INFECTION CONTROL SOLUTION CONCEPT

Implant-related infection control solution concept

Justinas Stučinskas

Department of Orthopaedics and Traumatology
Lithuanian University of Health Sciences

EUROPEAN UNION
EUROPEAN REGIONAL DEVELOPMENT FUND

Interreg Baltic Sea Region

BFCC Baltic Fracture Competence Centre

- Life Science Nord Management GmbH (Germany)
- Stryker Trauma GmbH (Germany)
- University Medical Center Schleswig-Holstein (Germany)
- University Medicine Greifswald (Germany)
- Sahlgrenska University Hospital (Sweden)
- ScanBalt fmba (Denmark)
- Lithuania University of Health Sciences (Lithuania)
- LifeScience Krakow Klaster (Poland)
- University Hospital in Krakow (Poland)
- University of Tartu (Estonia)
- Tartu Biotechnology Park (Estonia)
- Bone Index Finland Ltd. (Finland)
- BONESUPPORT AB (Sweden)

Implant-related infection control solution concept
Justinas Stučinskas
Department of Orthopaedics and Traumatology
Lithuanian University of Health Sciences

Layout & graphic design
amt tipografia design gráfico
Anne Mayer-Tasch
Friedrichsdorf, Germany
https://amt.myportfolio.com/

Photos & illustrations
Shutterstock.com:
Spotmatik Ltd (p. 4), Kateryna Kon (p. 7)
Adobe Stock:
Kamon Wongnon (p. 6), Robert Przybysz (p. 9), LUHS (p.10), Alexandra (p. 12), Rawpixel.com (p. 13), romaset (p. 15), peterschreiber.media (p. 18), Gorodenkoff (p. 20), alexandrink1966 (p. 26), BillionPhotos.com (p. 30)
X-ray images: LUHS

Published in February 2019

Lead partner & publisher
Baltic Fracture Competence Centre
Life Science Nord Management GmbH
Legienstraße 40, 24103 Kiel, Germany
+49 431 90 89 68 58
Contact: Imke Schneemann
schneemann@lifesciencenord.de
www.lifesciencenord.de

www.bfcc-project.eu

Supported by:

Interreg Baltic Sea Region
EUROPEAN UNION
EUROPEAN REGIONAL DEVELOPMENT FUND

CONTENTS

INFECTION CONTROL SOLUTION CONCEPT

BFCC—BALTIC FRACTURE COMPETENCE CENTRE

The Baltic Fracture Competence Centre (BFCC) is a pan-Baltic fracture cooperation network fostering innovation within fracture management. The project consortium consists of a transnational cross-sector partnership involving five hospitals, three companies from the medical technology industry, a university, three clusters and one technology transfer organization.

Due to an ageing society, the need for innovative products and clinical procedures for fracture treatment is increasing as a response to age-related fractures and co-morbidities such as osteoporosis, infections and non-unions. Innovations in fracture management must reduce the cost of care or clearly improve quality of care.

Clinicians will support the innovation process by identifying the clinical needs to ensure user-oriented product development. The collaboration between hospitals across countries will foster the innovation of clinical procedures through the exchange of best practice in fracture management influenced by different national, organizational and regulatory conditions.

However, clinicians and companies often lack insight information about total cost and effectiveness of fracture management and causes of adverse health outcomes in the hospitals. To overcome this information gap, the BFCC will develop and implement a transnational fracture registry with five hospitals from Estonia, Germany, Lithuania, Poland, and Sweden, respectively, providing evidence about fracture treatment in the clinical »real world« and reveal clinical needs as well as potentials for innovation.

The BFCC will publish two innovation reports. The Innovation Report No 1 deals with trends in the surgical treatment methods of proximal femur fractures. The Innovation Report No 2 based on results and findings from registry data analysis will identify innovation needs and potentials.

PHOTO: Shutterstock

1. INTRODUCTION

In 2010, 3.5 million new fractures, including approximately 610,000 hip fractures, 560,000 forearm fractures, 520,000 vertebral fractures and 1,800,000 other fractures were estimated in the EU. Moreover, it has been reported that the annual number of fractures in the EU will increase by 28% from 3.5 million in 2010 to 4.5 million in 2025.[1] As a result, the use of surgically implanted devices is also increasing. Surgical fracture treatment with various types of implants is usually successful. However, like every medical intervention, this is associated with the risk of complications, from which the most devastating is infection. Implant-related infections after fracture treatment are important to understand and to analyse as it requires repeated surgeries and hospitalisations. Which may come with secondary complications, sometimes amputations, chronic morbidity, and mortality related to the systemic antibiotic treatment and immobilization.[2–4] Prolonged and extensive systemic antimicrobial treatment courses can last for years and are related with adverse effects as well as it may lead to bacterial resistance. In addition, infection treatment is associated with significant costs. Approximately 700 million pounds (779.1 million euro) per year are spent by the National Health Services of the United Kingdom to treat patients with surgical site infections in acute care facilities.[5–6] Expert opinion suggests that costs can be as high as 20,000 pounds (22,260 euro) per surgical site infection for complex surgery.[6–7] These complications result in the highest overall increase in total healthcare costs and length of stay. Treatment costs were approximately 6.5 times higher compared to patients without infections.[8]

Thus, the prevalence of implant-related infections is one of the most challenging complication in orthopaedic and trauma surgery. Complex fractures have an overall 5% infection rate when treated with an implant.[9] In an effort to reduce this risk, the preoperative administration of antibiotics has become the standard treatment.[10] Furthermore, the sterilisation of implants and equipment as well as aseptic procedures during surgery are standardized. Still, invasive medical devices account for more than 50% of all hospital-acquired infections causing approximately one million new cases in the USA.[11]

Innovations and best practice transfer are still needed in the near future for the healthcare systems to accommodate the increasing burden of fractures as well as implant related infections. Changes for today's treatment regimens are necessary for hospitals and other caregivers. An evaluation of the current standard treatments and a comparison of treatment pathways in different hospitals could help to identify causes for infection and best-practice examples for infection control to reduce their overall occurrence. The Baltic Fracture Competence Centre (BFCC) and its established network can provide useful data to develop solutions for this problem, which this report is about.

2. PROBLEM AT HAND

2.1. Pathogenesis

An implant-related infection is defined as a host immune response to microbial pathogens on an indwelling implant.[4] It is important to understand the pathogenesis in order to treat an infection effectively. Development of implant-related infections begins with colonization of the foreign material and is typically caused by microorganisms that grow in biofilms. Interaction of granulocytes with implants result in local granulocyte defects. These defects are caused by so-called frustrated phagocytosis.[12–13] Experimental studies, reported that foreign material potentiates the risk for infection more than 100,000 times.[12] These data indicated a clinical interest and need to prevent the infection. Different studies aimed to identify especially modifiable risk factors, reasons and focused on preoperative infection prevention strategies. Also, there evidence based guidelines available to assist in the prevention and treatment of implant-related infection.[3, 14–15] However, guidelines may be not followed accurately, and do not have answers to all possible treatment options. National guidelines might produce more standardized care, and — consequentially — easier comparison for research, more transparency for patients, and less health care costs.[16] Furthermore, foreign bodies / orthopaedic implants are at lifelong risk of haematogenous infection. And rapid diagnosis is required as treatment of implant-related infection is very time dependent, since acute Prosthetic Joint Infection (PJI) can generally be treated with implant retention.[13]

2.2. Epidemiology and aetiology

It was reported that infection rates were 4.2% for closed and 10.6% for open fractures.[17] The observed infection rates after open fractures ranged from < 1% in Gustilo-Anderson grade I to 30% in grade III fractures[18–19] and with the use of external fixators incidence of infection up to 71%.[20]

Infection rates vary between hospitals and depend on patient-specific parameters. Trends in surgical site infection rate also vary according to operative site and type. The most common microorganisms causing prosthetic joint infection have been reported to be: Coagulase-negative staphylococci 30–43%, *Staphylococcus aureus* 12–23%, Streptococci 9–10%, Enterococci 3–7%, Gram-negative bacilli 3–6%, Anaerobes 2–4%, Polymicrobial 10–12%. However, there is a significant number of unidentified microorganisms 10–11%.[21] Regarding fracture and implant related infections, *Staphylococcus aureus* and coagulase-negative staphylococci are the most frequently isolated microorganism, followed by Gram-negative bacilli and *Streptococcus* spp. In comparison to prosthetic joint infection, polymicrobial infections are more common in fracture and implant related infections.[22]

PHOTO: Adobe Stock

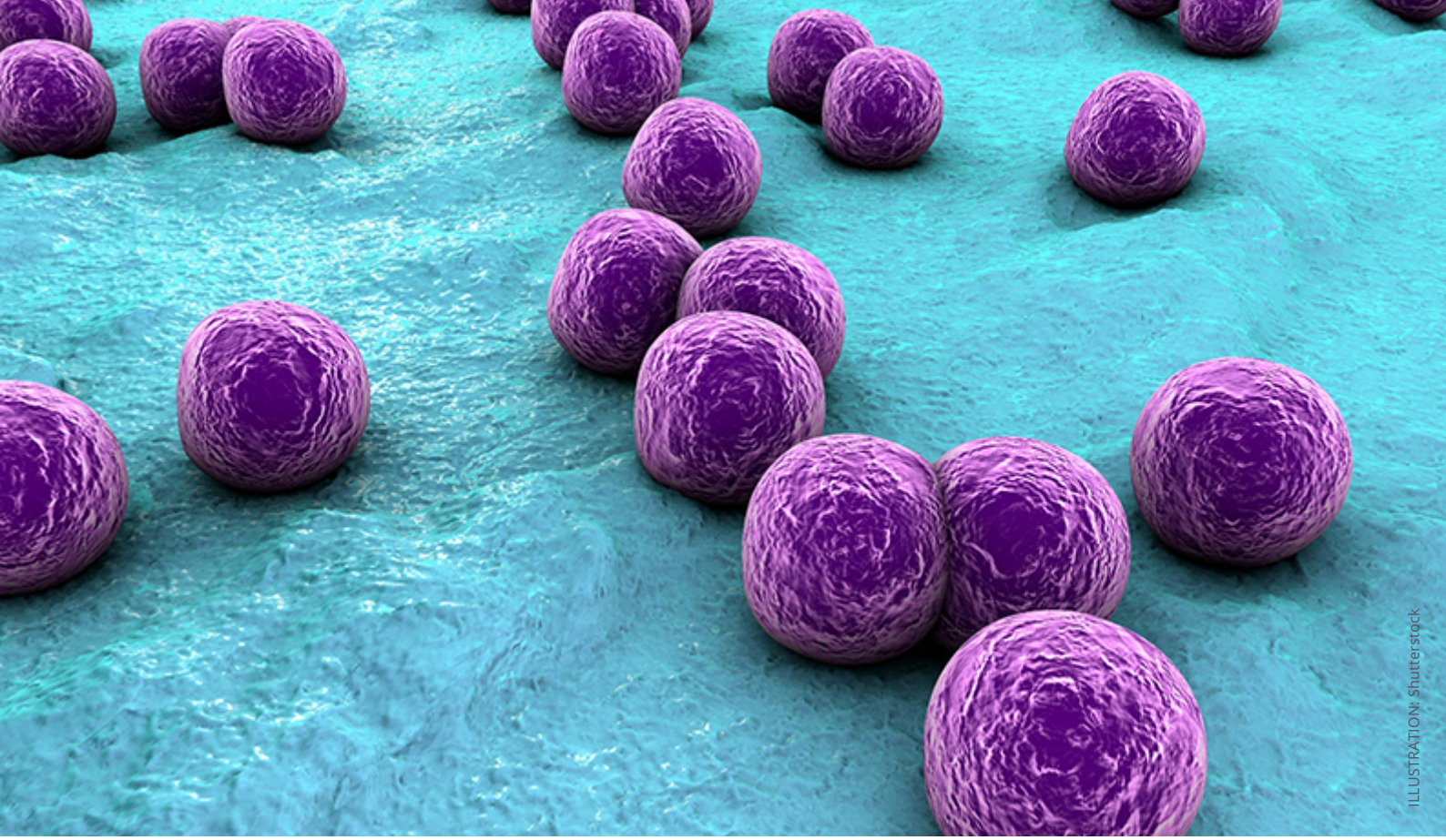


ILLUSTRATION: Shutterstock

2.3. Risk factors

Many potential risk factors for infectious complications in fractures have been reported. They could be divided to patient, trauma/fracture and treatment related risk factors.

In a recent systematic review and meta-analysis[16] 116 manuscripts were analysed and following factors for the development of infection after open fracture fixation were investigated:

- Patient and trauma-related factors: age, body mass index, gender, ethnicity, American Society of Anesthesiologists (ASA) score, diabetes mellitus, human immuno-deficiency virus, hypertension and systemic vascular disease, smoking, alcohol, and drugs, fracture localization, open versus closed fractures, Gustilo-Anderson classification, contamination, trauma mechanism, polytrauma versus monotrauma, and injury severity score (ISS).
- Treatment related risk factors: antibiotic prophylaxis and timing, timing of debridement, pulsatile lavage, fixation method, delayed wound closure, blood transfusion, and splenectomy.

Furthermore, several risk factors like duration of hospital admission, rheumatoid arthritis, geographical location, and level of experience of the centre and surgical team, and secondary or tertiary referral of patients were not investigated or were not reported in the analysed studies.

Male gender (risk ratio [RR] 1.42), diabetes mellitus (RR 1.72), smoking (RR 1.29), a lower extremity fracture (RR 1.94), Gustilo-Anderson grade III open fracture (RR 3.01), contaminated fracture (RR 7.85) and polytrauma patients (RR 1.49) were identified as statistically significant risk factors for the development of infectious complications. Of the treatment-related risk factors, only pulsatile lavage was associated with a higher infectious complication rate (RR 2.70).[16] It was suggested that further prospective and observational studies are needed to identify and quantify individual risk factors for infections after open fracture fixation.

2.4. Prevention

In general, the main goals of better fracture management are:

- prevention of infection,
- fracture healing
- restoration of function.

For open fractures, the principles are the following: careful patient and injury evaluation, early administration of systemic antibiotics supplemented by local delivery of antibiotics in severe injuries, thorough surgical debridement, wound management with soft tissue coverage if needed, and stable fracture fixation.[23] Preoperative, perioperative, intraoperative, and postoperative strategies to decrease infection rate were discussed in the literature.[24–25]

Preoperative measures include: management of patients colonized by *Staphylococcus aureus* (MRSA decolonization), nutritional optimization, management of medical comorbidities, and improvement of glucose control, decrease the BMI below 30 kg/m^2, skin control (psoriasis, eczema, ulcers) and smoke cessation. Perioperative measures include: skin preparation, surgical site clipping, skin decontamination with betadine shower or chlorhexidine wipes and prophylactic antibiotics. Intraoperative measures include: prophylactic antibiotics, skin preparation, draping, changing scalpel blades, bleeding control, dressing, body exhaust suits, laminar flow, ultraviolet light, operating-room traffic control, surgical suite enclosures, anaesthesia-related considerations, and local antibiotic administration. Postoperative measures include: continued antibiotic prophylaxis, blood transfusions, dressings, hematoma formation and wound drainage, duration of hospital stay, and antibiotic prophylaxis for future invasive procedures.

These measures suggest that infection prevention requires a multidisciplinary approach with various strategies. However, some infection prevention strategies are supported by the literature whereas others remain unproven.[24–25]

2.5. Diagnosis

Infections can be classified as early (those that develop less than 3 months after surgery), delayed (3 to 24 months after surgery), or late (more than 24 months after surgery). The onset and clinical manifestations of implant-related infections vary with the microorganism.[4]

Unfortunately, there is no single test which has an ideal sensitivity, specificity, and accuracy for the diagnosis of infection. Therefore, a combination of laboratory, histopathology, microbiology and imaging studies is usually required.[21, 26]

Early periprosthetic infections are typically manifested as an acute onset of joint pain, fever, effusion, erythema and warmth at the implant site, and are commonly caused by virulent microorganisms, such as *S. aureus* and gram-negative bacilli.[3] For early infected osteosynthesis elevated white blood cell count and/or left shift are usually observed. C-reactive protein (CRP) remains elevated in the follow-up or increases.[27] Sampling technique and good collaboration with microbiologists are crucial for detecting causative microorganisms. In the case of low virulent organisms, the clinical signs and standard diagnostic tools may not be as efficacious in establishing the presence of implant related infection.[28] Sonication can reveal different and more sensitive results than tissue samples.[22] During early radiological assessment, the stability of osteosynhtesis should be evaluated, also the anatomical reconstruction if the joint is involved. It is important for an anatomical-pathological classification as proposed by Romano *et al.*[29]: Type I — stable osteosynthesis with callus progression, Type II — stable osteosynthesis with scarce or absent callus progression, and Type III an unstable osteosynthesis without callus formation. For late infection, typically clinical manifestation is poor and laboratory tests are often normal. Careful assessment of dynamic radiographs for sequestra. In addition, computed tomography should be assessed, and three-phase, antigranulocyte scintigraphy, MRI fistulography may provide additional information in diagnosing late bone infection.[27]

2.6. Treatment

Eradication of infection can be achieved with various therapies: surgical removal of all infected tissue and the implant and a combination of debridement with implant retention and long-term antimicrobial therapy that is active against biofilm microorganisms.[3] From surgeon perspective, fracture fixation, union and hardware stability is important, as well as the anatomical reduction of the joint if involved. From microbiologist perspective, the time period from osteosynthesis to infection symptoms has been reported to be important as most of early infections can be treated with a combination of debridement, implant retention and antimicrobial therapy.[22]

Microorganisms, forming biofilms, develop on non-living surfaces and adhere either on dead bone (sequestrum) or implants. In a delayed infection, the effect of biofilm-active antibiotics is limited and the treatment includes a combination of implant removal, fracture fixation bypassing the infection zone and antimicrobial therapy.[22, 27]

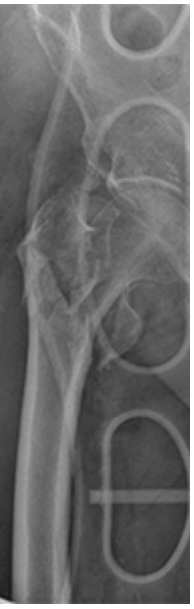
Fractures which are complicated by infection, may contain other clinical challenges such as bone comminution, defects, severe soft tissue damage, devascularisation, non-unions or sequestra. For dead space management local antibiotic therapy may be a part of treatment concept. One of the possible options is polymethylmethacrylate (PMMA) cement spacers or beads. However, they require removal thus additional surgery.[22, 30] Currently, another option is increasingly used, *i.e.* bioabsorbable material for local antibiotic delivery[31–34] and there is a high need for further clinical results. Bioresorbable hydroxyapatite / calcium sulphate bone graft substitutes can be used for treatment of fracture defects (as CERAMENT™|BONE VOID FILLER [CBVF])[34, 35] or for bone healing in combination with local delivery of antibiotics (as CERAMENT™|G and CERAMENT™|V for eluting gentamicin and vancomycin respectively). These antibiotic eluting CERAMENT products can be used for management of infections[36] or as antibacterial coating of implants to prevent bacterial adhesion and biofilm formation.[33]

PHOTO: Adobe Stock

3. WHAT IS IT ALL ABOUT? SOME CLINICAL CASES

Clinical case No 1

74 years old female patient experienced trochanteric fracture (Fig. 1a). Few weeks later, the wound started to leak (Fig. 1b) and pain in hip area increased. X-ray showed failure of osteosynthesis (Fig. 1c). The debridement procedure was performed together with culture samples: Two multidrug resistant microorganisms were identified. During another surgery foreign materials were removed and proximal femur was resected, spacer made from antibiotic (gentamycin) impregnated PMMA cement was inserted Fig. 1d). Six weeks intravenous antibiotic therapy was prescribed. Only after infection eradication is confirmed, final implantation of revision hip surgery implantation can be performed.



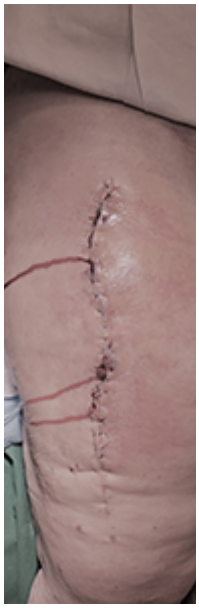
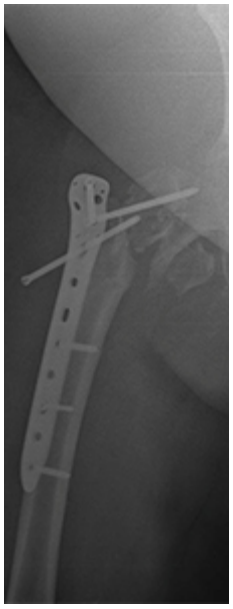
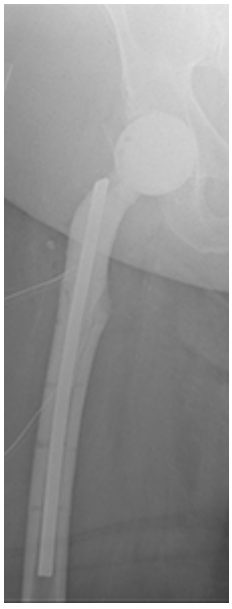


Figure 1a–b



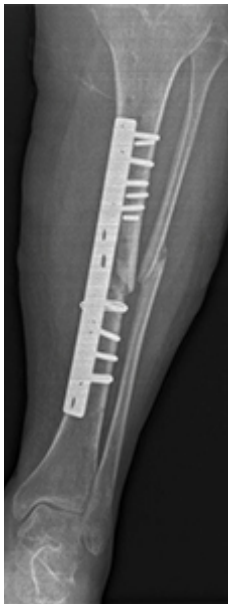


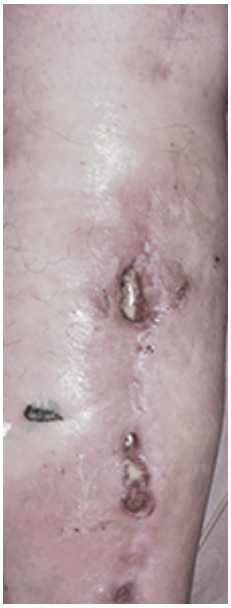
IMAGES: LUHS

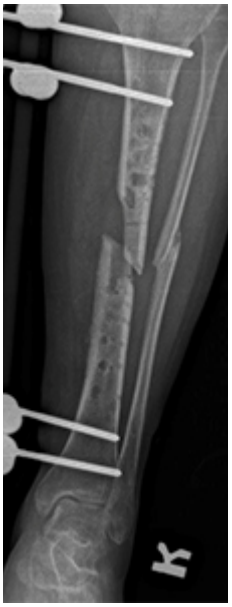
Figure 1c–d

Clinical case No 2

55 years old female patient experienced four surgical procedures due to non-healing tibial bone fracture (Fig. 2a). After the last osteosynthesis implant related chronic infection was diagnosed (Fig. 2b), implant was removed and positive cultures *(S. aureus)* were obtained. Six weeks intravenous antibiotic therapy was prescribed. After infection eradication was confirmed, several surgical procedures including distraction osteosynthesis were planned.





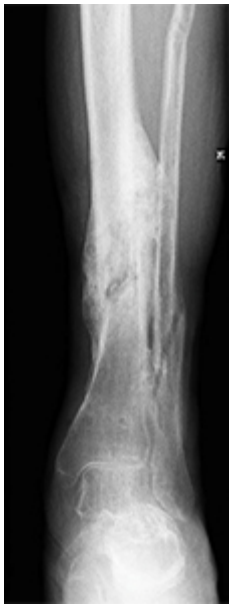


IMAGES: LUHS

Figure 2a–c

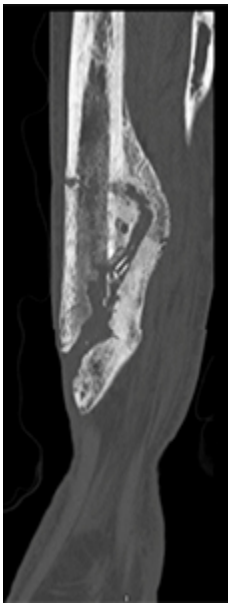
Clinical case No 3

40 years old male patient experienced open tibial bone fracture, which initially was treated with an external fixator. Chronic infection/osteomyelitis evolved but left untreated (Fig. 3a and b). After two years patient fell and a femoral neck fracture was diagnosed (Fig. 3c). Surgical treatment of the femoral neck fracture could not be performed due to the untreated chronic infection of the tibial bone and high risk of periprosthetic joint infection. Multiple surgeries and long-term antibiotic therapy was required, however, with high chance of failure.



IMAGES: LUHS

Figure 3a



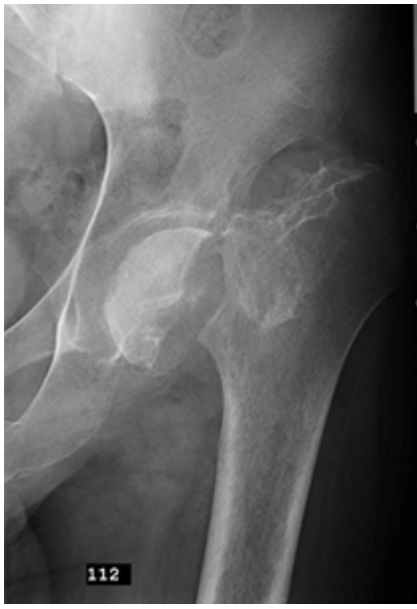
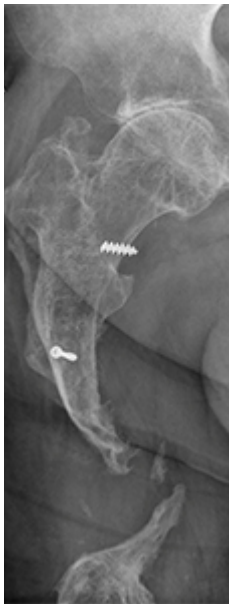
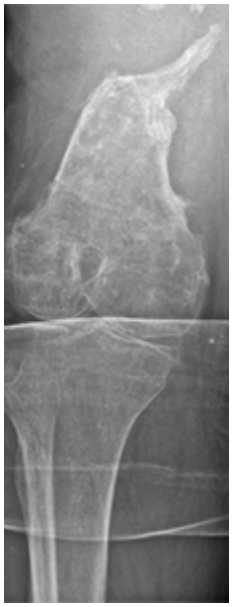
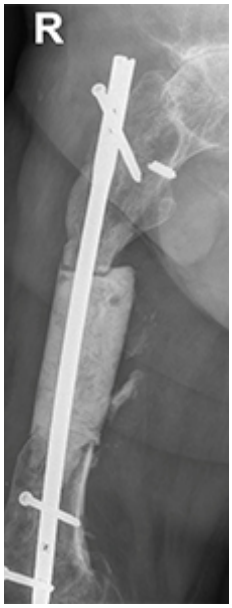


Figure 3b–c





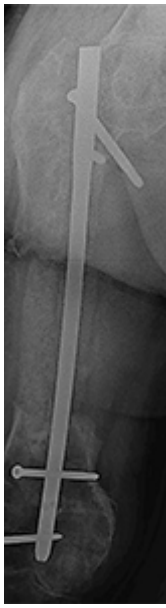


IMAGES: LUHS

Figure 4a–d

Clinical case No 4

53 years old male had an open 3B femoral fracture which after multiple surgeries due to non-unions and infection was partially resected, but eventually left with chronic infection (Fig. 4a and 4b). An infection treatment plan was developed: first, resection of dead bone, culture samples and defect treated with the Masquelet technique with temporary cement spacer. Six weeks of intravenous antibiotic therapy according to the sensibility of the microorganism was prescribed and infection was clinically eradicated. Then II stage surgery was performed: the femur defect was filled with allograft bone chips impregnated with rhBMP-2 (Medtronic), viable bone defects were filled with resorbable ceramic hydroxyapatite/calcium sulphate bone substitution (CERAMENT™|G and CERAMENT™|V) and the femur was fixed with locking intramedullary nail.



4. WHAT CAN BE DONE?

Those clinical cases represent only a minority of problems which occur when treating fracture/implant related infection. Looking from the patient perspective, this is a devastating complication which:

- limits mobility and self-support
- magnifies or causes comorbidities
- has side effects of long term antibiotic therapy
- has a high risk of treatment failure, sometimes may lead to amputations or joint resection
- requires repeated surgeries and hospitalizations
- affects mortality related to the systemic antibiotic treatment and immobilization or to multi-drug resistant bacteria.

The treatment can last for years, is a challenge for the healthcare/social systems and is associated with very high treatment costs and social burden. A multidisciplinary approach is required in order to prevent, diagnose and treat infection after fractures. Various strategies have to be addressed including:

- biofilm and infection resistance of biomaterials,
- coatings with antibacterial or antiseptic surface of the implants
- identification of new biomarkers for diagnosing infection
- better antibiotic prophylaxis and other preventive modalities
- antibiotic containing bone substitutes for infected bone defects.[35–37]

There are numerous reports/guidelines in infection prevention/treatment strategies, however, with a huge variability between continents, countries or even hospitals. This may be an effect of the lack of randomised controlled trials in the infection field, thus, making cohort studies crucial. Countries with implemented well defined infection prevention/treatment algorithms may have significantly lower infection rates as compared to countries which have no algorithms established on national level. This may be evaluated in international collaboration projects.

An innovation roadmap for fracture treatment to identify early infections and a health technology assessment (HTA) to evaluate costs for infections and treatment options as well as hospital management processes with regard to infection control can highlight innovation gaps, potentials, and ideas in the infection control innovation concept. The outcome is the basis for cooperation between industry and hospitals to test novel products/advanced medical technologies in future across clinical partners.

PHOTO: Adobe Stock


PHOTO: Adobe Stock

5. DEVELOPMENT OF A TRANSNATIONAL INFECTION CONTROL SOLUTION CONCEPT IN THE BALTIC SEA REGION

The BFCC project offered an opportunity to develop ideas and starting points for innovative solutions in fracture/implant related infection management. As variations exist in the clinical practice when treating fracture patients, the project's clinical partners performed several analyses addressing various measures, which may affect surgical site infections. To analyse fracture treatment, infection treatment pathways and costs, a questionnaire was created. Diagnosis of the infection process as well as outcomes and cost-effectiveness measures were evaluated. Further, comparison of clinical data between open, closed and infected tibial fractures was performed. A pilot study was conducted aiming at pharmacokinetic analysis of long term release of vancomycin from a biphasic ceramic carrier in major hip surgery.

5.1. Infection prevention strategies

A questionnaire was developed and distributed between the BFCC clinical partner hospitals (Germany — GER, Poland — PLN, Estonia — EST and Lithuania — LTU). The questionnaire consisted of preoperative, intraoperative, and postoperative strategy aspects which may affect infection rate.

PREOPERATIVE PHASE	INTRAOPERATIVE PHASE	POSTOPERATIVE PHASE
• Pre-operative patient shower • Hair removal only if necessary (clippers, not razors) — does not reduce the risk of infection • Patient and staff theatre wear • Operating theatre movements • Antibiotic prophylaxis	• Hand decontamination • Iodophor-impregnated drape • Sterile gowns and gloves • Antiseptic skin preparation • Normothermia, oxygenation	• Change dressings with aseptic, non-touch technique

1. PREOPERATIVE PROCESS MEASURES

- Do you have well defined a/b prophylaxis guidelines?
- Do you perform a/b prophylaxis in orthopaedic intervention
- What kind of antibiotics are you using for routine a/b prophylaxis
- What is the timing of first dose of a/b prophylaxis
- What is duration of a/b prophylaxis
- Do you use hospital defined guidelines as a rule when deciding on a/b prophylaxis?
- Do you remove hairs in the region of incision preoperatively?
- Do you use Tranexamic acid in surgically treated trauma cases?

2. OPERATIVE PROCESS MEASURE

- What kind of ventilatoin system is installed in operating room ?
- Do you use tourniquet?
- A/b prophylaxis dose injection in relation to tourniquet inflation
- Do you use drains?
- What is drainage duration?
- Do you use operative field films?
- Surgical gloves
- How many pairs of surgical gloves you wear during operation?
- Surgical gloves exchange frequency during operation
- Antiseptic used for surgical site preparation
- Solution used for surgical site wash
- How often nurse change surgical site wash solution during operation?
- How many blades used for skin and subcutaneous tissue cutting?
- Scalpel blades exchange frequency during operation
- Do you use coagulation for tissue cutting?
- Surgical site drapes
- Trauma implants storage place
- Operating theatre door type
- Personal equipment (mobile phones, watches, bracelets) in OR
- Does nurse cover unused instruments during operation?
- Local infiltration of anesthetic (LIA) in trauma cases

3. POSTOPERATIVE PROCESS MEASURE

- Who changes wound dressings for the operated patients, and where?
- How often wound dressings change is performed?
- Type of anticoaguliant
- Location of trauma patients in the department

4. INFECTION PROCESS MEASURE

- Most common bacteria for early surgical site infection
- Most common bacteria for late surgical site infection
- What are yours actions if you see the redness in area of surgical wound?
- Most common diagnostic methods used a when you suspect an infection
- Do you have hospital/department algorithm/guidelines for trauma related implants infections?

5. OUTCOME AND COST-EFFECTIVENESS MEASURE (CALCULATIONS)

- Surgical site infection rate = number of SSIs occurring postoperatively/ total number of operative trauma procedures
- Average length of hospital stay for uncomplicated trauma patient
- Average length of hospital stay for septic trauma patient
- Average price of mid shaft tibial fracture treated operatively

PHOTO: Adobe Stock

5.2. Quest analysis and summarized results

5.2.1. Preoperative and intraoperative process measure

The analysis of preoperative and intraoperative process measures showed differences between the countries:

- Lithuania, Poland and Estonia have adopted hospital a/b prophylaxis guidelines, in Germany there is no adopted a/b prophylaxis guidelines;
- LTU, EST and PLN for routine a/b prophylaxis using Cefazolin and the first dose is administered > 30 min. before skin incision, in GER Cefuroxim is used just before the incision;
- LTU, GER and EST standard duration of a/b prophylaxis — 24 hours, in PLN — 48 hours;
- LTU and EST routinely do not remove hair, in GER hairs are removed with clippers, in PLN the operative field is shaved with razor;
- in Germany, personal equipment (mobile phone, watches, bracelets etc.) is not allowed in the operating theatre, in Lithuania and Estonia personal belongings is allowed, but are placed in special boxes.

PRE- AND INTRA-OPERATIVE PROCESS MEASURE	LTU	GER	PLN	EST
What kind of ventilation system is installed in operating room?	Conventional (mixing) system	Passive air flow	Lamina air flow	Lamina air low
Do you use tourniquet?	Depends on case	Depends on case	Depends on case	Depends on case
A/b prophylaxis dose injection in relation to tourniquet inflation	Before	Before	Before	Before
Do you use drains	Depends on case	Routinely	Depends on case	Depends on case
Drainage duration?	Depends on case	48 hours	Depends on case	Depends on case
Operative field films?	Not used	Not used	Not used	Not used
Surgical gloves	Powder-free	Patented puncture indication system	Powder-free	Powder-free
How many pairs of surgical gloves you wear during operation?	2	2	2	1
Surgical gloves exchange frequency during operation	Every 2 hours	No algorithm	Every hour	Every 2 hours

PRE- AND INTRA-OPERATIVE PROCESS MEASURE	LTU	GER	PLN	EST
Antiseptic used for surgical site preparation	Alcohol-CHG (ChloraPrep)	Alcohol-iodophor (DuraPrep, Prevail-FX)	Other	Other
Solution used for surgical site wash	Chlorhexidine	Other	Other	Other
How often nurse change surgical site wash solution during operation?	Every hour	No algorithm	Every hour	Every hour
How many blades used for skin and subcutaneous tissue cutting?	2	2	2	2
Scalpel blades exchange frequency during operation	Each layer cut	Other frequency	Every hour	Every hour
Do you use coagulation for tissue cutting?	Depends on case	Depends on case	Depends on case	Depends on case
Surgical site drapes	Depends on case	Single-use	Depends on case	Depends on case
Trauma implants storage place	Separate sterile package	Special storage room	Separate sterile package	Separate sterile package
Operating theatre door type	Automatic	Automatic	Automatic	Automatic
Personal equipment (mobile phones, watches, bracelets) in OR	Special box in OR	Not allowed to bring	On shelf	Not answered
Does nurse cover unused instruments during operation?	Never	Depends on case	Always	Always
Local infiltration of anesthetic (LIA) in trauma cases	Never	Depends on case	Depends on case	Never

5.2.2. Postoperative process measure

The analysis of postoperative process measures showed small differences between countries:

- In Germany, Poland and Estonia, trauma patients are hospitalized in specialized trauma wards differently in Lithuania where all patients are located in general wards.
- In Lithuania and Germany, wound dressings are made by nurses in the wards compared to Poland and Estonia where dressings are performed in special dressing rooms.

POSTOPERATIVE PROCESS MEASURE	LTU	GER	PLN	EST
Who changes wound dressings for the operated patients, and where?	Nurse in general ward	Nurse in general ward	Nurse in special dressing room	Nurse in special dressing room
How often wound dressings change is performed?	Every 24 hours	Every 24 hours	Every 24 hours	Other frequency
Type of anticoaguliant	Low molecular weight heparins	Low molecular weight heparins	Low molecular weight heparins	Low molecular weight heparins
Location of trauma patients in the department	General wards	Specialized trauma wards	Specialized trauma wards	Specialized trauma wards

ILLUSTRATION: Adobe Stock

5.2.3. Infection process measure

Analysing infection process measures, differences between countries

- In Poland, most common causative bacteria for early and late surgical infections differ comparing remaining countries. In Poland *S. epidermidis* is responsible for early infections and *E. coli* for late infections where the *S. aureus* and *S. epidermidis* are causative bacteria for infections in remaining countries respectively;
- Analysis showed different diagnostic approach between the countries: in Poland and Lithuania biopsy and culturing are major tools for infection diagnostics comparing Germany where the major criteria for infection diagnostics remains clinical expression. In Estonia blood tests is the core evaluation criteria for infection diagnosis;
- Only in one country (Germany) there is no hospital/department guidelines for trauma implant related infections diagnostics and treatment.

INFECTION PROCESS MEASURE	LTU	GER	PLN	EST
Most common bacteria for early surgical site infection	*S. aureus*	*S. aureus*	*S. epidermidis*	*S. aureus*
Most common bacteria for late surgical site infection	*S. epidermidis*	*S. epidermidis*	*E. coli*	*S. epidermidis*
What are your actions if you see the redness in area of surgical wound?	Local dressing with antiseptic	Give antibiotics	No action — wait	Give antibiotics
Most common diagnostic methods used a when you suspect an infection	Biopsy and culturing	Clinical expression	Biopsy and culturing	Blood tests
Do you have hospital/department in-house algorithm/guidelines for trauma related implants infections?	Yes	No	Yes	Yes

5.2.4. Outcome and cost-effectiveness measure

Analysing outcome and cost-effectiveness process measures, differences between countries were noticed:

- No difference comparing length of stay in hospital for uncomplicated and septic trauma patients between countries was observed;
- Cost-effectiveness analysis showed 30 times higher costs of operations in Germany comparing remaining Eastern Europe countries.

OUTCOME AND COST-EFFECTIVENESS MEASURE	LTU	GER	PLN	EST
Average length of hospital stay for uncomplicated trauma patient	3–5 days	5 days	3–5 days	5 days
Average length of hospital stay for septic trauma patient	21 days	35 days	21–30 days	20 days
Average price of mid shaft tibial fracture treated operatively	1300 €	30047 €	600 €	1500 €
Surgical site infection rate	< 2%	n/a	< 1%	9% (4% requiring op)

PHOTO: Adobe Stock

5.3. Comparison of clinical data: closed vs. open tibia fractures

Surgeons have had difficulties treating open fractures for several decades. However, treatment improved by usage of improved surgical techniques, antibiotics and more recently because of improved soft tissue cover. The tibia is the most commonly fractured long bone, but treatment methods varies in different countries. Thus, we aimed to analyse the historical period (2015–2016) of all closed / open tibia fractures between countries with special focus on infected cases in regards to infections prophylaxis and treatment comparison. Prefilled Excel file was sent to four clinical partners (LTU, GER, PLN, EST) and retrospective analysis of patients' medical data with closed or open tibia fractures was performed in all 4 countries.

Results: 285 patients (Germany 69, Lithuania 35, Poland 96, Estonia 85) were included. Gender distribution was: 177 males (GER 45, LTU 23, EST 53, PLN 56) and 108 females (GER 24, LTU 12, EST 32, PLN 40) with the mean age 49 years. (GER 51, LTU 47, EST 50, PLN 47, p = 0.261). The most frequent tibia fracture zone was shaft (n = 165) and 62 was detected in Estonia (out of 85 patients). Fractures statistically significantly were caused by high energy trauma (p = 0.005) and the higher rate of open fractures were detected in Germany (p = 0.001).

OPEN FRACTURE CLASSIFICATION	LTU	GER	PLN	EST
Closed fracture	29	33	78	n/a
Grade I	4	19	5	n/a
Grade II	1	14	8	n/a
Grade III	1	3	5	n/a
	p = 0.001			

Reposition method (open vs closed) did not differ between countries (p = 0.370). Significantly higher number of locking plates was used in Poland (p = 0.064) and higher use of intramedullary nails (IMN) were observed in Estonia.

IMPLANT CHOICES	LTU	GER	PLN	EST
Conservative	0	0	2	5
Nonlocking plate	11	20	3	0
Locking plate	13	33	79	19
IMN	8	15	12	61
Screws fixation	0	1	0	0
External fixation	3	0	0	0
Total	35	69	96	85

No correlations between open fracture and treatment method were observed. Fracture zone, fracture type, surgery duration, comorbidities and type of implant do not have any impact on complication rate.

	OPEN FRACTURE CLASSIFICATION			
	CLOSED FRACTURE	GRADE I	GRADE II	GRADE III
Conservative	2	0	0	0
Nonlocking plate	25	6	3	0
Locking plate	91	13	15	6
IMN	20	9	4	2
Screws fixation	1	0	0	0
External fixation	1	0	1	1
Total	140	28	23	9
	p = 0.324			

FRACTURE LOCATION	NO COMPLICATIONS	IMPLANT FAILURE/ NONUNION
Proximal part	68	0
Shaft	157	8
Distal part	52	0
Total	277	8
	p = 0.2	

5.4. Comparison of clinical data: infected tibia fractures

Results: 25 patients (Germany 15; Lithuania 6, Poland 2, Estonia 2) were included for analysis using non-parametric statistical tests (Wilcoxon). There were 22 males and 3 females with the mean age 52 years. (GER 55; LTU 50; PLN 39, EST 48, $p = 0.131$). The highest infection rate was observed in Germany ($p = 0.034$). Age, gender, ASA, country, fracture type, treatment method does not have impact on complications rate. In all countries the most common bacteria was *S. aureus* (13 of 25 patients). Antibiotic treatment regimen: LTU, PLN, EST — Cefazolin, GER — Cefuroxim, ($p = 0.001$). Microorganism, comorbidities, smoking and alcohol abuse does not have impact on complications.

ALCOHOL USE	NO COMPLICATION	COMPLICATION
Abstinent	8	10
Former use	1	3
Ongoing use	1	2
Total	10	15
	p = 0.391	

SMOKING STATUS	NO COMPLICATION	COMPLICATION
Never	5	9
Former use	1	3
Ongoing use	4	3
Total	9	15
	p = 0.3	

5.5. Pilot study: antibiotic containing bone substitute in major hip surgery: a long term vancomycin elution study

Together with the BFCC project partner BONESUPPORT AB, a pilot study was conducted aiming to investigate a new commercially available biphasic ceramic bone substitute that elutes antibiotics (vancomycin), with *in-vitro* data showing an initial high local release and a sustainable antibiotic level to prevent recurrence of infection. The goal with the study was to compare the *in-vitro* elution of vancomycin from this synthetic bone substitute (CERAMENT™|V) with elution and efficacy in clinical applications.

In this pilot study, the partners aimed to analyse the pharmacokinetic aspects of the long term release of vancomycin from CERAMENT™|V in hip surgery. The hypothesis was that vancomycin in the first week would reach high local concentrations but with safe low systemic trough levels and resulting in a complete antibiotic release during the first month.

Methods: 9 patients (6 women, 3 men) with trochanteric hip fractures (classified as A1 and A2 according to the AO-classification) had internal fixations. The mean age was 75.3 years (± S.D. 12.3 years, range 44–84). An injectable ceramic carrier with hydroxyapatite embedded in a calcium sulphate matrix containing 66 mg vancomycin per mL (CERAMENT™|V, BONESUPPORT AB, Lund, Sweden) was inserted to augment the fixation (Fig. 5 and 6). A mean of 9.7 mL (± S.D. 0.7 mL, range 8–10 mL) was used. The elution of vancomycin was followed by collecting drain fluid, blood (4 days) and urine (4 weeks).

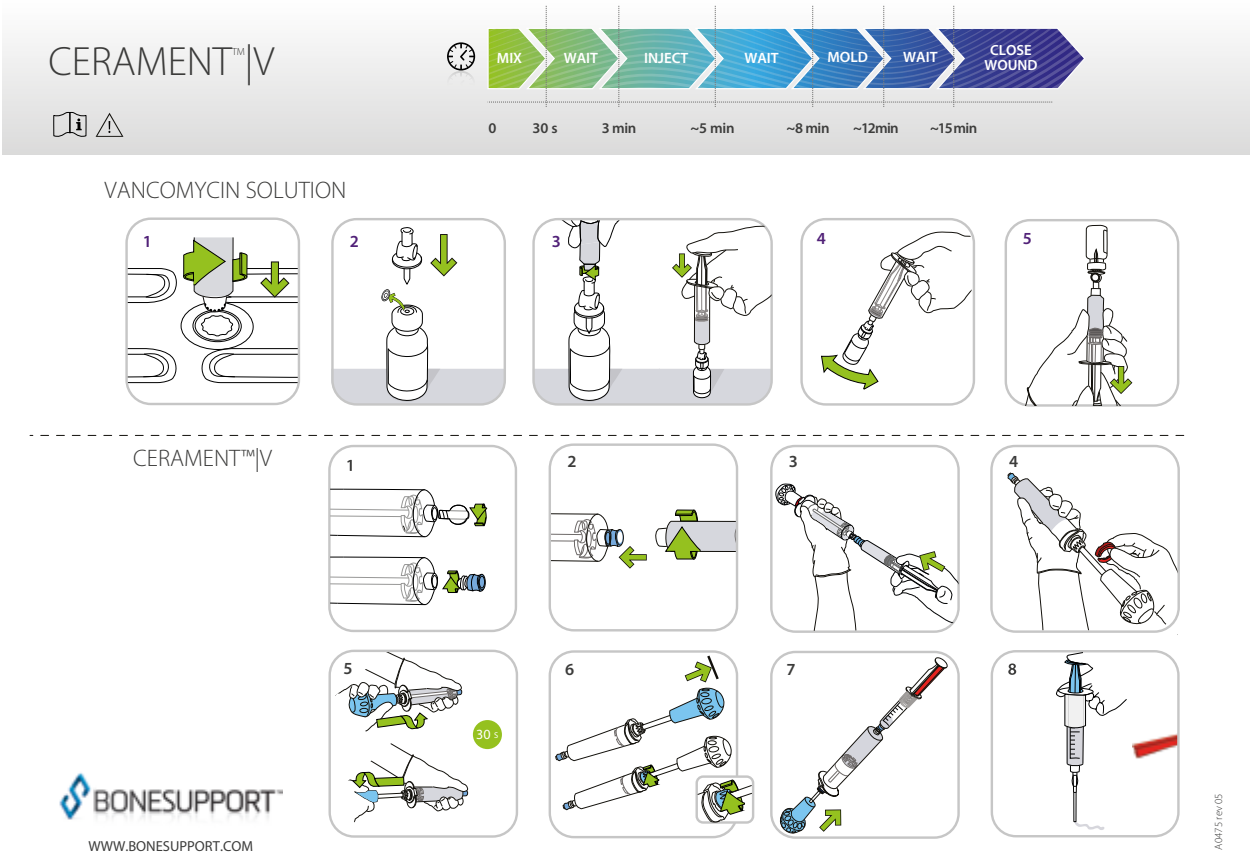
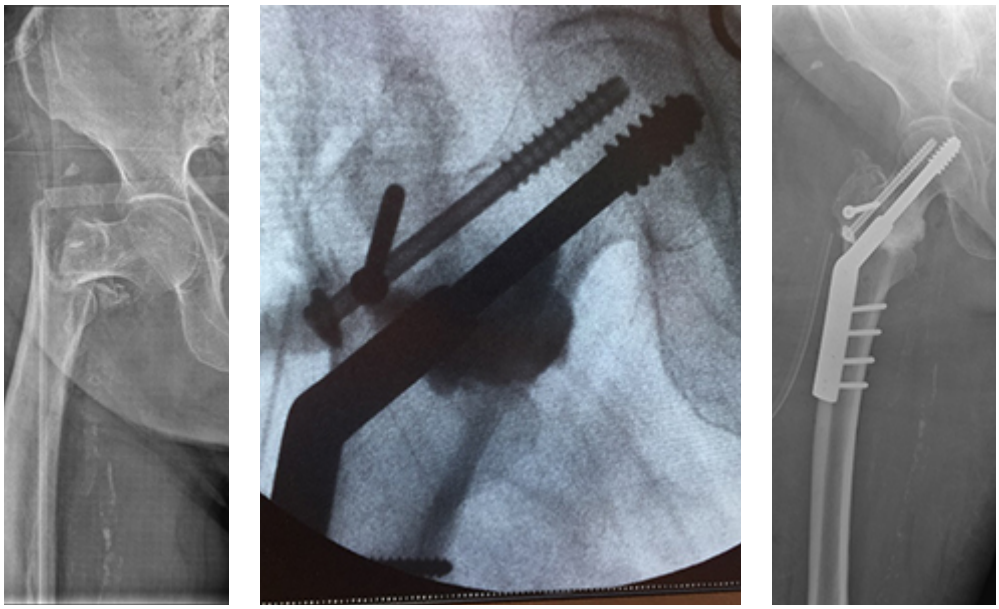


Figure 5: CERAMENT® V Mixing Instructions Chart (https://www.bonesupport.com)



IMAGES: LUHS

Figure 6: X-ray of 83 years old female patient with intertrochanteric fracture in the right hip (Fig. 6a). Perioperative fluoroscopy, injection of vancomycin containing bone substitute (Fig. 6b). X-ray of the first postoperative day (Fig. 6c).

Results: The concentration of antibiotics in the drain showed a high burst during the first 6h after surgery, with a mean value of 966.1 mg/L (± S.D. 546.3), which decreased linearly to a mean value of 88.3 mg/L at 2.5 days. In the urine, the vancomycin concentration reached 99.8 mg/L (± S.D. 49.8) during the first day which was maintained during day 2 followed by a logarithmic decease over the first two weeks to reach zero at 20 days. The systemic concentration of vancomycin measured in blood serum was low and decreased linearly from 2.17 mg/L (± S.D. 0.29) at 1h post-op to levels below the detection level (< 0.1 mg/L) at 4 days post-op.

Conclusions: This is the first long term pharmacokinetic study reporting vancomycin release from a biphasic injectable ceramic bone substitute. The study shows initial high targeted local vancomycin levels, sustained and complete release at three weeks and systemic concentrations well below toxic levels. Hence, the elution results from the clinical study are in line with the earlier reported *in-vitro* data. The plain ceramic bone substitute has hitherto proved to regenerate bone but should be useful in preventing and treating bone infection.

The analysis of this study was submitted to Bone & Joint Research journal and accepted for publication: **Vancomycin elution from a biphasic ceramic bone substitute: A prospective long-term pharmacokinetic study in hip fracture patients.**

Moreover, the study was presented at the 37th Annual meeting of the European Bone and Joint Infection Society, 6–8 September 2018, Helsinki, Finland: **Vancomycin elution from a biphasic bone substitute: antibiotic concentrations measured in drainage fluid, serum and urine over four weeks.**

6. INFECTION CONTROL SOLUTION CONCEPT

To characterise the preferences and to identify areas of consensus regarding specific clinical presentations, an online survey registry platform within the participating hospitals of Baltic Fracture Competence Centre (BFCC) was administered. Based on the analysis of the transnational fracture registry, we aimed at comparing the transnational overview of quality and efficiency of clinical procedures and health outcome of infection prevention and management. Together with the industrial BFCC project partner BONESUPPORT AB, a pilot study was conducted to investigate a new bone substitute that elutes antibiotic vancomycin and evaluate a potential efficacy in clinical applications.

Based on the results of the BFCC project and together with the other clinical partners, the variations between countries were evaluated. Lithuania, Poland and Estonia have adopted hospital antibiotic prophylaxis guidelines, while in Germany there is no adopted antibiotic prophylaxis guidelines. Cefuroxime was used just prior to incision in Germany, while cefazolin was used in other countries for routine prophylaxis in a first dose at least 30 minutes prior to skin incision. In Poland most common causative bacteria for early and late surgical infections differ comparing remaining countries. In Poland, *S. epidermidis* is responsible for early infections and *E. coli* for late infections where the *S. aureus* and *S. epidermidis* are causative bacteria for infections in remaining countries respectively. The analysis showed different diagnostic approaches between the countries: in Poland and Lithuania biopsy and culturing are major tools for infection diagnostics comparing Germany where the major criteria for infection diagnostics remains clinical expression. In Estonia blood tests is the core evaluation criteria for infection diagnosis. Only in one country (Germany) there was no hospital/department guidelines for fracture/implant related infections diagnostics and treatment. There

PHOTO: Adobe Stock

was a higher rate of open fractures detected in Germany, probably this was one of the reasons that the highest infection rate was observed also in Germany. No correlations between open fracture and treatment method was observed. Fracture zone, fracture type, surgery duration, comorbidities and type of implant do not have any impact on complication rate. No differences comparing length of stay in hospital for uncomplicated and septic trauma patients between countries were observed. However, cost-effectiveness analysis showed substantial differences. There were 30 times higher costs of operations in Germany comparing with other countries. The plain ceramic bone substitute has so far proved the effect on bone regeneration but according to our pilot study with CERAMENT™|V, it may also be useful in preventing and treating bone infection. These findings may input to a field for improvement for the »fracture community«. A similar product — CERAMENT™|G — which is eluting the antibiotic gentamicin, has already been proven to be useful in managing infections.[36]

In general, it is accepted that guidelines might produce more standardized care, and consequentially, easier comparison for research, more transparency for patients, and less health care costs. There are a number of guidelines discussing protocols, guidelines for infection management. However, variations exist between hospitals, and local protocols may deviate. In addition, many studies are retrospective, and cohorts are often small and provide a generalized approach. Furthermore, clinical and surgical variables as well as different health care system financing influence diversity.

Many countries have introduced strict guidelines as part of nationwide policies in order to reduce the rate of surgical site infections. Thus, there is a high demand to further investigate, the classification of infections, the description of anatomical variations, patient and other factors, and into guides of infection treatment and new technologies. Until then, infection management should follow well recognized guidelines of a combination of surgery and targeted antibiotic therapy.

With the transnational fracture registry development more clinically important variables could be assessed to provide knowledge about evidence based correlations and thereby offer opportunities to develop ideas and starting points for innovative solutions in the area of fracture/implant related infection management.

7. POCKET GUIDE FOR INFECTION CONTROL

Fracture/implant related infection is a devastating complication that requires a multidisciplinary approach between orthopaedic surgeon, microbiologist, and infectious disease specialists to prevent, diagnose and treat infection after fractures. In order to successfully eradicate infection, restore function of the patient an algorithmic approach is suggested in each hospital.

Implant-related infection control solution concept and pocket guidelines are created according international knowledge and guidelines[37–39], but cannot be interpreted as definitive and cannot be held responsible for any treatment failures.

PREVALENCE	Closed fractures — 0.5–2% Open fractures — up to 30% (External fixators — up to 71%)		
TIME RELATED CLASSIFICATION (ARBITRARY)	Early up to 2 weeks	Delayed 2–10 weeks	Late > 10 weeks
CLASSIFICATION (BIOFILM)	Immature 4–6 weeks	Mature > 4–6 weeks	
DIAGNOSTIC CRITERIA	Confirmatory criteria: 1 Fistula, sinus or wound breakdown. 2 Purulent drainage or presence of pus. 3 Phenotypically indistinguishable pathogens identified by culture from at least two separate deep tissue/implant specimens. 4 Presence of more than 5 polymorphonuclear neutrophil per high power field, confirmed by histopathological examination.	Suggestive Criteria: 1 Clinical signs: pain increasing over time, local redness, local swelling, increased local temperature or fever. 2 Radiological and nuclear imaging signs. 3 Pathogenic organism identified by culture from a single deep tissue/implant specimen. 4 Elevated serum inflammatory markers: ESR, WBC, CRP. 5 Persistent or increasing wound drainage. 6 New-onset of joint effusion in fracture patients	
MICROORGANISM	High-virulent: *Staphylococcus aureus,* aerobic gram-negative Bacilli, beta-hemolytic *Streptococcus*	Low-virulent: coagulase-negative *Staphylococcus, Cutibacterium,* Enterococci	
TREATMENT STRATEGY DEPENDS ON	• The aim: Infection suppression or eradication • Fracture: healed/healing/non-union, osteomyelitis • Implant: stable/non-stable and possible to debride/not possible (e.g. intramedullary nail) • Infection: early/late and biofilm active antibiotic exists/not • Soft tissue, skin: good/bad condition		
SURGICAL OPTIONS	• Debridement and implant removal • Debridement and implant retention • One-stage exchange • Two-stage exchange • Debridement only		
ANTIBIOTIC THERAPY	• Duration: 6/12/long-term suppression • According to susceptibility, oral bioavailability, bone penetration, biofilm activity, surgery		
LOCAL ANTIBIOTIC DELIVERY	Allografts, polymethylmethacrylate bone cement, bioresorbable hydroxyapatite/calcium sulphate, antimicrobial coating, etc.		

8. REFERENCES

1 **Hernlund E, Svedbom A, Ivergard M, Compston J, *et. al.*** Osteoporosis in the European Union: Medical Management, Epidemiology and Economic Burden. A report prepared in collaboration with the International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industry Associations (EFPIA). Arch Osteoporos 2013; 8:136. doi: 10.1007/s11657-013-0136-1.

2 **Jämsen E, Furnes O, Engesaeter LB, Konttinen YT, Odgaard A, Stefánsdóttir A, Lidgren L.** Prevention of deep infection in joint replacement surgery. Acta Orthop. 2010; 81(6): 660–6.

3 **Zimmerli W, Trampuz A, Ochsner PE.** Prosthetic-joint infections. N Engl J Med. 2004; 351(16): 1645–54.

4 **Vinh DC, Embil JM.** Device-related infections: a review. J Long Term Eff Med Implants. 2005; 15(5): 467–88.

5 **HPA. English National Point Prevalence Survey on Healthcare-associated infections and Antimicrobial Use,** 2011: preliminary data. 2012 London: Health Protection Agency. Available from: http://www.hpa.org.uk/Topics/InfectiousDiseases/InfectionsAZ/AntimicrobialResistance/HCAIPointPrevalenceSurvey/

6 **Under the Knife Report:** Taking a zero tolerance approach to preventable surgical site infections in UK hospitals. 2011.

7 **Frampton L.** Calculating the cost of surgical site infection. Microbiology update, The Biomedical scientist, December 2010.

8 **Metsemakers WJ, Smeets B, Nijs S, Hoekstra H.** Infection after fracture fixation of the tibia: Analysis of healthcare utilization and related costs. Injury. 2017 Jun; 48(6): 1204–1210. doi: 10.1016/j.injury.2017.03.030. Epub 2017 Mar 22.

9 **Jenkinson RJ, Kiss A, Johnson S, Stephen DJG, Kreder HJ.** Delayed wound closure increases deep-infection rate associated with lower-grade open fractures: a propensity-matched cohort study. Bone Joint Surg Am. 2014; 96(5): 380–386.

10 **Schmidmaier G, *et al.*** Prophylaxis and treatment of implant-related infections by antibiotic-coated implants: a review. Injury. 2006; 37(Suppl 2): S105–12.

11 **Hetrick EM and Schoenfisch MH.** Reducing implant-related infections: active release strategies. Chem Soc Rev. 2006; 35(9): 780–9.

12 **Zimmerli W, Waldvogel FA, Vaudaux P, Nydegger UE.** Pathogenesis of foreign body infection: description and characteristics of an animal model. J Infect Dis. 1982 Oct; 146(4): 487–97.

13 **Zimmerli W, Lew PD, Waldvogel FA.** Pathogenesis of foreign body infection. Evidence for a local granulocyte defect. J Clin Invest. 1984 Apr; 73(4): 1191–1200. doi: 10.1172/JCI111305.

14 **National Institute for Health and Care Excellence:** NICE support for commissioning for surgical site infection. 2013. Available from: http://www.nice.org.uk/guidance/qs49/resources/qs49-surgical-site-infection-support-for-commissioning2

15 **Osmon DR, Berbari EF, Berendt AR, Lew D, Zimmerli W, Steckelberg JM, Rao N, Hanssen A, Wilson WR.** Infectious Diseases Society of America. Diagnosis and management of prosthetic joint infection: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis. 2013 Jan; 56(1): e1–e25. doi: 10.1093/cid/cis803.

16 **Kortram K, Bezstarosti H, Metsemakers WJ, Raschke MJ, Van Lieshout EMM, Verhofstad MHJ.** Risk factors for infectious complications after open fractures; a systematic review and meta-analysis. Int Orthop. 2017 Jul 25. doi: 10.1007/s00264-017-3556-5.

17 **Papakostidis C, Kanakaris NK, Pretel J, Faour O, Morell DJ, Giannoudis PV.** Prevalence of complications of open tibial shaft fractures stratified as per the Gustilo-Anderson classification. Injury. 2011; 42: 1408–1415. doi: 10.1016/j.injury.2011.10.015.

18 **Gustilo RB, Mendoza RM, Williams DN.** Problems in the management of type III (severe) open fractures: a new classification of type III open fractures. J Trauma. 1984; 24: 742–746.

19 **Ktistakis I, Giannoudi M, Giannoudis PV.** Infection rates after open tibial fractures: are they decreasing? Injury. 2014; 45: 1025–1027. doi: 10.1016/j.injury.2014.03.022.

20 **Saleh M.** External fixation — the incidence of pin site infection: a prospective audit. J Orthop Nursing. 2000; 4: 59–63. doi: 10.1054/joon.2000.0067.

21 **Trampuz A, Zimmerli W.** Prosthetic joint infections: update in diagnosis and treatment. Swiss Med Wkly. 2005 Apr 30; 135 (17–18): 243–51.

22 **Zimmerli W, Sendi P.** Orthopaedic biofilm infections. APMIS. 2017 Apr; 125 (4): 353–364. doi: 10.1111/apm.12687.

23 **Zalavras CG.** Prevention of Infection in Open Fractures. Infect Dis Clin North Am. 2017 Jun; 31 (2): 339–352. doi: 10.1016/j.idc.2017.01.005.

24 **Matar WY, Jafari SM, Restrepo C, Austin M, Purtill JJ, Parvizi J.** Preventing infection in total joint arthroplasty. J Bone Joint Surg Am. 2010 Dec; 92 (Suppl 2): 36–46. doi: 10.2106/JBJS.J.01046.

25 **Illingworth KD, Mihalko WM, Parvizi J, Sculco T, McArthur B, el Bitar Y, Saleh KJ.** How to minimize infection and thereby maximize patient outcomes in total joint arthroplasty: a multicenter approach: AAOS exhibit selection. J Bone Joint Surg Am. 2013 Apr 17; 95 (8): e50. doi: 10.2106/JBJS.L.00596.

26 **Trampuz A, Steckelberg JM, Osmon DR, Cockerill FR, Hanssen AD, Patel R.** Advances in the laboratory diagnosis of prosthetic joint infection. Rev Med Microbiol. 2003; 14: 1–14.

27 **Ochsner PE, *et al.*** Swiss Orthopaedics, Swiss Society for Infectious Diseases. Infections of the musculoskeletal system: basic principles, prevention, diagnosis and treatment. Grandvaux: Swiss Orthopaedics, 2014. First English edition.

28 **Boyle KK, Wood S, Tarity TD.** Low-Virulence Organisms and Periprosthetic Joint Infection-Biofilm Considerations of These Organisms. Curr Rev Musculoskelet Med. 2018 Sep; 11 (3): 409–419. doi: 10.1007/s12178-018-9503-2.

29 **Romano CL, Romano D, Logoluso N, Drago L.** Bone and joint infections in adults: a comprehensive classification proposal. Eur Orthop Traumatol. 2011; 1: 207–17.

30 **Kanellakopoulou K, Giamarellos-Bourboulis EJ.** Carrier systems for the local delivery of antibiotics in bone infections. Drugs. 2000; 59: 1223–32.

PHOTO: Adobe Stock

31 **McKee MD, Li-Bland EA, Wild LM, Schemitsch EH.** A prospective, randomized clinical trial comparing an antibiotic-impregnated bioabsorbable bone substitute with standard antibiotic-impregnated cement beads in the treatment of chronic osteomyelitis and infected nonunion. J OrthopTrauma. 2010;24:483–90.94.

32 **Ferguson JY, Dudareva M, Riley ND, Stubbs D, Atkins BL, McNally MA.** The use of a biodegrad-able antibiotic-loaded calcium sulphate carrier containing tobramycin for the treatment of chronic osteomyelitis: a series of 195 cases. Bone Joint J. 2014;6:829–36.

33 **Logoluso N, Drago L, Gallazzi E, George DA, Morelli I, Romanò CL.** Calcium-Based, Antibiotic-Loaded Bone Substitute as an Implant Coating: A Pilot Clinical Study. J Bone Jt Infect. 2016 Oct 1;1:59–64. doi: 10.7150/jbji.17586. eCollection 2016.

34 **Nusselt T, Hofmann A, Wachtlin D, Gorbulev S, Rommens PM.** CERAMENT treatment of fracture defects (CERTiFy): protocol for a prospective, multicenter, randomized study investigating the use of CERAMENT™ BONE VOID FILLER in tibial plateau fractures. Trials. 2014 Mar 8;15:75. doi: 10.1186/1745-6215-15-75.

35 **Abramo A, Geijer M, Kopylov P, Tägil M.** Osteotomy of distal radius fracture malunion using a fast remodeling bone substitute consisting of calcium sulphate and calcium phosphate. J Biomed Mater Res B Appl Biomater. 2010 Jan;92(1):281–6.

36 **McNally MA, Ferguson JY, Lau AC, Diefenbeck M, Scarborough M, Ramsden AJ, Atkins BL.** Single-stage treatment of chronic osteomyelitis with a new absorbable, gentamicin-loaded, calcium sulphate/hydroxyapatite biocomposite: a prospective series of 100 cases. Bone Joint J. 2016 Sep;98-B(9):1289–96.

37 **Metsemakers WJ, Morgenstern M, McNally MA, Moriarty TF, McFadyen I, Scarborough M, Athanasou NA, Ochsner PE, Kuehl R, Raschke M, Borens O, Xie Z, Velkes S, Hungerer S, Kates SL, Zalavras C, Giannoudis PV, Richards RG, Verhofstad MHJ.** Fracture-related infection: A consensus on definition from an international expert group. Injury. 2018 Mar;49(3):505–510. doi: 10.1016/j.injury.2017.08.040. Epub 2017 Aug 24.

38 **Pocket Guide to Diagnosis and Treatment of implant-associated infections after fracture fixation.** PRO-IMPLANT Foundation (N Renz, A Trampuz). Available from: www.pro-implant-foundation.org

39 **Proceedings of the Second International Consensus Meeting on Musculoskeletal Infection.** Chairmen: Javad Parvizi, Thorsten Gehrke. Available from: https://icmphilly.com/

KEY FACTS

- Duration: 36 months (2016–2019)
- Total budget: about EUR 3.6 million
- Programme: Interreg Baltic Sea Region
- Fund: European Regional Development Fund
- Flagship project of the EU Baltic Sea Region strategy

PROJECT PARTNERS

- Life Science Nord Management GmbH (Germany; Lead Partner)
- Stryker Trauma GmbH (Germany)
- University Medical Center Schleswig-Holstein (Germany)
- University Medicine Greifswald (Germany)
- Sahlgrenska University Hospital (Sweden)
- ScanBalt fmba (Denmark)
- Lithuania University of Health Sciences (Lithuania)
- LifeScience Krakow Klaster (Poland)
- University Hospital in Krakow (Poland)
- University of Tartu (Estonia)
- Tartu Biotechnology Park (Estonia)
- Bone Index Finland Ltd. (Finland)
- BONESUPPORT AB (Sweden)

EU STRATEGY FOR THE BALTIC SEA REGION
FLAGSHIP

www.bfcc-project.eu