INFECTION PREVENTION IN TRAUMA WITH THE ZNN BACTIGUARD TECHNOLOGY

Results of an international multi-center multi-surgeon operational survey

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1. INTRODUCTION: INFECTION IN TRAUMA

Healthcare-associated infections are one of the major challenges in medicine, with a significant socioeconomical impact [1]. It has been estimated that up to 30% of orthopaedic trauma cases may result in an infection [2], which is expected to increase healthcare costs of a patient by 1.2-fold to 6-fold [3]. Moreover, implant associated infection not only deteriorates the quality of life of patients but also significantly impacts their family, surgeon, and wider society [4-10].

Almost 80% of all open fractures present some bacterial contamination [11], many of which may develop into early, delayed and/or late infections. A recent linear regression analysis of the available literature published since 2000 in peer-reviewed journals estimated that, on average, infections following intramedullary nailing were diagnosed in 1.6% of cases with closed fractures and 11.9% of cases with open fractures [12] and overall infection rate varied from 1.3 to 7.9% depending on the site of infection [12].

1.1 THE BIOFILM CHALLENGE

The primary challenge with treating or eradicating implant-associated infections is the ability of certain bacteria to create a protected community called biofilm. Once planktonic or 'free floating' bacteria come into contact with an implant surface, they start to adhere and proliferate on the surface and embed themselves in an organic matrix known as extracellular polymeric substances. 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 [13]. 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 colonization of a surface by planktonic bacteria to the creation of a mature biofilm can take place in a few days [14]. It has been estimated that biofilms account for over 80% of microbial infections in the body as publicly announced by the US National Institutes of Health [15] [16].

1.2 OPTIONS FOR INFECTION CONTROL

1.2.1 ANTIBIOTIC ELUTING SOLUTIONS

Current strategies for the control of Fracture Related Infections (FRI) rely primarily on the administration of local and systemic antibiotics. This includes the use of antibiotic-coated nails for local delivery of antibiotics. However, it is well known that bacteria develop resistance to antibiotics, even more so in healthcare facilities rather than in the community [17]. 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 [18].

1.2.2 NON-ELUTING ANTIBIOTIC-FREE SOLUTION: BACTIGUARD TECHNOLOGY

The Bactiguard technology addresses the growing concerns over antibiotic resistance and ensures responsible antibiotic stewardship by providing an alternative non-antibiotic-releasing approach to tackle biofilms. This coating technology consists of a thin, non-continuous layer of silver, gold, and palladium noble metals. The electro potential differences between these noble metals result in a "galvanic effect", which is the generation galvanically-induced electrical currents (approximately between 0 to almost 250 pA [19]). These currents are intended to reduce the adhesion of microbes and the subsequent risk of biofilm formation on the device surface but are too small to interact with human cells or tissues.

Comprehensive laboratory testing has established the mechanism of action of Bactiguard technology by confirmation of the physical mechanism of reduction of microbial adhesion by galvanic currents and absence of mechanisms based on antimicrobial elution [20-25].

Microbiological testing has confirmed the reduction of adhesion for multiple microbial species (Gram-positive bacteria, Gram-negative bacteria, antimicrobial resistant strains and fungal species) on various Bactiguard-coated surfaces [26] (See Table 1).

Substrate Material and Product	Microbial Strain	% Reduction in adhesion
Ti6Al4V	S.aureus	84%
Ti6Al4V	P.aeruginosa	99.997%
Silicone BIP Foley catheter	S.aureus (including MRSA)	97%
Silicone BIP Foley catheter	P.aeruginosa	81%
Silicone BIP Foley catheter	E.coli	96%
Latex Foley Catheter	C.albicans	70%
Latex Foley Catheter	P.aeruginosa	85%
Latex Foley Catheter	E.coli	93%
Polyvinyl chloride BIP ETT	S.aureus (including MRSA)	91%
Polyvinyl chloride BIP ETT	E.coli	99.7%
Polyvinyl chloride BIP ETT	P.aeruginosa	97%
Polyurethane BIP CVC	S.aureus	72%
Polyurethane BIP CVC	P.aeruginosa	77%

Table1.
Reduction in adhesion of microbes when the Bactiguard coating was applied to different substrates, compared to uncoated controls. MRSA: methicillin resistant Staphylococcus aureus. ETT: Endotracheal tube. CVC: Central venous catheter [26].

The absence of elution-based antimicrobial mechanisms has been confirmed by widely-used microbiological/ analytical tests [20-25].

2. OPERATIONAL SURVEY BACTIGUARD TECHNOLOGY

2.1 METHODS

To collect early clinical evidence of the Bactiguard Technology applied on intramedullary nails for fracture treatment, a multi-center, multi-surgeon Operational Survey was set up in 2022. The aim of the survey is to collect early clinical evidence from surgeons' users and gather early data to support Post-Market Surveillance activities of the Bactiguard coated Zimmer Natural Nails (ZNN).

The Operational Survey targets surgeries performed in all anatomical locations with implantation of the ZNN coated with the Bactiguard Technology: Tibia, Femur, Hip. The hip indication includes both long and short nails, and the femoral indication includes both antegrade and retrograde nails.

Only surgeries performed according to the Instruction for Use and Surgical Techniques are and will be included in this survey. The survey has been conducted between January 2022 and December 2023.

One survey is to be completed for each nailing surgery. The survey consists of two stages. In Stage 1, which is filled out immediately after the surgery, baseline information is collected. Surgeons are asked about patient's demographics, anatomical location that was covered, fracture type and severity, and type of surgery conducted (primary or revision). In the case of revision surgeries, a distinction is made between revisions due to resolved infection or other reasons. If a Fracture Related Infection (FRI) occurs, surgeons are asked to fill out Stage 2 of the survey and a case investigation begins. If no Stage 2 survey is received within one year after surgery, it is considered that no FRI occurred.

Each survey has a unique identifier that allows only the surgeon or hospital to identify the patient. Surveys received are verified for completeness. If any answers are missing, the surgeon who completed the survey is contacted to retrieve the information. Any survey missing the reference number or anatomical location has not been considered for the analysis. Before including any survey in the report, an additional follow up asking if any FRI occurred was done.

2.2 RESULTS

At the time of data analysis, on October 20th, 2023, a total of seven EMEA (Europe Middle East Africa) countries and over 50 hospitals had participated in the survey. A summary of the contribution of each country is shown in Figure 1. To that date, 264 surveys were received, of which 236 were included in the analysis and 28 were excluded as they did not contain the minimum information required to be considered. A total of 85 surveys were finalized, meaning that a year had passed since the time of surgery. The remaining 151 surveys are still open until they reach the 1-year post surgery timepoint. To the date of data analysis, no infections have been reported.

Regarding the indication distribution, 39% of the surveys were for the hip fracture indication (corresponding to 93 surveys), 38% for the tibia (87 surveys) followed by 23% for the femur (54 surveys) (Figure 2A). Of all the fractures, 81% were closed fractures and 19% were open fractures (Figure 2B). Within open fractures, the majority were Gustillo Type II [27] and IIIA (Figure 2B).

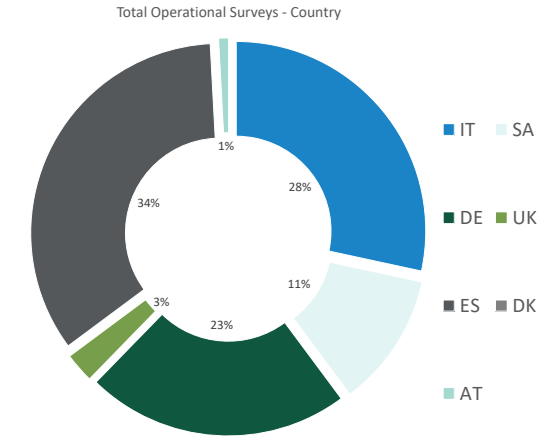

Figure 1.
Country distribution of the Operational Survey included. IT, Italy, SA, South Africa; DE, Germany, DK Denmark; UK, United Kingdom; ES, Spain; AT, Austria

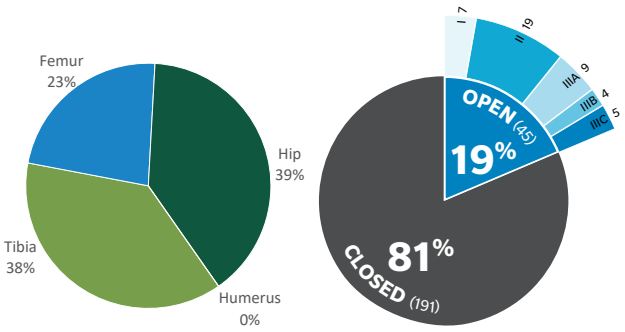

Figure 2.
Operational survey distribution. A Indication distribution. B Open and Closed fractures distribution and Gustillo Type classification

The range of age distribution is shown in Figure 3. Most of the patients were in the range between 75-89 years old (30% of the surveys), followed by 60-74 and 30-34 age range (17% and 18% respectively). Fewer surveys were received for the youngest patients (18-29, 13%) and elderly (greater than 90, 12%). The lowest number of patients were in the range of 45-59 years (9%).

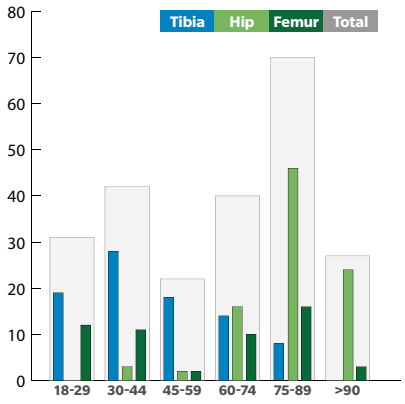

Figure 3.
Range of age per indication

3. DISCUSSION

Microbial biofilm formation on implants is one of the biggest challenges to overcome in the battle against implant-associated infections. Traditionally, antibiotics are used to manage biofilm-related infection, however increasing incidence of antimicrobial resistance has shown the limitations of the excessive use of antibiotics and has resulted in a new health and socioeconomic threat. Consequently, there is increased interest in the development and use of alternative solutions for infection control. The Bactiguard technology offers a non-eluting and antibiotic-free approach that targets the initial stages of biofilm formation by reducing the adhesion of microbes on implants. This technology has a long history of use with over 200 million Bactiguard-coated medical devices sold in the last 25+ years. No adverse events or safety issues related to the Bactiguard coating have been reported so far [28] [29].

Recent publications provided safety and efficacy evidence of the Bactiguard technology in orthopedic trauma. Two articles using intramedullary nailing systems with the Bactiguard coating were published in 2022 and 2023. The first study was a retrospective, single-center case series study in Malaysia using the OrthoSyn™ Nails [30]. Fracture-related infections and bone healing were analyzed in patients with Gustilo type IIIa or IIIb open femoral and tibial fractures. The study showed positive results, with an infection rate of 8.6% (3/35) and a fracture union rate of 93.8% (30/32). Another single-center retrospective study using the ZNN Bactiguard Tibia Nails was conducted in a Level 1 Major Trauma center in the UK [31]. In this study, open and closed tibial fractures at risk for developing complications were included and followed up over 12 months. The authors reported infection and union rates of 3.2% (1/31) and 96.7% (30/31), respectively. Despite the low number of cases in these studies, the results show that Bactiguard technology has great potential for infection control in fracture patients.

This international, multi-center, multi-surgeon operational survey collects information about the demographics and infection rate for a wide and heterogeneous group. So far, seven EMEA countries participated in the survey, collecting input from over 50 hospitals and almost 100 surgeons.

In this interim analysis, a first snapshot of the results collected until October 20th, 2023 is provided. To that date, 85 surveys have been finalized (1-year post-index surgery), but new cases surveys will be collected until the end of 2023 and will be followed up for one year.

The hip indication represented 39% of the survey results, and therefore was found to be the most common anatomical location. This result combined with the patient age data indicates that hip indications are prevalent in an

aging population, which also agrees with the current literature [32] [33]. In general, more than 1.5 million patients experience hip fractures worldwide each year. This number is estimated to increase exponentially with time, resulting in direct and indirect costs exceeding $ 130 billion per year worldwide [32] [33]. Moreover, the length of hospital stays increases about three times for an infected case, further reflecting the socioeconomical impact of infections on the present and future health system.

To the date of analysis, no infections have been reported in the survey. The analysis of the injury characteristics revealed that most of the cases were closed fractures (81%). Closed fractures are known to have a lower risk of infection compared to open fractures [34] [35], and therefore may have contributed to no infections reported so far in the survey. When comparing the infection results of this survey with the above-mentioned publications [30] [31], one must consider the nature of the fractures studied. All efforts were made to capture potential infections. In addition to the reminders sent during the collection of the results, an additional reminder with a two-week notice was given to all participating sites before the creation of this interim white paper.

This Operational Survey allows to build early clinical evidence regarding the use of Bactiguard Technology on trauma implants. Nonetheless, it is important to acknowledge its limitations given the nature of the survey and the early stages in which we are publishing the results. Although more than 50 hospitals have participated in the survey so far, the number of surveys included and completed is still low. More surveys are expected to be completed and finalized for the final survey report. In parallel to the survey distribution, four international multicenter prospective post-market clinical follow-up (PMCF) studies have been set up to build stronger clinical evidence. These PMCF studies are covering all indications of the ZNN coated with the Bactiguard technology (Tibia, Proximal Femur, Distal Femur, and Hip), and include 8 EMEA countries so far. Overall, they intend to enroll up to 600 Bactiguard cases. The Bactiguard Operational Survey brings value by offering the possibility to collect meaningful heterogeneous data from all hospitals using the ZNN Bactiguard nailing systems.

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