the risk of implant related infections, but are not indicated for the treatment of established infections.

Use of this product does not replace existing standard practice for infection control such as the use of prophylactic antibiotics.

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