BALTIC FRACTURE COMPETENCE CENTRE
GoA5.3 Demonstration Pilot 1 - Infections

O5.3.2 Literature Analysis: Overview of Diagnosed Infections

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1. Introduction

In 2010, it was estimated that 3.5 million new fractures occurred in the EU, including approximately 620,000 hip fractures, 560,000 forearm fractures, 520,000 vertebral fractures and 1,800,000 other fractures (1). According to Hernlund et al., the annual number of fractures in the EU is expected to rise up to 28 % from 3.5 million in 2010 to 4.5 million in 2025. As result, the use of surgically implanted devices will also be increasing. Surgical fracture treatment with various types of implants is usually successful. However, like every medical intervention, it is associated with various complications, from which the most devastating is infection. Implant-related infections after fractures are important to understand as they require repeated surgeries, hospitalisations, secondary complications, sometimes amputations, chronic morbidity, and mortality related to the systemic antibiotic treatment and immobilisation (2-4). Prolonged and extensive systemic antimicrobial treatment courses can last for years and are related with adverse side effects as well as it may lead to bacterial resistance. In addition, infection treatment is associated with significant costs. Approximately 700 million pounds a 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 23,500 euros per surgical site infection for complex surgery (6-7). This complication results in the highest overall increase in total healthcare costs and length of stay. Treatment costs were approximately 6.5 times higher compared to uninfected patients (8).

Thus, the prevalence of implant-related infections is one of the most challenging complications 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 standardised procedures. Still,

invasive medical devices account for more than 50 % of all hospital-acquired infections causing approximately one million new cases in the USA alone (11).

This literature review aims to understand the published state of the art of infection prevention, diagnosis and treatment after fractures. This will be followed by a systematic on-site analysis at the participating hospital partners in order to identify local differences in patient population, treatment standards, and related costs. An evaluation of the current standard treatments and a comparison of treatment pathways between hospitals could help to identify causes for infection and best-practice examples for infection control to reduce their overall occurrence.

2. Pathogenesis, Epidemiology, Etiology and Risk Factors of implant-related Infection

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. The development of implant-related infections begins with the colonisation of the foreign material and is typically caused by microorganisms that grow in biofilms. The interaction of granulocytes with implant results in a local granulocyte defect. These defects are caused by so-called frustrated phagocytosis (12-13). In experimental studies, it was reported that foreign material potentiates the risk for infection more than 100,000 times (12). These data indicated a clinical interest to prevent the infection. Different studies aim to identify especially modifiable risk factors, reasons and concentrates on preoperative infection prevention strategies. Moreover, there are 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 standardised care, and consequentially, easier comparison for

research, more transparency for patients, and less health care costs (16). Furthermore, foreign bodies/orthopedic implants are at lifelong risk of hematogenous 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 Etiology

It was reported that infection rates after mid-shaft tibial fractures were 4.2 % for closed and 10.6 % for open fractures (17). The infection rates after open fractures ranging from <1 % in Gustilo-Anderson grade I to 30 % in grade III fractures (18-19).

The infection rate varies between hospitals and between patient related categories. Trends in surgical site infection rate also vary according to operative site and type. The most common microorganisms causing prosthetic joint infection: 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 % (20). 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 (21).

2.3. Risk factors

There are many potential risk factors for infectious complications in fractures. They could be divided to patient, trauma/fracture and treatment related risk factors.

In a recent systematic review and meta-analysis (17), 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 anaesthesiologists (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, 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. Also, several risk factors like duration of hospital admission, rheumatoid arthritis, geographical location, level of experience of the centre and surgical team, and secondary or tertiary referral of patients were not investigated as these were not reported in the analysed studies.

Male gender (risk ratio (RR) 1.42), diabetes mellitus (RR 1.72), smoking (RR1.29), 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) (17). In addition, it was suggested that further prospective, observational studies are needed to identify and quantify individual risk factors for infection after open fracture fixation.

3. Prevention

In general, the goals of fracture management are prevention of infection, fracture healing, and restoration of function. Infection prevention principles vary between closed and open fractures.

For open fractures, the principles are the following ones: 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 (22). Also, preoperative, perioperative, intraoperative, and postoperative strategies to decrease infection rate are discussed (23-24).

Preoperative measures include: management of patients colonised by Staphylococcus aureus (MRSA decolonization), nutritional optimisation, and management of medical comorbidities, improvement of glucose control, decrease 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 (23-24).

4. 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 (20, 25).

Early periprosthetic infections are typically manifested as an acute onset of joint pain, effusion, erythema and warmth at the implant site, as well as fever, which are usually caused by virulent microorganisms, such as S. aureus and gram-negative bacilli (3). Early infected osteosynthesis is associated with elevated white blood cell count and/or their left shift in the formula. C-reactive protein (CRP) remains elevated in the onset of infection and subsequently increases if infection is untreated (26). Sampling technique and good collaboration with microbiologists are crucial for detecting causative microorganisms. Sonication can reveal different and more sensitive results than tissue samples (21). For early infection, the assessment of the radiological bone fragments stability is of importance and it is classified using the system proposed by Romano et al. (27): 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 is also necessary. In addition, computed tomography should be assessed, and three-phase, antigranulocyte scitigraphy, MRI (Magnetic Resonance Imaging) fistulography may provide additional information in diagnosing late bone infection (26).

5. Treatment

Eradication of infection can be achieved with various therapies: surgical removal of all infected tissue and the implant or 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's perspective, the time period from osteosynthesis to infection symptoms is important as most of early infections can be treated with a combination of debridement, implant retention and antimicrobial therapy (21). Microorganisms forming biofilm develop on non-living surfaces and adhere either on dead bone (sequesters) 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 (21, 26).

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 polymethyl methacrylate (PMMA) cement spacers or beads. However, they require removal and, thus additional surgery (21, 28). Currently, another option is increasingly used, i.e. bioabsorbable material for local antibiotic delivery (29-32) and there is a high need for further clinical results. Bioresorbable hydroxyapatite/calcium sulphate bone substitutes - CERAMENT™ - can be used for treatment of fracture defects (CERAMENT™|BONE VOID FILLER (CBVF)) (32) or as antibacterial coating of implants (CERAMENT™|G and CERAMENT™|V containing Gentamicin or Vancomcycin) to prevent bacterial adhesion and biofilm formation (31).

6. Résumé

A multidisciplinary approach is required in order to prevent, diagnose and treat infection after fractures. Various strategies must be addressed including: biofilm and infection resistance of biomaterials, coatings with antibacterial or antiseptic surface of the implants, new biomarkers for diagnosing infection, best antibiotic prophylaxis and other preventive modalities, antibiotic containing bone substitutes for infected bone defects.

There are numerous reports/guidelines in infection prevention/treatment strategies, however, with a huge variability between continents, countries or even hospitals. This may be effected by the lack of randomised controlled trials in 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 can 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.

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