Diagnosis and management of periprosthetic joint infections

Karin Svensson

Department of Orthopaedics

Institute of Clinical Sciences

Sahlgrenska Academy, University of Gothenburg

UNIVERSITY OF GOTHENBURG

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karin.am.svensson@vgregion.se

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ABSTRACT

Periprosthetic joint infection (PJI) is a severe complication to hip and knee arthroplasty surgery. In the light of its devastating implications for the affected patient, its great economic impact on the health care system and the increasing antimicrobial resistance, it is important to develop efficient diagnostic methods, identify optimal treatment pathways and improve the care for patients.

Using a microbiological approach, Paper I aimed to identify the impact of biofilm production and susceptibility on clinical outcome. The result showed a greater risk of persisting PJI in patients infected by strong biofilm producing staphylococci compared to non- or weak biofilm producers, suggesting the implementation of biofilm diagnostics in clinical routine. Paper II aimed to compare two surgical techniques of DAIR (debridement, antibiotics and implant retention) treatment using a register-based approach. The superiority of modular component exchange compared to non-exchange was established and the exchange of modular components should be employed in cases where DAIR is a viable option. In terms of implant extracting treatment, Paper III aimed to identify re-revision rates after one- and two stage revision procedures using a national register. No difference in re-revision rates were observed, supporting the use of the one-stage procedure which is a more economic choice and more lenient alternative for patients. Paper IV aimed to investigate the experiences and emotional impact of PJI on surgeons using qualitative analysis. The results confirm a negative emotional impact in surgeons and highlight the importance of multidisciplinary work and inter-collegial support for optimal PJI management and for the wellbeing of surgeons.

Keywords: arthroplasty surgery, periprosthetic joint infection, biofilm
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SAMMANFATTNING PÅ SVENSKA

Protesinfektion är en svår komplikation efter höft- och knäproteskirurgi. För drabbade patienter är den förenad med stort fysiskt och psykiskt lidande men innebär också höga samhällskostnader i form av sjukvård, hemvård och arbetsfrånvaro. Under 2018 opererades cirka 19 000 höftproteser och 15 000 knäproteser i Sverige. Protesinfektion kan vara svårt att fastställa men uppträder hos cirka 1% av patienter. Eftersom befolkningen blir allt äldre kommer efterfrågan av proteskirurgi sannolikt att öka inom nära framtid. Därmed förväntas också protesinfektioner bli ett större problem också med tanke på den ökande antibiotikaresistensen hos bakterier.

Trots ett ökat forskningsintresse de senaste åren saknas det tillräckligt med vetenskapligt belägg för hur man på bästa sätt ska diagnostisera, behandla och förhindra protesinfektioner. Behandlingen innebär oftast kirurgi där man spolar rent och/eller ersätter de infekterade protesdelarna. Samtidigt behandlas patienten med antibiotika under längre tid, ibland flera månader, för att bekämpa infektionen. Det finns flera sätt att lägga upp behandlingen på. Ofta anpassas och påverkas den av flera faktorer såsom typ av infektion samt patientens och kirurgens preferenser. Dessvärre leder inte all behandling till att infektionen läker ut. Ibland får patienten genomgå ett flertal behandlingsomgångar med antibiotikakurer och operationer vilket leder till umbäranden för patienten. I vissa fall läker infektionen inte ut utan att protesen behöver tas bort permanent och i sällsynta fall måste benet amputeras. Protesinfektion är förknippat med en ökad dödlighet.

Studierna i den här avhandlingen syftar till att förbättra kunskapen om olika aspekter av protesinfektioner genom att utvärdera sjukdomsbildande egenskaper hos bakterier i relation till infektionsutläkning, olika kirurgiska behandlingsmetoder samt att kartlägga och bättre förstå proteskirurgers erfarenheter och upplevelser av arbetet med protesinfektioner.

För att utvärdera sjukdomsbildande egenskaper hos bakterier, har vi studerat bakterier som är tagna under operationer för höft- och knäprotesinfektioner (**studie I**). Dessa bakterier har sedan analyserats avseende sin förmåga att bilda en hinna på protesen och omkringliggande vävnad, så kallad biofilm, som skyddar dem från kroppens immunförsvar och gör dem svåråtkomliga för antibiotikabehandling. Biofilmen tros vara en anledning till att vissa bakterier blir svårare att bekämpa. I vår studie kunde vi se att bakterier i biofilm är mycket tåliga mot antibiotika och att infektioner orsakade av starka biofilmsproducerande bakterier har en högre risk för att inte läka utan

upprepade operationer. Att mäta biofilm ingår inte i rutindiagnostik men skulle kunna vara fördelaktigt för att på ett tidigt stadium kunna lägga upp ett bättre behandlingsförfarande.

Det finns olika kirurgiska behandlingsmetoder för protesinfektioner. Överlag visar forskning att man uppnår bäst resultat med metoder där man byter ut hela protesen. Detta förfarande innebär dock stora påfrestningar för patienten och är också dyrt varför man ofta prövar alternativ behandling. En sådan möjlighet är en ”DAIR” operation. Det innebär att man spolar och noggrant rengör protesen samt omkringliggande vävnad och ofta byter ut utbytbara icke-benförankrade delar av protesen. De flesta studier angående behandlingseffekten av DAIR-metoden omfattar ett begränsat antal patienter. Därför valde vi att studera behandlingsmetoden DAIR via ett nationellt register (Svenska Höftprotesregistret) där protesoperationer registreras samt komplettera data med hjälp av insamlat journalmaterial (**studie II**). Vi fann att DAIR, med byte av protesdelar, är en överlägsen metod och bör användas i möjligaste mån.

När DAIR inte anses vara ett alternativ byts hela protesen ut, antingen under en och samma operation (en-seans-operation) eller att protesen tas bort vid ett tillfälle och när infektionen sedan anses utläkt sätts en ny protes in vid ett annat tillfälle (två-seansrevision). Traditionellt har två-seansrevision mestadels använts då man trott att detta gett bättre chans till utläkning. Däremot är perioden däremellan utan protes, påfrestande för patienten. Det är också dyrare med två operationstillfällen varför en-seansrevision är önskvärt. Under de senaste åren har forskning inte kunnat påvisa någon större skillnad i infektionsutläkning mellan dessa operationsmetoder. Vi jämförde dem med hjälp av Svenska Höftprotesregistret och fann inte någon skillnad (**studie III**). Fyndet stödjer användandet av en-seansrevision, även om mer forskning krävs för att bekräfta den slutsatsen.

Mot bakgrund av att protesinfektioner orsakar stort lidande för patienter och kan vara svåra att behandla valde vi att göra en intervjustudie om protesoperatörens erfarenheter och känslomässiga påverkan av protesinfektion (**studie IV**). Vi fann att dessa infektioner hade en negativ känslomässig påverkan med stora skuldkänslor hos operatören. Operatörerna upplevde att det var extra viktigt med stöd från kollegor liksom samarbete, inte minst med infektionsläkare. Denna studie belyser medarbetarperspektivet och ger en bättre förståelse för operatörens komplexa situation. Den identifierar också förbättringsområden för att underlätta situationen för både patient och behandlande läkare. Vi hoppas att förståelsen för de svårigheter som protesinfektioner innebär skall öka, och leda till att arbetet med protesinfektioner förbättras.

LIST OF PAPERS

This thesis is based on the following papers, referred to in the text by their Roman numerals.

I. Svensson, K, Tillander, J, Zaborowska, M, Hoffman, M, Lasa I, Thomsen P, Malchau H, Rolfson O, Trobos, M.
Biofilm properties in relation to treatment outcome in patients with first-time periprosthetic hip or knee joint infection.
In manuscript

II. Svensson, K, Rolfson, O, Nauclér, E, Lazarinis, S, Sköldenberg, O, Schilcher, J, Johansson, P.E, Mohaddes, M, Kärrholm, J.
Improved success after exchange of modular components in Debridement, Antibiotics and Implant Retention: an observational study on 575 patients with infected primary total hip arthroplasty.
In manuscript

III. Svensson, K, Rolfson, O, Kärrholm, J, Mohaddes, M.
Similar risk of re-revision in patients after one- or two-stage surgical revision of infected total hip arthroplasty: an analysis of revisions in the Swedish Hip Arthroplasty Register 1979-2015.
Journal of Clinical Medicine, 2019;8(4):485.

IV. Svensson, K, Rolfson, O, Mohaddes, M, Malchau, H, Erichsen Andersson, A.
Reflecting on and managing the emotional impact of prosthetic joint infections on orthopaedic surgeons - a qualitative study.
The Bone and Joint Journal, 2020;102-B(6):736-743.

TABLE OF CONTENTS

ABBREVIATIONS

AEs	Adverse events
AMR	Antimicrobial resistance
ASA-class	American Society of Anaesthesiologists Physical Status - classification
BAI	Biomaterial-associated infections
CBD	Calgary Biofilm Device
CDC	Centre for Disease Control
CFU	Colony-forming units
CLI	Clindamycin
CIP	Ciprofloxacin
CoNS	Coagulase-negative staphylococci
CRP	C-reactive protein
CV	Crystal violet
DAIR	Debridement, antibiotics and implant retention
EPS	Extracellular polymeric substances
ESR	Erythrocyte sedimentation rate
EUCAST	The European Committee on Antimicrobial Susceptibility Testing
FA	Fusidic acid
ICM	International Consensus Meeting
ID specialist	Infectious diseases specialist
IQR	Interquartile range

LZD	Linezolid
MBEC	Minimum biofilm eradication concentration
MIC	Minimum inhibitory concentration
MLST	Multi-locus sequence typing
MSIS	Musculoskeletal Infection Society
OD	Optical density
OR	Operating room
o.n.	overnight
OXA	Oxacillin
PJI	Periprosthetic joint infection
RIF	Rifampicin
S. aureus	*Staphylococcus aureus*
SD	Standard deviation
SEM	Standard error of the mean
SHAR	Swedish Hip Arthroplasty Register
SKAR	Swedish Knee Arthroplasty Register
SUL	Sulfamethoxazole
SXT	Trimethoprim/sulfamethoxazole
THA	Total hip arthroplasty
TKA	Total knee arthroplasty
TRI	Trimethoprim
VAN	Vancomycin
WBC	White blood cells

DEFINITIONS IN SHORT

Arthroplasty	A surgical procedure in which the articulating surfaces of a skeletal joint are replaced with anatomically restoring artificial joint implants.
PJI	Periprosthetic joint infection. This thesis only focuses on PJI of the hip and knee (mainly hip) and does not consider any other types of periprosthetic joint infections.
Reoperation	A surgical procedure related to previous hip arthroplasty with or without exchange or removal of the entire implant or any of its parts.
Revision	A surgical procedure related to previous hip arthroplasty with the exchange or removal of the entire implant or any of its parts. In this thesis revision refers to the exchange or removal of the entire implant.
in vivo	A biological process in its natural environment.
in vitro	A biological process out of its natural context.
Implant preserving surgery	Any surgical procedure in which bone-anchored prosthetic components have not been extracted.
Implant extracting surgery	Any surgical procedure in which bone-anchored prosthetic components have been extracted and/or replaced.
Recurrent infection	Indications of further infection such as clinical symptoms, continued antimicrobial treatment, further reoperations due to infection. In this thesis recurrent infection can be due to relapse or the establishment of a new microorganism.

"Your life is destroyed, absolutely destroyed. There is nothing you can do. You lose your privacy. You lose your dignity. You lose your independence. You have no life. For someone like me who lived a very physically—and I'm a very gregarious person, I would have happily—in fact I would have happily ended it all. I stood at the top of the stairs many times and thought, "If I just went, could I guarantee that this would get me out of this?" because it was that desperate, and I'm a very strong person."

Maggie in *Moore et al.*[1]

1 PROLOGUE

At the time of writing, I am a first-year orthopaedic resident and alongside trying to familiarise with surgical manuals, fracture management and trying to find my favourite implant, this thesis project has kept me rather occupied for the past few years. As a medical student I had the opportunity to work in the arthroplasty ward at Mölndal's hospital which is where I had my first encounter with patients suffering from periprosthetic joint infections. It had a deep impact on me. Some of these patients were in the ward throughout my three-month placement, pending from hope to despair. I met one patient on a daily basis and witnessed the mental and physical withering of this person first-hand. This patient had suffered of mobility pain for several years and had been over the moon after undergoing arthroplasty surgery. Finally pain free. Only to be struck by an infection some weeks later. An infection that after some years of struggling with repeated surgery, antibiotic treatment, long periods of hospitalisations, mental distress and further physical disability, led to this patient's passing.

Originally, I had been very interested in sports medicine, having a career as an athlete (and as a patient!) behind me. However, my encounters at the arthroplasty ward changed my focus. A while later the projects of this thesis started taking form, much thanks to the help of Henrik Malchau, Johan Kärrholm, Ola Rolfson and Maziar Mohaddes who further introduced me to Margarita Trobos and Annette Erichsen Andersson.

There is yet a lot to be done within this research field and my hope is that the results of this thesis may contribute to the improvement in care of patients, and raise awareness of the complexity of periprosthetic joint infections and the associated problems that they entail.

Thank you to everyone who has made this thesis possible and who has been with me on this journey!

2 INTRODUCTION

Treatment with orthopaedic implants such as hip and knee arthroplasties has improved the quality of life for patients with degenerative joint diseases. In Sweden, 18,629 primary total hip arthroplasties (THA) and 15,430 total knee arthroplasties (TKA) were performed in 2018.[2, 3] Complications after arthroplasty surgery include aseptic loosening of the implant, periprosthetic fractures, dislocation and infection.[2] Periprosthetic joint infection (PJI) is the most common cause of reoperation and typically appears within two years after primary surgery.[2, 4] PJI is a devastating complication that induces a great level of patient suffering.[1, 5, 6] Although relatively low, PJI is associated with mortality rates of 2.2-3.5%.[7, 8] In addition, it leads to high healthcare and societal costs due to various factors such as prolonged hospital stays, further surgical procedures and home care.[9-13]

Incidence rates of PJI after TKA and THA are elusive, but have been reported at around 0.89 to 2.3%.[4, 10, 14-17] During the past years an increase in revision procedures due to infection has been observed in the Nordic countries,[4, 18] and increased incidence of PJI has been projected in non-Nordic countries.[19-21] The increase in revision procedures may suggest an actual increasing incidence of infection.[22] The increasing incidence of infection may also be due to other factors such as enhanced diagnostic methods enabling a higher rate of accurate diagnoses. In contrast, there is also research suggesting a plateaue,[23] and decline in infection incidence.[16] At the same time, the numbers of THA and TKA are expected to increase in the coming decades due to an increasing elderly population rendering in greater demands for total joint arthroplasty.[24, 25] Therefore, regardless of the projections for PJI incidence, the absolute number of PJI cases is expected to increase. In parallel with the emerging antimicrobial resistance (AMR) and development of difficult-to-treat pathogens, PJI may become a greater problem in the near future. A higher incidence and poor treatment outcomes along with a global increase in antibiotic resistance, which by 2050 is estimated to cause more annual deaths than cancer,[26, 27] stresses the need for research efforts within infection control.

In summary, it is of importance to recognize all the economic, societal and individual implications that PJI has in order to address preventative measures, improve treatment efficacy and care. Thankfully, PJI has gained a lot of attention during the past years. In Sweden, an initiative called PRISS (Prosthetic Joint Infections Shall Be Stopped) started in 2009 to increase

awareness of PJI nationwide and establish guidelines based on current evidence. Globally, the initiative of Professors Thomas Gehrke and Javad Parvizi has led to an international consensus meeting (ICM) on orthopaedic infections, where multiple aspects of PJI are discussed in an evidence-based manner using the Delphi method in an attempt to reach consensus.[28] Thankfully, the research interest for PJI has increased greatly the past years (Figure 1), and this thesis aims to add on to the ongoing work on some of the aspects of PJI of the hip and knee using variable approaches.

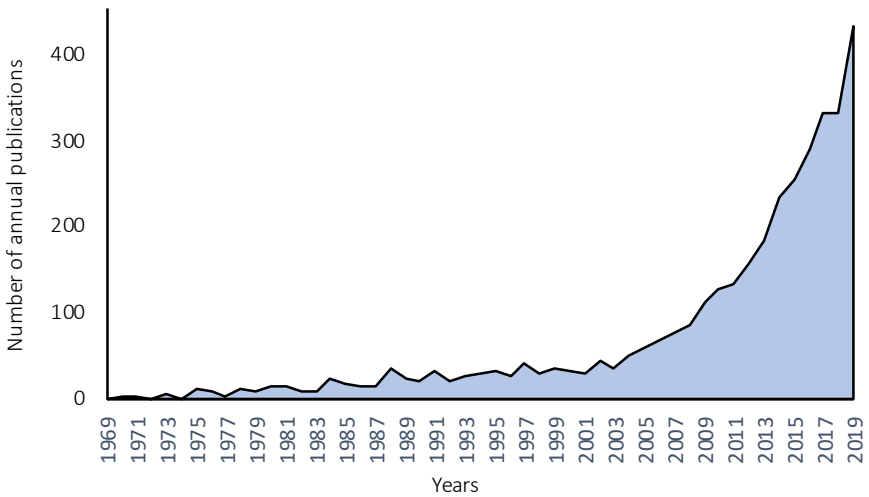

Figure 1. *The increase in publications on PJI from the years 1969 to 2019 in the PubMed database.*

2.1 AETIOLOGY

"Nobody knew where the infection had come from...I hadn't had any broken skin. I hadn't had an accident of any form, I had no viral problems of any sort."

Patient Rory (*Moore et al.*[1])

There are several known routes of contamination for PJI. Infection sources can be either endogenous or exogenous. *Endogenous* spread of infection is when microorganisms present in the patient's normal flora, *e.g.* on the patient's skin, enter the sterile environments of the muscle tissue and joint capsule. In PJI, this type of spread can occur whenever there is a skin opening, such as during surgery or postoperatively during the healing of the wound.[29] Another endogenous route is the haematogenous spread of infection where bacteria present in the blood stream spread to the prosthesis and surrounding tissue. *Exogenous* sources of infection involve external bacteria that do not reside in the normal flora of the patient. Exogenous bacteria can enter the patient's body through particles from the air in the operating room (OR), contaminated surgical equipment or healthcare staff.

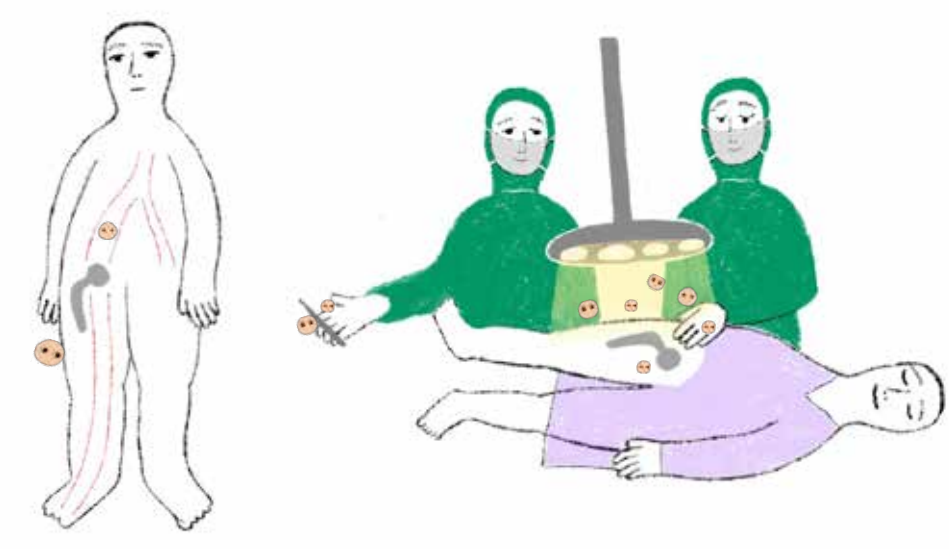

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Figure 2. *The microbial contamination route can be either endogenous such as via the blood stream or the patient's normal skin flora, or exogenous such as via air particles, contaminated surgical equipment or healthcare personnel.*

The aetiology of PJI is multifactorial and the possible contributing causes such as the pathogen's virulence, patient-related factors, peri-operative risk factors, and implant-related aspects will be discussed in this chapter. However, firstly, a distinction between the terms related to timing of infection will be made. *Early* infection is regarded as symptom onset within three months of receiving an implant.[30] Early infections may be caused perioperatively, either by endogenous, or exogenous bacteria in the OR or hospital ward. Up to 90% of PJI are classified as early infections making it the most common presentation.[31] *Late* infection is defined as symptom onset after three months of receiving an implant.[30] The onset of late PJI may be the result of low virulent bacteria or a haematogenous spread.

Both early and late infections can be either acute or chronic (Figure 3). *Early acute* or *late acute* symptom onset implies an acutely swollen, red and painful joint, sometimes together with sepsis. Patients with *early chronic* onset present with persisting wound leakage, whereas *late chronic* infections are associated with chronic pain, sometimes with a sinus tract or signs of loosening on X-rays.[30] The definitions of timing of infection vary, *e.g.* Zimmerli *et al.* suggest that early infection occurs within two months of surgery, delayed infection three to 24 months after surgery, and late after two years.[32] Acute infections are suggested to be caused by highly virulent microbes compared to chronic infections which are caused by low-virulent pathogens.[33]

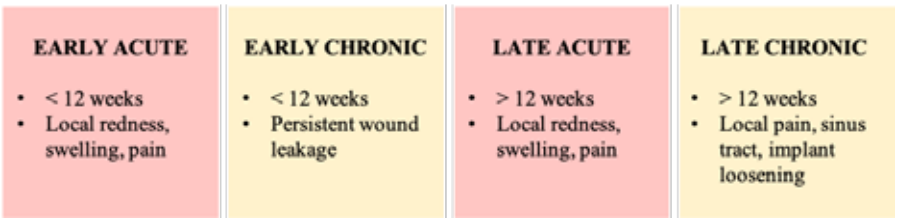

Figure 3. *Classification of infection onset as suggested by Barrett et al.*[30]

2.1.1 Bacterial pathogenicity and virulence

In Europe, the two most common causative pathogens of PJI of hip and knee are *Staphylococcus aureus* (*S. aureus*) and coagulase-negative staphylococci (CoNS),[15, 34-38] followed by *Escherichia coli*, enterococci, *Cutibacterium acnes* (*C. acnes*) and streptococci.[39, 40] The microbial profile may differ depending on if the infection is early onset, late onset or haematogenous spread. *Staphylococcus aureus* is the most common pathogen in early onset,[41] while CoNS are more common in late onset[41] (with the exception of haematogenous

origin in which *S. aureus* dominates[32]).[36] In the present thesis, the main focus will be on staphylococci as they are the most common cause of PJI.

For staphylococci, the ability to colonise an implant surface and the severity of the infection depends on the expression of virulence factors. Staphylococci involved in the pathogenesis of PJI display several virulence factors such as production of toxins, adhesion factors and immune evasion proteins.[41] The pathogenic factors vary by species and *S. aureus* is known as a highly virulent species associated with several pathogenic mechanisms.[41, 42] One such is its ability to persist intracellularly in host cells.[43] *Staphylococcus epidermidis,* a CoNS, is not recognized as equally virulent as *S. aureus* and produces less pathogenic toxins than *S. aureus*. However, *S. epidermidis* carries determinants promoting persistence such as immune evasion molecules and can transfer its genes to enhance the pathogenicity of *S. aureus*.[44] Both CoNS and *S. aureus* can form biofilm which is a virulence factor considered of great importance within medical device-related infections, such as PJI.

Features of the bacterial biofilm

The mode of growth of bacteria can either be planktonic *i.e.* in their free-floating single-cell form, or they can form a biofilm and grow in multi-cellular communities. Biomaterial-associated infections (BAI) are believed to be caused by bacteria growing as biofilms on implants or surrounding tissues.[45] Two-thirds of BAIs are caused by *S. aureus* and *S. epidermidis*.[46]

The biofilm is a gel-like substance composed of cells and self-produced extracellular polymeric substances (EPS) such as proteins, polysaccharides and extracellular DNA.[45, 47, 48] It has several properties contributing to its recalcitrance such as its viscoelasticity, heterogeneity (composed of clusters of communicating cell communities *i.e.* microcolonies) and increased tolerance to the host immune response and antimicrobials despite being susceptible as planktonic cells.[49, 50] In addition, bacteria in biofilms have special characteristics making them more recalcitrant in comparison to planktonic infections.[45, 49-51] Examples of such characteristics are:

- Adhesion mechanisms.
- The aggregation in self-produced EPS which serves as a protector for the bacterial cells.
- A slowed metabolic activity leading to slow-growing bacterial colonies consisting of inactive dormant cells and small-colony variants, which are more tolerant to antimicrobial agents.

- A capability of inter-cellular communication via quorum sensing which regulates the expression of virulence genes in response to fluctuations in cell-population density.

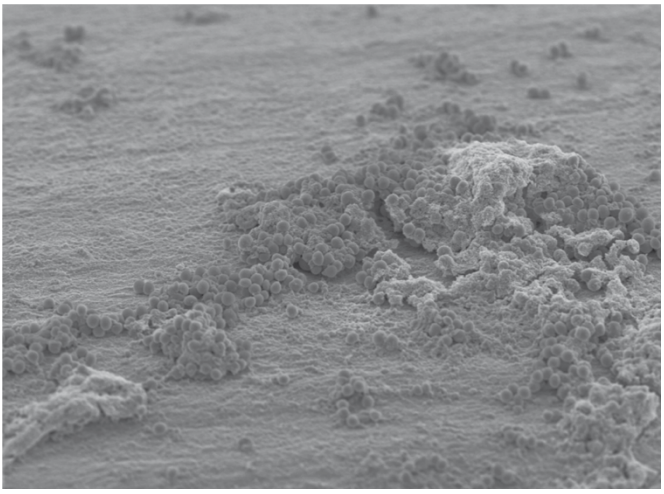

Figure 4. *Scanning electron microscopy (SEM) of Staphyloccocus epidermidis biofilm grown on a titanium screw. Image taken by Sara Svensson.*

The pathogenesis of a biofilm

In an orthopaedic context, the bacterial cells adhere to orthopaedic implants and surrounding tissue and form biofilm.[52] There is no universal biofilm mechanism and there are differences among the mechanisms that induce biofilm formation in diverse bacterial species. Simplified, in staphylococci, the biofilm life cycle consists of four steps: adherence, accumulation, maturation and dispersal (Figure 5).[41, 47]

1. Adherence

Physiochemical interactions (phase 1, reversible): Bacteria first adhere to the material surface by hydrophobic, van der Waals and electrostatic forces.[47] These are reversible interactions.

Molecular and cellular interactions (phase 2, irreversible): Then bacteria initiate specific adherence interactions between their adhesins (autolysins, *Microbial Surface Components Recognizing Adhesive Matrix Molecules* (MSCRAMMs) and the host extracellular matrix (ECM).[47]At first, the adherence of the planktonic cells is reversible, and the bacteria are yet

susceptible to antimicrobial agents, but at the end of this phase bacterial cells have attached to the surface irreversibly.[50] Genes involved in the regulation of adhesion are suggested to be part of the accessory genome, thereby not a characteristic of all bacterial strains.[47]

2. Accumulation

Once bacterial cells attach, they mediate intercellular adhesion via polysaccharide intercellular adhesin (PIA), accumulation associated proteins and eDNA to form a microcolony on the implant or the surround tissue and accumulate in layers.[47] In this state, bacteria produce extracellular polymeric substances (EPS) and interact with newly arriving planktonic bacterial cells. The bacterial cells multiply and form a microcolony. A simultaneous dispersal of cells is suggested to occur at this stage, referred to as the "exodus".[53] The exodus restructures the biofilm, but its significance is yet unknown.

3. Maturation

In the maturation phase, the microcolony thickens and forms characteristic mushroom or tower structures.[50] The generation of adenosine triphosphate (ATP) through arginine catabolism is an important aspect of biofilm maturation. In addition, through generation of ammonia, induction of arginine deiminase operon may be important for pH homeostasis within certain biofilm niches. Antimicrobial resistance increases in mature biofilms.[50]

4. Dispersal

The dispersal phase implies the detachment of bacterial cells from the mature biofilm. This phase is regulated by the accessory gene regulator (*agr*), which regulates the synthesis of delta toxin and phenol-soluble modulins. The latter cause disruption of non-covalent forces in the biofilm matrix to form channels for the delivery of nutrients to deeper layers of biofilm, and provide the disruptive forces for the detachment of clumps of biofilm. The dispersed cells can then colonise other sites of the surface.[32, 50]

There is currently no research that establishes the exact timing of biofilm formation. This has been studied *in vitro* and *in vivo* in animal models with varying results showing biofilm formation occurs within minutes to hours.[54, 55]

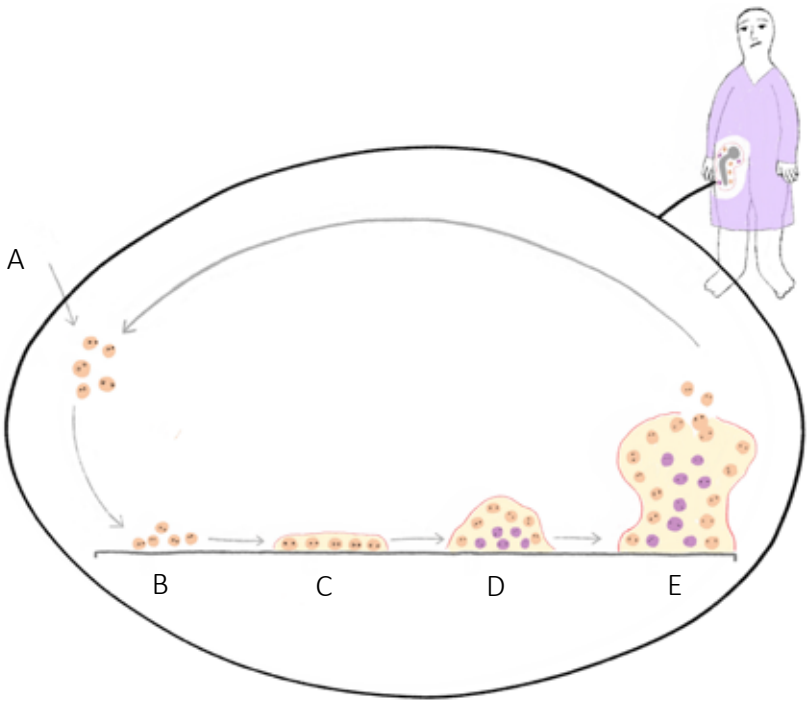

Figure 5. *A schematic illustration of the biofilm cycle. Planktonic bacteria (A) adhere to the implant surface (B). Initially in this phase, the bacteria remain susceptible to antimicrobial agents, but as they adhere irreversibly their susceptibility decreases. The cells form EPS (yellow background) and accumulate in monolayers (C). The monolayers thicken and the biofilm matures (D). The mature biofilm can disperse bacteria (E) which in turn can colonise other sites of the surface.*

Role of biofilms on the host response function and on the susceptibility towards antimicrobial agents

The biofilm protects the bacteria from the host immune system, as well as from antimicrobial penetration and activity.[50] The host immune system produces cytokines in the presence of a biofilm which activate the polymorphonuclear neutrophils (PMNs).[32] Furthermore, the complement system is activated through different pathways.[32] The chronic inflammatory response activated by biofilm presence leads to an increased rate of mutations in biofilm embedded bacteria.[32] These mutations may further induce antimicrobial resistance (AMR).[50] Bacteria induce local bone destruction (osteolysis) which aids the

spread and persistence of infection and is responsible for the septic loosening of an implant.[47]

Bacteria in biofilms are less susceptible, by up to 51,200 times, to antimicrobials than when in their planktonic state.[56-58] In biofilms, bacteria have the ability to communicate with each other through quorum sensing enabling them to regulate their pathogenic factors and increase their AMR.[32] The availability of nutrients and oxygen varies throughout the layers of the biofilm. The bacteria cells closest to the surface layer of the biofilm have greater access to nutrients and oxygen which is why they are metabolically active.[59] In contrast, the bacterial cells in the deeper layers of the biofilm are the least active, so called persistent or dormant cells (Figure 6). The difference in the metabolic activity of the cells in the different layers of the biofilm is a contributor to AMR and important to consider in antimicrobial treatment. Also, the persistent or dormant cells are suggested to play an important role in the recalcitrance of biofilms in arthroplasty surgery.[60] Furthermore, polymicrobial biofilms need to be considered as a threat to the success of antimicrobial therapy as several species may need targeting.[49]

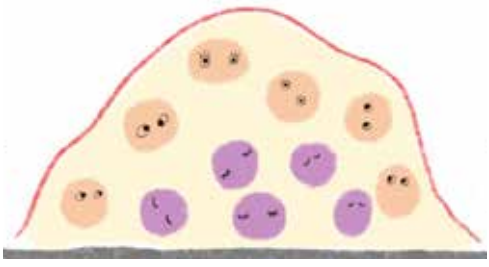

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Figure 6. *In the biofilm, the metabolism of the layers differs. The superficial layer of bacterial cells is more metabolically active (orange bacteria) whereas the inner layers harbor fewer active cells, i.e. dormant or persistent bacteria (purple bacteria).*

2.1.2 Patient-related risk factors

Several patient-related risk factors for PJI have been identified,[28] and these should be considered prior to primary arthroplasty surgery. In accordance with the ICM documents, patient risk factors can be categorised as modifiable and non-modifiable (Table 1).[28] Despite lacking evidence, modifiable risk factors should be optimised prior to surgery as a means to try and prevent PJI.[61]

Table 1. *Modifiable and non-modifiable patient-related risk factors suggested by the ICM workgroup.*[28]

Modifiable risk factors	Non-modifiable risk factors
Active infection	Age
Alcoholism	ASA > 2
Cardiovascular disease	Bariatric surgery
Congestive heart failure	Chronic anticoagulation
Cardiac arrhythmia	Gender
Chronic kidney disease	Hemiplegia/paraplegia
Chronic obstructive pulmonary disorder	Hepatitis B
Coagulation disorders	Osteonecrosis
Depression	Previous joint surgery
Diabetes	Previous joint infection
Drug abuse	Previous infection
Frailty	Transplant
HIV/AIDS	
Immunosuppression	
Intra-articular steroids	
Viscosupplementation	
Malnutrition	
MRSA/MSSA colonization	
Obesity	
Peripheral vascular disease	
Psychosis	
Rheumatoid arthritis	
Smoking	
Hepatitis C	

In this thesis, the following patient risk factors have been obtained and evaluated: ASA-class (American Society of Anaesthesiologists Physical Status), age, body mass index (BMI), diabetes, sex, primary diagnosis for arthroplasty surgery and previous surgery.

ASA-class

The ASA-class is used by anaesthesiologists in clinical practice to determine which physical status the patient has pre-operatively (Table 2). This score can be used to evaluate the patient's comorbidities. Several studies have unanimously reported on high ASA-class (defined as >2) as a risk factor for postoperative complications, including PJI.[62-66]

Table 2. *The American Society of Anaesthesiologists Physical Status classification (ASA-class) and definitions.*

ASA- class	Definition
I	Healthy
II	Mild systemic disease
III	Severe systemic disease
IV	Incapacitating disease
V	Moribund patient

Age

Age can be assumed a risk factor of PJI as the predisposition for infection increases with age due to various physiological changes *i.e.* a less active immune system and altered vascular conditions. However, for PJI, age is an ambiguous risk factor both associated,[67] and not associated with it.[18, 61, 68, 69]

BMI

Patients with high BMI have a higher risk of PJI.[61, 66, 68] There is no cut-off value for increasing BMI regarding increased risk of PJI.[70] However, pooled data shows an increase in the relative risk of PJI with increasing BMI.[61] Patients with BMI > 40 kg/m^2 have a higher risk,[61] up to a threefold risk increase,[71] of PJI and this is currently the cut-off value at which postponing surgery is recommended.[28] Alongside associated comorbidities, obesity can impose a surgical difficulty expanding tissue exposure and the greater layer of low-vascular subcutaneous fatty tissue may impair wound healing.[72] Further, obesity may increase surgical time which in turn may contribute to PJI.

Research in underweight patients (<18.5 kg/ m^2) and its effect on the risk of PJI is limited and controversial. Underweight compared to normal weight, has been reported as an independent risk factor for postoperative complications, whereof PJI was dominant.[73] In contrast, underweight has not been associated with a greater risk for PJI.[70] However, underweight and overweight could be confounders for malnutrition which in turn may increase the risk of PJI.[74-76] To date, planned pre-operative weight loss, bariatric surgery, or weight gain have not been shown to affect the risk reduction of PJI.[77, 78]

Diabetes

Diabetes is a risk factor for PJI.[61, 68, 79] In a study comparing patients with uncontrolled and controlled diabetes, patients with uncontrolled diabetes had

two times the risk of surgical site infection after arthroplasty surgery,[80] supporting the recommendations to optimize glycaemic control prior to surgery. Furthermore, it is important to maintain normoglycemic levels in both diabetic and non-diabetic patients during the peri-operative period to decrease the risk of infection. Patients undergoing orthopaedic surgery may develop a stress-induced hyperglycaemia which in turn has been associated to surgical site infection in orthopaedic surgery.[81]

Sex

Sex is an inconsistent risk factor of PJI. Female sex has been associated to a higher risk for surgical site infection subsequent THA,[67] whereas several studies indicate male sex as a risk factor for revision due to PJI.[18, 61, 66, 68, 69]

Primary diagnosis

Patients with rheumatoid arthritis have a higher risk of PJI.[69, 79, 82] However, due to new treatment possibilities for RA patients, treatment with arthroplasty surgery has become less common. Trauma as cause of a THA or TKA has also been associated with a greater risk for postoperative infection.[67] Patients who receive a prosthesis due to a tumour have a greater risk of PJI, especially if they undergo chemotherapy.[83]

Previous surgery

Previous arthroplasty surgery in the affected joint increases the risk of PJI.[61] Patients who undergo revision arthroplasty have a higher rate of PJI, which may be due to compromised soft tissue and the risk of bacterial dissemination during revision surgery.[29] Furthermore, patients who have had PJI and then receive a primary TKA in another joint have a greater risk of PJI.[84] Although knowledge is scarce, patients who have undergone previous arthroscopy surgery have been reported being at greater risk of PJI.[85]

2.1.3 Perioperative risk factors and preventive measures

Although it is largely unknown how PJI arises, 80% are suggested to originate from the perioperative period and 20% from non-surgical factors.[86] Furthermore, surveillance of infection has proved successful in reducing the incidence of healthcare associated infections.[87] This measure has not been studied in PJI, but may further strengthen the nosocomial origin of infections.

Skin flora, constituting a bacterial reservoir, may contaminate the operating area and cause infection as the skin barrier is broken. Preoperative use of antiseptic applications, such as chlorhexidine, reduce the bacterial load on the patient's skin, but need further evaluation due to small study sizes.[28, 88-91] The

use of alcohol-based antiseptic applications is also recommended for perioperative surgical site preparation, but need further evaluation.[28, 92] Plastic adhesive draping of the surgical site was introduced as an anti-infective measure, and although further evidence for its use in arthroplasty surgery is warranted, it has not been proven efficient in reducing contamination during other surgical procedures.[93, 94]

A lot of focus is concentrated on the OR environment in regard of microbial contamination, often measured as viable colony-forming units (CFU) per m^3. In the European Union, the World Health Organization state that the OR air should not exceed 10 CFU/m^3 during orthopaedic surgery.[95] However, little is known on how the number of CFU/m^3 correlates to clinical outcome and it is not continuously registered or measured in a standardized way.

The air cleanliness of an OR is a debated subject in terms of contamination and ultraclean ventilation systems are widely used in arthroplasty surgery.[95] Ultraclean ventilation implies the use of laminar airflow (LAF) and high-efficiency particulate filters. LAF has been reported efficient in providing clean air in the OR and in reducing the number of CFU by 89% compared to air displacement systems.[96] Previously, no benefit was established using ORs with LAF to reduce PJI,[18, 97] however, in 2020, Langvatn *et al*. proved a significant risk reduction of PJI when using LAF.[98]

Many factors contribute to air cleanliness and these can be difficult to control in studies on airflow. There are no standard protocols for air measurement. Furthermore, the OR staff may constitute a source of contamination, despite hand wash, sterile clothing and the use of surgical masks. One study reported on the contamination of the OR and found that the same bacteria were present in the nasopharynx of OR staff.[99] Observational data on contamination in the OR showed several actions and behavioral patterns of the OR staff increasing the risk for cross-contamination.[100] These observations did not include the surgeon's behavior but the activities of other members of the OR staff such as when inserting an intravenous catheter or during respiratory intubation. Other factors contributing to air contamination in the OR may be the number of people present and the number of door openings.[101]

Furthermore, surgeons believe that surgery duration is a risk factor of PJI[102], and long duration of surgery,[67] of more than 100 minutes,[18, 103, 104] has been associated with an increased risk for PJI. The risk of PJI is suggested to increase by 9% for every 15 minutes of surgery.[65] However, surgeon work experience does not seem to affect the risk for PJI in studies on TKA.[65, 66]

2.1.4 Implant related factors and implant surfaces

Race for the surface

Host cells and bacterial cells can both compete for the colonization of the surface of a newly implanted prosthesis. This was defined as “race-for-the-surface" by Gristina in 1987 describing the first steps of a pathogenic process involving bacteria and host cells and their ability to adhere to, and compete for the colonisation of, an exogenous surface.[105] If the race is won by tissue cells then the implant surface is less susceptible to biofilm formation. However, if the implant surface is colonized by bacteria, tissue cell functions are hindered by bacterial virulence factors.

As described in the previous section, microorganisms are frequently introduced on an implant surface during surgery, getting a head start on the race for the surface, before tissue integration is established.[105] Further, the presence of a foreign material, such as a prosthesis, reduces the pathogen’s inoculum size needed for infection establishment. In an animal model, with and without implant, contamination of 50 bacteria resulted in infection compared to 10 000 bacteria, respectively.[106]

After the implantation of a prosthesis, there is an accumulation of granulocytes around the prosthesis. It is suggested that the granulocytes become impaired and that this may contribute to the possibility for local bacterial spread on the implant.[107] As previously indicated, bacteria are attracted to the material surface by hydrophobic, van der Waals and electrostatic forces and can thereafter colonise the implant.[47, 105] The physiochemical properties of an implant surface is an important factor in the pathogenesis of medical device-related infection. *In vitro* and *in vivo* studies have reported on differences in bacterial adhesion and biofilm formation depending on the physiochemical properties of the biomaterial surface.[108, 109]

Anti-infective surfaces

Creating antimicrobial surfaces is an important part of infection prevention. However, the optimal anti-infective implant surface needs to meet several requirements: good biocompatibility, mechanical properties withstanding stress intra- and postoperatively with an established and durable anti-infective effect.[110] Preventing bacterial adhesion using hydrophilic polymer coatings is one such strategy, however, such materials may compromise the non-adherence of host cells which may be problematic for osseointegration.[109, 111]

Metallic coatings of implants have been tested, and a combination of gold, silver and palladium has been reported to promote osseointegration and reduce bacterial adhesion.[112] Another coating strategy is attracting host cells for tissue integration prior to bacterial adhesion. This strategy is based on "the race for the surface" and in orthopaedics it involves coating implants with hydroxyapatite. Further strategies could be the use of resorbable hydrogel coatings of the implant loaded with antimicrobial agents,[113] or the addition of vitamin E in resorbable coating materials as a measure to reduce bacterial adhesion whilst avoiding toxicity of chemical compounds.[114] Another method of antimicrobial delivery may be its incorporation in polyethylene.[115]

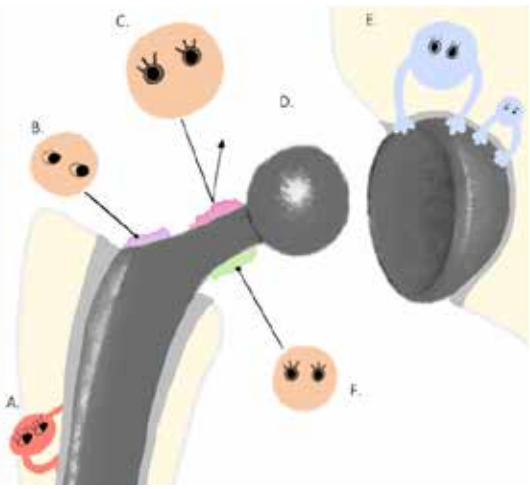

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Figure 7. *The properties of an optimal prosthesis surface are biocompatibility (A), contact killing properties (B), anti-adhesive properties (C), wear resistance (D), ability to stimulate osseointegration (E) and bactericidal properties (F). Adapted from Gallo et al.[110]*

Along with the chemical properties of an implant, surface topography has also been pointed out as a risk factor for infection.[109] Implants with rough surfaces enable the bacterial adhesion and biofilm formation to a greater extent.[116] Further, the use of antibiotic-impregnated cement for fixation of an implant may also be an anti-infective strategy.[28, 117, 118] Dale *et al.* found that uncemented THA or THA fixated with plain cement had a higher risk for revision due to PJI than THAs fixated with antibiotic-impregnated cement.[18] The use of a spacer (a temporary implant) is another method for local antimicrobial delivery during treatment of PJI (Figure 8). Spacers can be

handmade, prefabricated or custom molded. For patients who undergo two-stage revision (page 24), the use of spacers is debated, but may improve mobility,[119] alongside having an anti-infective purpose if loaded with antimicrobial agents. However, spacers can cause pain,[119] and lead to complications such as dislocation and fractures.[120]

Figure 8. *A hip cement spacer mold. Image kindly provided by Lars Ek at Zimmer Biomet.*

2.2 DETECTION AND DIAGNOSIS

"You wouldn't have thought you would have got an infection after five years [...]
Out of the blue, that's what I can't understand."

Patient Jim (Moore *et al.* [1])

Linnéa Teljas Puranen

Figure 9. *Common symptoms of PJI are persistent wound leakage (patient to the left), pain (patient in the middle), erythema and fever (patient to the right).*

The most common symptoms of PJI are pain, persistent wound leakage, erythema and fever (Figure 9).[5, 31] Although these symptoms are associated with PJI it can be difficult to detect and diagnose PJI, impeding the confirmation of diagnosis. PJI does not always present in a typical way. Pain, without any further objective signs of PJI, is sometimes the only symptom a patient presents with. In late chronic PJI, secondary radiographical signs of bone remodeling may appear, or the development of a sinus tract.

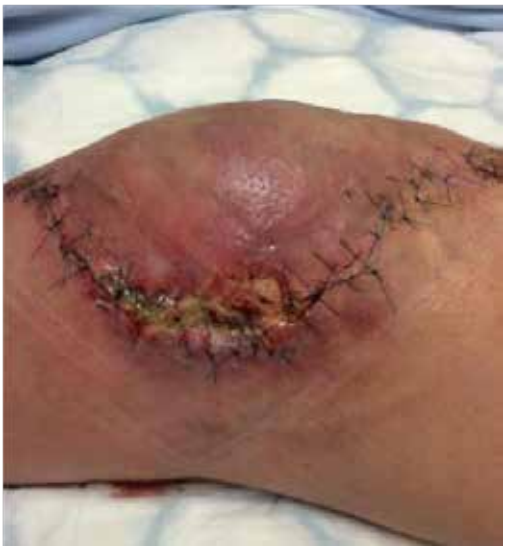


Figure 10. *Patients with PJI may present with typical symptoms such as local erythema, wound leakage and purulence (as shown in the photo) or diffuse symptoms such as pain with no objective signs of infection. An atypical presentation can imply difficulties in detection and diagnosis. Photo used with the permission of Ola Rolfson.*

Thus, due to atypical symptoms PJI should be ruled out in cases of dislocation and aseptic loosening. In studies investigating the final diagnosis of patients initially diagnosed with aseptic loosening, 8-12% turned out to have PJI.[121, 122]

Yet another difficulty may be the absence of objective signs such as elevated inflammatory markers. It is recommended that C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) should be measured in patients with suspected PJI.[123] However, these inflammatory markers are not specific and may even not be elevated in cases of low virulent PJI.

2.2.1 Diagnostic criteria

Several attempts have been made to define the diagnostic criteria of PJI. The most recent was developed by Parvizi *et al*. and is referred to as the 2018 Musculoskeletal Infection Society (MSIS) criteria and has a sensitivity of 97.7% and specificity of 99.5% (Table 3).[124] However, this algorithm is not fully adopted by the orthopaedic community,[28] but is widely used in research.

Table 3. *Diagnostic criteria as proposed by Parvizi et al.*[124]

Major criteria (at least one of the following)				Decision
Two positive cultures of the same organism Sinus tract with communication to the joint or visualization of the implant				Infected
Preoperative diagnosis	Minor criteria		Score	Decision
	Serum	Elevated CRP or D-dimer	2	≥ 6 Infected 2-5 Possibly infected* 0-1 Not infected
		Elevated ESR	1	
	Synovial	Elevated synovial WBC count or LE	3	
		Positive alpha-defensin	3	
		Elevated synovial PMN (%)	2	
		Elevated synovial CRP	1	
Intraoperative diagnosis	Inconclusive pre-op score or dry tap*		Score	Decision
	Preoperative score		-	≥ 6 Infected 4-5 Possibly infected** 0-1 Not infected
	Preoperative histology		3	
	Positive purulence		3	
	Single positive culture		2	

Note: *If the minor criteria are inconclusive, intraoperative criteria can be used.
**If the intraoperative criteria are inconclusive, the authors suggest the consideration of molecular diagnostics.
CRP=C-reactive protein, D-dimer=fibrin degradation product, ESR=erythrocyte sedimentation rate, WBC=white blood cell count, LE=leukocyte esterase, PMN=polymorphonuclear leukocytes

In a clinical setting, the number of positive culture samples for one species can be interpreted differently depending on the type of species present. In cases where there is growth of a possible contaminant species such as *C. acnes* or CoNS, more than one positive culture with the same organism is needed. In cases where a highly virulent bacteria such as *S. aureus* is retrieved, one positive sample may be enough to confirm PJI.[123] Furthermore, PJI can be diagnosed if a single positive culture from tissue samples shows identical bacterial species growth to that of a pre-operative joint aspiration.[123]

2.2.2 Verifying the diagnosis

Verifying the diagnosis may be difficult as certain circumstances may obstruct the ability for representative sampling. Some patients receive pre-operative systemic, or local, antimicrobial treatment which may lead to false-negative results. It is therefore recommended, if possible, that patients stay off systemic antimicrobial treatment at least two weeks prior to pre-operative or intra-operative testing, if possible.[125]

Pre-operative testing

An arthrocentesis is recommended in patients prior to surgery if symptoms allow for it.[123, 126] Joint aspirations should be analysed for a total cell count, white blood cell (WBC) count, and both aerobic and anaerobic bacterial culturing.[123] Aspirations of synovial fluid may be inconclusive as bacterial aggregates may not be captured in samples.[127]

Intra-operative tissue sampling

Intra-operative tissue sampling is regarded the "gold standard" for PJI verification.[128] In Sweden, intraoperative histopathological examination with direct microscopy is not conducted. All tissue samples are sent to a clinical laboratory for further analyses. Five intra-operative tissue samples are recommended to optimize the chance for diagnosis,[123, 129] however, there is evidence suggesting that four samples may be sufficient.[37]

The type of tissue sample may affect the rate of positive cultures. Sampling of joint fluid and surrounding tissue in contact with prosthetic material are the best providing 90% true culture positivity.[37] Further, large samples up to 1 cm^3 are recommended.[126] Using a mix of culture media (Schaedler broth, chocolate agar, and a blood culture bottle) can reduce the number of culture media needed whilst upholding diagnostic efficacy.[37]

Time to culture positivity is dependent on culture media, type of bacteria and bacteria susceptibility.[37, 129] Kheir *et al.* reported that a majority of bacterial strains (98%) are culture positive within eight days,[129] but others, such as *C. acnes*, take up to 14 days to grow.[129, 130] However, for aerobic bacteria, time to growth can be reduced to 24h depending on culture media.[37] Resistant bacterial strains, bacteria isolated in acute infections, and bacteria with high virulence are associated with a higher frequency of culture-positive results.[128, 129]

Sonication is suggested as a mean to increase the sensitivity for diagnosis as the use of an ultrasound apparatus dislodges bacterial cells from their biofilm.[126, 131] Sonication has been reported to have a higher sensitivity and specificity than standard tissue culture.[121, 131] However, the largest existing study reports on higher sensitivity when using standard tissue culturing compared to sonication.[128] Culture positivity is lower in patients with pre-operative antimicrobial treatment compared to without.[132] Further, it is important to have a routine for how culture samples are handled and transported. Prolonged transportation time may affect culture results.[125]

Radiological and nuclear medical verification

The use of radiological methods may aid in the diagnosis of PJI. Plain radiographs can reveal gas formation, immature periostitis and signs of prosthetic loosening.[125] Furthermore, computed tomography (CT) scanning may also be useful as signs of joint distension and fluid collection in soft tissue can be evaluated with this technique. Ultrasound imaging can detect fluid around the prosthesis, and although not specific for PJI these findings can contribute to strengthening the suspicion of infection.[125] Other radiological and nuclear medical methods with diagnostic value in PJI include different types of scintigraphy, magnetic resonance imaging (MRI), positron emission tomography with the use of a glucose analogue (FDG-PET) and hybrid single-photon emission computed tomography (SPECT)/CT.

2.2.3 Microbiological methods to facilitate treatment choice

Minimum inhibitory concentration

The minimum inhibitory concentration (MIC) is the lowest concentration of an antimicrobial agent at which visible growth of planktonic bacteria *in vitro* is inhibited. In clinical practice MIC is used as the standard microbiological guidance for antimicrobial treatment. Susceptibility is determined using pre-defined clinical breakpoints for the microbe and antimicrobial agent. The European Committee on Antimicrobial Susceptibility Testing (EAUCAST) is an organisation that defines clinical breakpoints.[133] In this thesis, susceptibility categories are used in accordance with the EUCAST clinical breakpoints for staphylococci (Appendix, Supplementary Table 1).[133]

As MIC is defined for planktonic bacteria it may be insufficient as a treatment guide for bacteria in biofilm-associated infections. Bacteria in biofilm are often reported to be less susceptible to antimicrobial agents, sometimes requiring antimicrobial concentrations up to 51,200 times higher than the MIC.[56, 57, 134]

Minimum biofilm eradication concentration

The minimum biofilm eradication concentration (MBEC) is the lowest concentration of an antimicrobial agent needed to eradicate a biofilm *in vitro*. Currently there are no methods used for determining biofilm production and biofilm susceptibility in clinical practice. There are suggestions on the use of clinical markers for biofilm production such as the quantification of eDNA (extracellular DNA) produced by *S. epidermidis*,[135] and the use of MBEC.

MBEC can be determined *in vitro* using a Calgary Biofilm Device (CBD). This method is mainly used in research and is described in Paper I.

Recently, Zaborowska *et al.* investigated the biofilm production and MBEC in bacteria isolated from infected percutaneous orthopaedic implants.[58] Although not of statistical significance due to the sample size of the study, they observed that bacteria with higher biofilm production were more common in patients with worse clinical outcome. In their study, seven of eleven patients experienced treatment failure. Of the seven, six displayed high MBECs for the administered antimicrobial treatment.

Using a biomarker such as MBEC to identify biofilm production and susceptibility may facilitate the choice of treatment. Guiding antimicrobial treatment using MBEC may be difficult as it may imply toxic effects. However, MBEC could guide antimicrobial treatment by empirically giving a notion on whether the bacteria may be difficult to treat. In such cases, surgical treatment may be directed differently to be more radical. So far, little is known about any correlation between biofilm production and the clinical outcome in PJI and if MBEC is correlated to biofilm production.

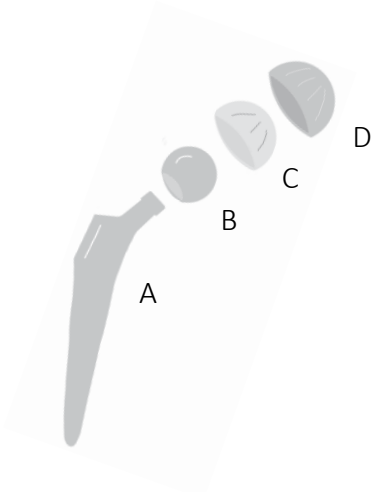
2.3 TREATMENT

PJI is often treated with a combination of surgery and antimicrobial therapy. The surgical treatment aims at removing infected tissue to achieve vital vascular tissue and mechanically disrupting biofilm. There are different types of surgical methods and the most common will be described in the next section.

2.3.1 Surgical methods

In this section the most common surgical methods and current recommendations will be described. Surgical treatment aims at eradicating the infection by either preserving or extracting the infected implant (entire prosthesis or modular components). This section focuses on the hip as the papers of this thesis mainly involve THA. However, the principles are the same for infected TKA.

A total hip prosthesis generally consists of bone-anchored components (the femoral stem and the acetabular cup) and of modular components (femoral head and acetabular polyethylene or ceramic liner) (Figure 11). The acetabular liner is not always modular, as is the case for most cemented cups. In this thesis, hip implant preserving surgery is defined as any procedure in which the femoral stem and acetabular cup have not been replaced. Implant extracting procedures are all types of procedures where the bone-anchored components *i.e.* the acetabular cup and/or femoral stem are exchanged or extracted.



Karin Svensson

Figure 11. *The components of a hip implant. A total hip prosthesis consists of the femoral stem (A), femoral head (B), liner (C) and acetabular cup (D).*

Implant preserving surgery

Implant preserving surgery can be conducted as a DAIR procedure (Debridement, Antibiotics and Implant Retention). A DAIR procedure can be performed in two different ways, either with or without an exchange of modular components (Figure 12A and B, respectively).

Although there are no clear indications for DAIR, it is mainly recommended for early acute infections,[123] and for acute hematogenous infections.[136] Since a successful DAIR is advantageous from a patient and cost perspective,[10, 40] it is desirable to identify which patients benefit from it, and how it should be performed. Reports on the success rates of DAIR vary from 27%-87%.[10, 15, 34, 40, 137-141] However, it should be noted that many studies are of a small sample size.[142] Also, the vast range in success rates can be explained by a heterogeneity in study designs and outcome definitions (Table 4).

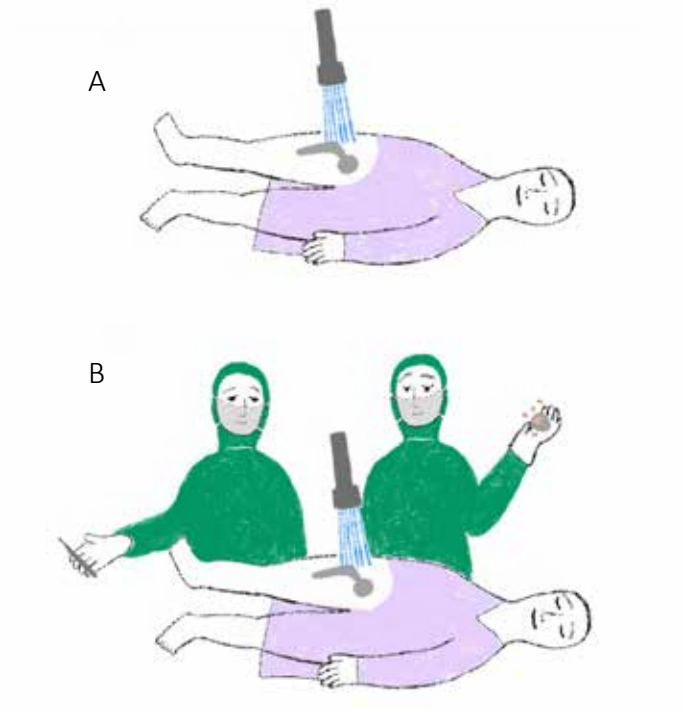


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Figure 12. *DAIR with debridement and irrigation but no exchange of modular components (A) and DAIR with debridement, irrigation and the exchange of modular components, in this case an exchange of the femoral head (B).*

Table 4. *The differences in definitions and success rates in recent studies on the DAIR procedure.*

Study	Success rate	Population	Follow-up	Time from index surgery	Definition of success
Kamp *et al.* 2019[15]	87%	236 (THA, TKA)	1 yr	<90 days	Infection free
Jacobs *et al.* 2019[34]*	85%	91 (THA, TKA)	1 yr	<90 days	Infection free
Löwik *et al*. 2019[138]**	62%	769 (THA, TKA)	1 yr	<12 weeks	No further surgery
Grammatapoulus *et al*. 2017[40]	67% (single DAIR) 85% (multiple DAIR)	122 (THA)	M 7 yrs	<13 weeks	Separate definitions for single and multiple DAIR
Uriarte *et al*. 2019[141]	27%	26 (THA)	>1 yr	<3 months	No further surgery or AB

yr= year, AB=antibacterial treatment, THA=total hip arthroplasty, TKA=total knee arthroplasty, M=mean
*=Patients with negative culture growth were included, multiple DAIR allowed.
**=Revision THA included in study cohort.

Many factors may need consideration when choosing DAIR.[137] Timing is one such factor. DAIR is recommended within four weeks from previous surgery.[123] However, there is reason to believe that it may be beneficial in patients with longer time to symptom onset, up to 90 days,[40, 138] and that timing may not correlate with failure.[34] DAIR has also proved most successful when conducted as soon as symptoms arise, and some studies recommend its use within 7 days of symptom onset.[39, 136, 137] Thresholds are yet to be determined for optimal timing of DAIR in relation to symptoms.

Knowing the causative microorganism has been argued as desirable when proceeding with a DAIR.[28] Jacobs *et al*. found a higher failure rate when the infection was caused by *Enterococcus faecalis*.[34] *Staphylococcus aureus* has also been associated with higher failure,[8] and streptococcal infection has been associated with both better and worse outcomes when using DAIR.[40, 140] However, to date, there is not enough evidence to support a delay of DAIR until culture growth is known.[136]

The exchange of modular components is associated with greater success than a non-exchange.[8, 40, 136, 137, 140] However, this evidence is based on smaller study samples. In a meta-analysis of 1296 PJI patients exchanging components in THA had a mean success rate of 74% compared to no exchange at 61%.[137] Previous surgery such as multiple DAIRs, is associated with a higher failure

rate.[34] The experience of the surgeon conducting DAIR may also affect results, with an experienced hip surgeon having a better success rate.[141]

Implant extracting surgery

Implant revision surgery is most often conducted in chronic infections and in patients where DAIR has been unsuccessful. In patients with late acute infections (>3 months after previous surgery), implant revision has a higher success rate (75%) compared to DAIR with exchange (64%) and DAIR with non-exchange (48%).[8]

The most common types of implant extracting procedures are the one- and two-stage revision procedures. Both methods imply the extraction and re-implantation of an implant. However, the timing of re-implantation is what differs between the methods. In the one-stage procedure, the infected implant is extracted and a new one is implanted during the same procedure (Figure 13A). The patient is thereafter subjected to antimicrobial therapy. For the two-stage procedure, the implant is extracted and then re-implanted once the patient is considered infection free (Figure 13B). During the interim period of the two-stage procedure, the patient receives antimicrobial treatment. Antimicrobial treatment is ceased at least two weeks prior to re-implantation to increase chances of representative culture results at stage two.[32]

The interim period without a prosthesis can last for several months. During this period, the patient is left without a functioning hip joint (a so-called Girdlestone situation, Figure 14) or is given a temporary articulating joint *i.e.* a spacer, most often combined with antibiotic-loaded cement. The interim period is associated with a lot of emotional and physical distress for the affected patient.[1]

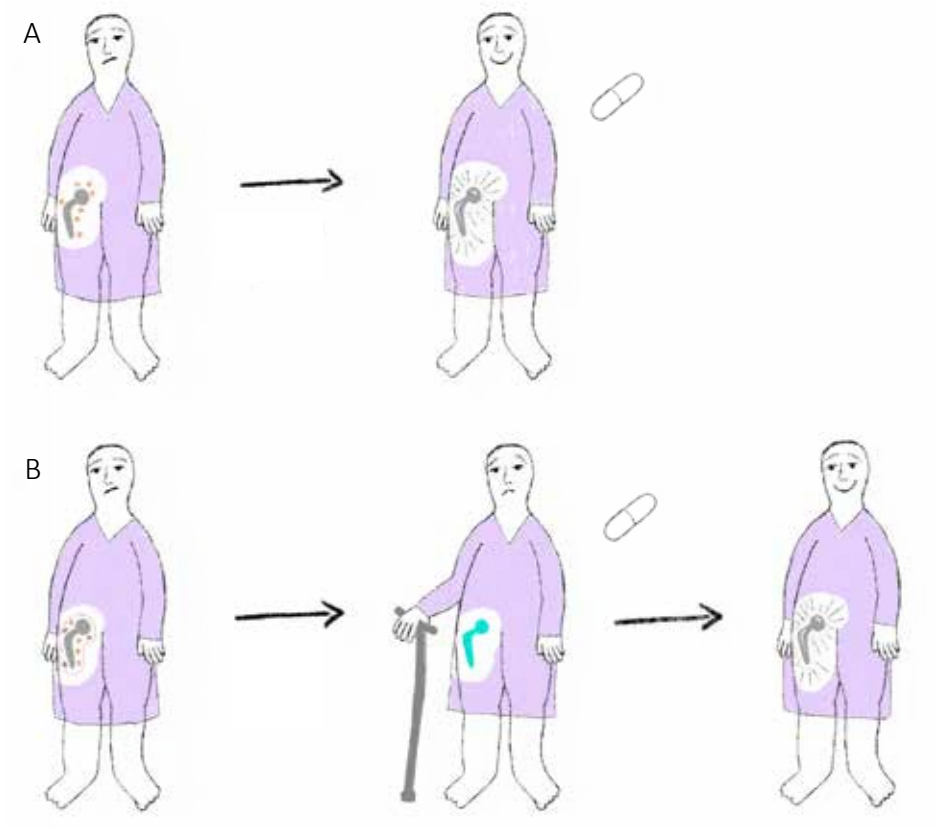

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Figure 13. *A schematic illustration of the one-stage method where the infected implant is exchanged within the same procedure and the patient thereafter continues with systemic antimicrobial treatment (A), and the two-stage method where the patient is left without implant after the infected implant has been extracted (B). The patient in 14B has received a temporary joint (spacer) during the interim period without a prosthesis. During this period the patient also receives systemic antimicrobial treatment.*

One- or two-stage treatment?

"It's taken a lot of mobility away so that actually takes away entertainment, interests [...] It's just the pure reduction in mobility that is the nuisance. It's taken away the bowls, it's taken away the walking".

Patient, Roger in Moore *et al.*[1]

Overall, success rates of the one- and two-stage revision procedures lie between 70%-94%.[143-146] The two-stage method has traditionally been considered the gold standard due to better infection resolution. However, recent data has not been able to show a difference in infection resolution between the two methods.[147-149] Furthermore, the one-stage method has recently gained more attention due to its assumed patient and cost benefits, being just one procedure instead of two. Great distress has been described in patients undergoing the two-stage procedure, with one study participant reporting thoughts of suicide during the interim period.[1] Further, surgeons find evidence for decision-making is lacking,[150] and there is an ongoing debate on how to best utilize the methods. The first randomized study to evaluate them is currently being conducted and results are expected in 2020.[151]

Given the recent findings in favour for the one-stage procedure, UK surgeons report on being more open-minded to the one-stage.[150] However, the two-stage method is still used in the majority of cases. According to current recommendations the one-stage can be considered in patients with good tissue conditions and in whom the causative agent is known and has good susceptibility to antimicrobial agents.[123, 152]

Salvage procedures

In some infected patients, salvage procedures may be the most viable option. Usually, the patient undergoes Girdlestone resection arthroplasty in which the components of the prosthesis are removed (Figure 14). Patients may, or may not, undergo a re-implantation of a new implant later on when the infection has healed. A permanent Girdlestone hip, arthrodesis of the knee, or in the worst-case amputation and even exarticulation may occasionally become an alternative in desolate cases with long standing infection. These alternatives should only be considered when prior surgical treatment has failed.

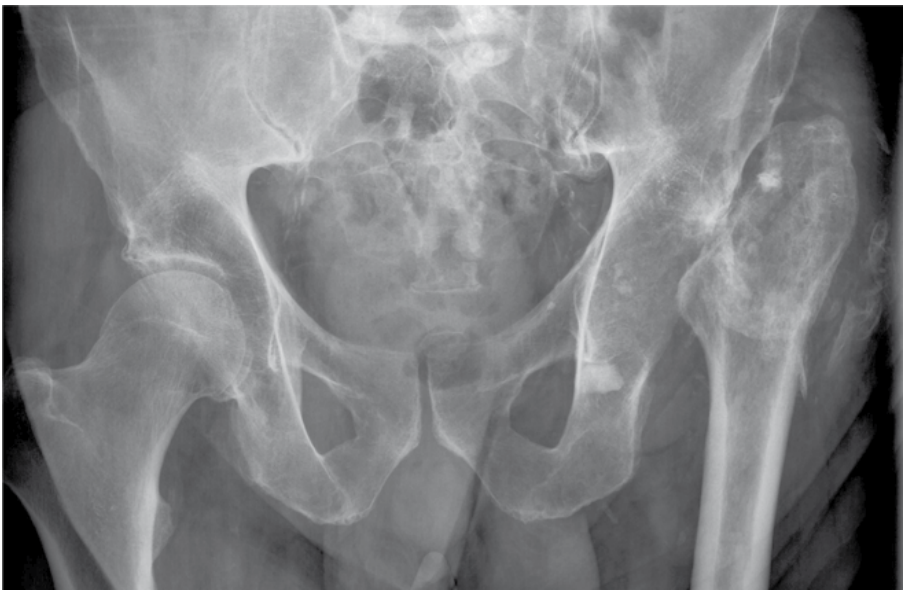

Figure 14. *An X-ray image of a Girdlestone hip (to the right in the image). The hip prosthesis has been excised leaving the patient without a functioning hip joint.*

Algorithms for surgical treatment

The CRIME80-score and KLIC-score are suggested algorithms that may pre-operatively aid in the choice of surgical treatment as they can be used to predict failure rates of DAIR (Figure 15, Figure 16).[38, 136, 153] The algorithms consider patient related factors and may be of use in early PJI or PJI of haematogenous origin when the causative bacterium is unknown.[136]

The KLIC-score considers kidney disease, liver disease, index surgery (due to femoral neck fracture or revision), fixation of implant and the systemic inflammation measured using C-reactive protein (CRP) (Figure 15). A KLIC-score of two or less has been associated with a failure rate of 4.5%[38] to 27.9%[154] after DAIR. The KLIC-score may be a good predictor of failure of DAIR,[38, 154] and is suggested to add value for patients with KLIC-score < 3.5 or >6,[154] but needs to be further evaluated.

The CRIME-80 score considers chronic pulmonary disease (COPD), CRP-levels, rheumatoid arthritis, index surgery, sex, exchange of modular components during DAIR and age (Figure 16). A CRIME80-score ≥ 3 seems

to favour the choice of revision surgery, as DAIR has a success rate of 32% compared to 83% after revision surgery.[8]

The choice of treatment may become more difficult if the first intervention fails. Several factors, such as patient comorbidities, type of bacteria, complexity and consequences of implant removal and not least the personal opinion of the patient have to be considered.

K	Chronic renal failure (kidney)	2
L	Liver cirrhosis	1.5
I	Index surgery due to fracture or revision	1.5
C	Cemented implant CRP > 115 mg/L	2 2.5

Score	**Failure rate** (%)
≤ 2	4.5
2-3.5	19
4-5	55
5.5-7	71
≥ 7	100

Figure 15. *The KLIC-score model as suggested by and adapted from Tornero et al.[38]*

C	Chronic obstructive pulmonary disease CRP > 150 mg/L	2 1
R	Rheumatoid arthritis	3
I	Index surgery due to fracture	3
M	Male	1
E	Exchange of modular components	-1
80	Over 80 years of age	2

Score	**Failure rate** (%)
-1	22
0	28
1-2	40
3-4	64
≥ 5	79

Figure 16. *The CRIME-80-score as suggested by and adapted from Wouthuyzen-Bakker et al.[153]*

2.3.2 Antimicrobial treatment

Antimicrobial therapy alone is not sufficient for the treatment of PJI.[60] As treatment consists of a combination of antimicrobial agents and surgery, it is necessary that the antimicrobial therapy is adequately tailored to optimize the

chance of successful treatment outcomes. Antimicrobial treatment needs to be tailored considering factors such as type of microbe and its antimicrobial susceptibility, the patient's comorbidities, medications, allergies and intolerances.

Type of antimicrobial treatment

Antimicrobial treatment needs to target both actively dividing and dormant bacteria in order to be efficient in BAI. Therapy most often includes rifampicin which has a high activity towards biofilm producing bacteria, especially staphylococci.[155] Rifampicin has a good effect on dormant bacteria and is associated with a high bioavailability.[32, 155] However, rifampicin is never administered as monotherapy due to the development of resistance, therefore it should be reserved for selected patients.[155] Rifampicin in polytherapy with fluoroquinolones, such as ciprofloxacin, has been reported ideal.[155, 156] The microorganism's ability to reside internally in connective tissue and muscle cells poses a difficulty, stressing the importance of choosing an antimicrobial agent which targets intracellular bacteria.[109]

Systemic antimicrobial treatment

Systemic antimicrobial treatment can be administered either intravenously or orally. Vancomycin or isoxazolylpenicillin *e.g.* cloxacillin are frequently used as empirical postoperative intravenous antimicrobials. Vancomycin has been reported to impair biofilm growth when sensitive *S. aureus* are grown *in vitro*.[56] Intravenous antimicrobial treatment administered for less than two weeks may contribute to a greater resistance to subsequent rifampicin.[157]

Antimicrobial treatment is recommended for a period of two weeks to six months.[123, 156] There is a dearth of evidence on treatment duration in correlation to treatment success. Zimmerli *et al.* proposed treatment of 12 weeks regardless of type of surgery.[32] However, combined with two-stage revision surgery, treatment duration can be reduced, in Sweden the current recommendation is six to eight weeks.[158] There are reports on good treatment success (rates of 88-89%) using systemic treatment during an even shorter period of time, from using no systemic antimicrobials,[146] to a regime of one week, in two-stage revision surgery.[159]

Local antibiotic treatment

Intra-operatively, local antimicrobial treatment in the proximity of the hip or knee joint can be used. Broad-spectrum antimicrobials such as vancomycin and aminoglycosides (gentamycin, tobramycin) are commonly used for local

therapy. The use of more than one local antimicrobial agent has proven more efficient in microbial eradication.[160] The use of antibiotic-impregnated cement has increased.[4] A recent study showed lower revision rates in primary THA due to PJI when antibiotic-impregnated cement was used.[118] Alongside antimicrobial-impregnated cement, antimicrobial-loaded beads are a further alternative.[160] The use of local antimicrobials without further intravenous or oral treatment has been evaluated in two-stage revision for PJI of TKA, and local delivery may be sufficient on its own.[146]

Side effects and medical interactions

"Oh, they were terrible. It was a hard time to keep food down and things. It's awful."

Patient Catherine (Moore *et al.*[1])

Antimicrobial treatment can be associated with side effects in patients such as bowel symptoms, urticaria and nausea.[5, 6, 155] Side effects may be of such a troublesome nature that compliance to medication may become threatened.[5] For rifampicin, if side effects arise, dose reduction or switching to single daily dose can be considered.[155]

"So when I came home, I stopped taking the medicine because I decided I couldn't sit on the loo forever. So I told a few lies."

Patient (Andersson *et al.*[5])

For some patients, treatment options may be limited due to AMR. Furthermore, in these patients there may be no viable oral treatment alternative due to interactions or side effects in which case an extended period of intravenous should be used.[123] The patient's general medication prior to the initiation of antimicrobial treatment needs to be considered. Potential medical interactions can be difficult to manage if resistance in antibiograms of causative bacteria limit the choice of antimicrobial strategies.

Dosage

An adequate dose of antimicrobial agents is important for infection eradication. Dosage is guided using the MIC susceptibility testing, as previously described. However, MIC values are obtained *in vitro* and the dose and uptake of different types of tissue *in vivo* needs to be considered. Furthermore, MIC guidance of treatment may not be suitable in BAI since dormant biofilm bacteria may be exposed to sub-inhibitory concentrations.

Several factors may affect the antimicrobial concentration reached at the infected site. One such factor is the tissue penetrance, where bone, especially cortical bone, can present a challenge. Serum concentrations of antimicrobials need to be high in order to achieve adequate concentrations in bone tissue. Furthermore, the antimicrobial activity is determined by how much of the antimicrobial agent is freely circulating and not protein-bound. MIC is based on the freely circulating active antimicrobial concentration. The patient's compliance to treatment and the bioavailability are other factors which also affect the antimicrobial concentration and are difficult to monitor.

Suppressive antimicrobial treatment

Suppressive antimicrobial therapy is used in patients who are not deemed suitable for or who do not wish to undergo further surgery. It is considered a viable option if an adequate antimicrobial, tolerated by the patient, can be administered. Suppressive treatment, most often lifelong, is generally considered in patients where previous surgical treatments have failed, or in elderly or frail patients in whom further surgery is contraindicated. One study investigated the efficacy of suppressive treatment and reported it successful in 56.5% of patients.[161] In this study, the majority of patients (82.6%) had undergone previous revision surgery. In 80% of the failed cases, Girdlestone resection arthroplasty was used as final treatment.

Prophylactic antimicrobial use during surgery

During the reversible adherence of bacteria, namely before forming a biofilm, bacteria are still susceptible to antimicrobials which supports the use of prophylactic antibiotics during arthroplasty surgery.[50] Although a small study set, THA patients who did not receive intravenous prophylaxis had a 60% higher risk for revision due to PJI.[18] The risk for revision decreases when combining intravenous antimicrobial treatment and local treatment (*i.e.* cement loaded with antimicrobial agents) as prophylaxis.[162] However, it is suggested that local antimicrobials may elute sub-inhibitory concentrations which may enable bacterial adhesion and growth on implants, and promote the development of AMR.[54]

2.3.3 Antimicrobial resistance

Antimicrobial resistance (AMR) is a microbe's ability to grow in presence of antimicrobial agents.[163] An increase in multi-resistant bacteria causing PJI has been reported.[36] In patients treated with a two-stage procedure and antibiotic-loaded spacer, an increase in resistance in relapsing *S. aureus* from stage one

to stage two have been observed.[164] In this study, patients were treated with vancomycin spacers in the interim period and in nine (30%) cases, the strains recovered from stage two were more resistant to vancomycin than in the first stage. Further, viable bacteria have been found on retrieved spacers from patients treated with two-stage revision after antimicrobial treatment has cessated.[165] This finding adds on to knowledge on the importance of biofilm formation for AMR.

In the US, an estimate of 38.7% to 50.9% of microorganisms causing surgical site infection may be resistant to routinely used antimicrobial agents.[166] This most likely has consequences for procedures requiring prophylactic antimicrobials such as prosthetic joint surgery. An improper use of antimicrobial agents, such as for growth promotion in the livestock industry, has resulted in an increased AMR. Resistance genes can be transferred from animals to humans.[167, 168] Patients infected by multi-resistant bacteria have a greater risk for treatment failure than if infected with susceptible bacteria.[169, 170] In Sweden, methicillin-resistant *S. aureus* (MRSA) are relatively uncommon,[171, 172] and screening programs have been established for patients at risk for MRSA prior to hospital admission as a measure to reduce its spread within the healthcare system.[173]

AMR is projected to be one of the greatest challenges of our time.[174] To address AMR, several tentative strategies are discussed and evaluated in research. One such in BAI is to target the biofilm at different stages of the biofilm life cycle, such as adhesion, cell-to-cell interactions such as quorum sensing, production of the EPS matrix and inducing biofilm detachment.[47, 49, 109, 175] However, the complexity of biofilms impose challenges in developing targeted anti-biofilm therapeutics and biofilm-associated infections should perhaps be treated using the combination of multi-targeting therapeutics.[49] Another preventative measures is vaccines, this has not yet had a break-through, although several attempts to find a vaccine against *S. aureus* have been made.[176]

A general decrease in infection rates have been observed in the U.S. which may be a result of the Centres for Disease Control and Prevention's (CDC) work on prevention strategies and AMR awareness.[174] As the successors to antimicrobial agents yet have to be found, it is important to work with stringent infection prevention, focusing on minimizing the known risk factors for PJI. As described, research in PJI has greatly increased during the past years and there is no reason to believe that this will change in the near future. However, it is of importance that researchers collaborate and bring in different competences in their teams to ensure a comprehensive multidisciplinary approach, combine research methodologies and translate pre-clinical studies and protocols to clinical significance.

2.4 THE IMPACT OF PROSTHETIC JOINT INFECTIONS

As briefly mentioned, PJI has a great impact on the affected patient,[1] on health care resources,[9-11] and on the treating surgeon.[177] This is important to keep in mind when managing PJI and may influence treatment directions. All three aspects will be further described in this section.

2.4.1 Patient impact

Patients report on psychological and physical suffering when reflecting on their experiences of PJI.[1, 5, 6] Andersson *et al*. interviewed patients with implant related surgical site infection whereof eight had PJI.[5] There were several stages during an infection which affected the patient negatively; insecurity about their own role in the emergence of infection with feelings of fear and panic at symptom onset, uncertainty during diagnostics, in part due to the doctor's uncertainty and due to lack of answers after different examinations, and the feeling of not being taken seriously. The latter was further confirmed in a UK-based study by Moore *et al.* on the patient experience of PJI.[1]

"I knew there was something seriously wrong. I was going to my GP probably once a fortnight saying, "I can't stand this anymore. I don't seem to be getting any better" [...] I knew that the pain was not a muscle pain. I'd been through the procedure once before. It was a most distressing time because nobody seemed to be actually hearing what I was saying."

Patient Maggie (Moore *et al.*[1])

Patients felt feelings of worry, suspense, isolation and had experiences of depression while waiting for infection resolution. Some had persistent wound leakage and returned to the hospital several times.[5] Many worried about persisting physical disabilities, particularly patients undergoing two-stage treatment. In this group, negative social consequences of their physical disability were described, and confirmed by Moore *et al.*[1]

"Well we used to go out almost every week [...] with our friends, we don't seem to do that much now, my husband tends to have to do a lot for me now, I mean silly things like you know my feet, my toenails, because when I bend this is hurting me all and everything like that so..."

Patient Wendy (Moore *et al.*[1])

Patients witnessed on not being able to return to their normal life after having recovered from PJI due to different physical limitations. Others were able to manage without further problems. Some felt bitter towards the hospitals and doctors, whereas others reflected upon their journey with a new-found gratitude towards life. Further, patients could continue feeling fear of recurrent infection after treatment.[1, 6]

"That's my biggest fear because it's a painful experience I can tell you because I did it three times and it's the most excruciating painful experience you can have [...] I'm still living in fear of doing things right, after the operation you know?"

Patient Don (Moore *et al.*[1])

Andersson *et al.* described that the patient's social relationships were the key source of support during treatment and sometimes the patient's situation put a strain on their relationships.[5] Some patients also described their relationship with their doctor as an important source of strength and support.[5]

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Figure 17. *A patient and surgeon meeting.*

2.4.2 Surgeon impact

Given the mentioned uncertainties within several aspects of PJI, the management of PJI consists of many challenges. Prosthetic joint surgeons feel uncertain when deciding on treatment plans for PJI as there is lacking evidence to support the superiority of available methods.[150] As mentioned, low virulent infections can be hard to diagnose as patients can present with unspecific symptoms. It can be difficult to secure reliable cultures that represent the causative microbe, and it is hard to interpret which bacterial growth is significant and which is sample contamination.

Meeting patients who are in a distressed state and seeing how they, in some cases, physically and mentally deteriorate may be a difficulty. Physicians may be exposed to a risk of developing anxiety, burnout and/or depression in encounters with traumatic events or adverse events. Physicians with ill-being and workplace related stress may be unable to give optimal care to their patients due to higher frequencies of adverse events and reduced productivity.[178] The term *second victim* was first used in 2000 to describe how adverse events can have a negative impact on the treating physician.[179]

After an adverse event, a physician may experience feelings of guilt, frustration, anger, fear and distress.[180-182] Study participants have reported high emotional impact when missing a diagnosis, doubting a medical decision, during life-threatening moments and bad news conversations, when severe complications arise, and when meeting unsatisfied patients.[183]

Within orthopaedics, Mallon *et al.* investigated the impact of PJI on prosthetic joint surgeons in the UK.[177] They reported that PJI had a deep negative impact on the surgeon and that surgeons felt accountable for the infection.

Several studies have shown that physicians would like the possibility of peer support after an adverse event.[183-185] Many physicians are of the opinion that the support systems are insufficient and desire structured support.[180, 186, 187] However, some do not seek help or speak up due to stigma.[187] Little is known about what support strategies prosthetic joint surgeons may need.

2.4.3 Economic impact

PJI is associated with a significant economic burden and the economic impact has been investigated in several different countries.[9-12, 188, 189] Considering the projections on an increase in the numbers of primary arthroplasty

procedures,[20, 24, 25, 190] PJI-related costs will increase. Furthermore, the increase of AMR, such as methicillin-resistance, has also been linked to greater costs.[13]

A Finnish study reported on the following mean cost per patient for THA and TKA procedures: primary procedure (€7,200), DAIR treatment (€18,461) and two-stage treatment (€38,428 for stage one and €17,240 for stage two).[10] Another study reported on a near five-fold increase in costs for revision due to PJI compared to the primary procedure.[9]

PJI patients were hospitalized for a longer time period, up to an average of seven times longer compared to primary procedures,[9, 10, 188, 189] which implies a greater cost. Also, in presence of methicillin-resistant bacteria, length of stay significantly increased.[13] PJI patients also required more out-patient visits.[9, 10, 189] Furthermore, the impact of indirect hospital costs should be considered. In the US, the total costs of PJI calculated in a model of direct hospital and indirect societal costs for one patient ranged from USD 390,806 up to USD 474,004.[11] This model also considered loss of productivity.

In light of the economic perspective, it is important to identify time-efficient and less expensive methods for diagnosis and treatment of PJI.

2.5 CURRENT GAPS IN KNOWLEDGE THAT MOTIVATE THIS THESIS

The gaps of knowledge mentioned in this section are those that motivate the projects included in this thesis.

- There is a need for improved diagnostic tools to aid tailored treatment of PJI. It is important to determine the bacterial virulence factors involved in the pathogenesis of PJI and at an early stage. Biofilm production and susceptibility may be associated with clinical outcome in PJI and MBEC may be a surrogate marker for biofilm producing bacteria, but this has yet to be evaluated. (**Paper I**)

- The success rates of DAIR vary in the current literature. The success rate of DAIR in PJI of the hip has not been investigated using the Swedish Hip Arthroplasty Register. The role of DAIR in treatment algorithms in regard of the exchange or non-exchange of modular components has not been established for this population. (**Paper II**)

- Globally, there is an uncertainty in which method (one- or two-stage revision) is superior to the other, thus presenting a difficulty in treatment choice. The SHAR has collected information on one- and two-stage revision procedures due to infection since its start in 1979, allowing for a uniquely long follow-up time. The success rate of the two methods has not previously been studied in the SHAR. (**Paper III**)

- A solitary study outside Sweden has found a deep impact of PJI on the treating surgeon. However, little is known about how PJI surgeons cope with the difficulties they may face during management of PJI. Furthermore, no study has been conducted to describe the emotional impact and experiences of PJI on Swedish surgeons or identified improvements in PJI management desired by surgeons. (**Paper IV**)

3 AIMS

The specific aims of each study in this thesis were the following.

- To identify whether biofilm production in staphylococci causing PJI correlates to clinical outcome, defined as infection resolution or recurrence, and to evaluate whether biofilm susceptibility testing measured as MBEC has a correlation to clinical outcome. (**Paper I**)

- To establish the success rate of DAIR for PJI with or without the exchange of modular components. (**Paper II**)

- To establish the rates of re-revision after one- and two-stage surgery for PJI. (**Paper III**)

- To investigate the experiences and emotional impact of PJI on prosthetic joint surgeons and identify facilitating factors in the management of PJI. (**Paper IV**)

4 METHODS AND MATERIALS

Ethical approvals

All studies received approval from the Regional Ethical Board in Gothenburg, Sweden, prior to study start.

Paper I Written consent was obtained from study participants prior to the study start. Participants were allowed to withdraw from the study at any point without further explanation. Ethical application approved 2016-11-10, entry number 654-16.

Paper II Patient consent was not needed for this study according to the Patient Data Act in Sweden. Ethical application approved 2017-10-23, entry number 804-17. Amended to include sending out supplementary data sheets to all orthopaedic units in Sweden, approved 2018-01-17, entry number T053-18. Amended to include medical record retrieval from orthopaedic units in Sweden, approved 2019-03-15, entry number 2019-00957.

Paper III Patient consent was not needed for this study according to the Patient Data Act in Sweden. Ethical application approved 2015-07-07, entry number 430-15.

Paper IV Written and oral consent was obtained from study participants prior to the interviews. Participants were allowed to withdraw from the study at any point without further explanation. Ethical application approved 2017-02-20, entry number 1190-16. Anonymity of the study participants was ensured by coding each interview, and only KS had access to the code key. Furthermore, geographical location has not been disclosed as a measure to prevent identification of study participants.

4.1 PAPER I

Study population

The medical records of patients operated due to PJI between 1st January 2012 to 30th June 2015 were reviewed until 31st December 2018 to collect variables of infection interest (Paper I, Table 1). Follow-up was at least 3.5 years for all patients (mean follow-up time of 5 years).

Intraoperative tissue samples sent to the Clinical Bacteriological Laboratory (Sahlgrenska University Hospital) for culture growth were isolated and stored according to routine. For this study, isolated bacterial strains were cultured and matched to their respective reoperation and patient, and anonymously coded at the Clinical Bacteriological Laboratory. The strains were frozen and transported to the Department of Biomaterials (University of Gothenburg) where they were further analysed.

Strains were compared with medical records to determine growth in at least two out of five or more samples to certify the saved strain's causative significance. Patients were included if they met the following criteria:

- First-time PJI of the hip or knee according to the MSIS criteria.[124]
- Infection caused by monomicrobial growth of *S. aureus* or CoNS.
- Infection caused by polymicrobial growth of two different staphylococcal species.

Patients without saved strains, who did not consent to analysis of their strains, had negative growth, or bacterial growth other than staphylococci, were excluded from the study (Paper I, Figure 1). Furthermore, patients with an additional diagnosis (e.g. cancer) or bilateral prostheses were also excluded.

Outcome measures

The primary outcome was to identify whether biofilm production (non/weak or strong) correlates to clinical outcome (infection resolution or recurrence). The secondary outcome was to evaluate the correlation between biofilm susceptibility (MBEC, MBEC/MIC-ratios and antibiogram patterns) and clinical outcome.

Bacterial inoculum preparation and identification of the bacterial strains

The bacterial strains were transported under frozen conditions and immediately stored in -80°C upon arrival to the Department of Biomaterials. Prior to analysis strains were cultured on 5% horse blood Columbia agar plates at 37°C overnight (o.n.). The API® Staph test kit (bioMérieux, Marcy-l'Etoile, France) was used to identify CoNS to the specific species level.

Biofilm formation ability of the strains and biofilm quantification

There are several methods to quantify microbial biofilm.[191] In the present study, the microtiter plate test using crystal violet (CV) was used for biofilm quantification. CV is a dye that stains both live and dead cells as well as the EPS, allowing for quantification of the total biofilm biomass. One colony from each strain was further inoculated overnight (o.n.) in tryptic soy broth (TSB, Scharlau, Barcelona, Spain) with an addition of 0.25% glucose for *S. aureus* and incubated at 37°C on a shaker o.n. The optical density (OD) of CV is determined by using a microtiter-plate reader. The cell suspension was adjusted to OD_{546}=1 and diluted 1:40 in TSB (with an addition of 0.25% glucose for *S. aureus*). Equal amounts of the bacterial suspension (200 µL) was added to three wells in a 96-well microtiter plate (BioLite Cell Culture Treated Plates, Thermo Scientific™, MA, USA). The plates were incubated statically for 24h at 37°C and thereafter washed three times in water. The biofilms still adherent to the wells were stained with 200 µL of 2% CV (VWR, PA, USA) for five minutes and gently washed in water. The wells were thereafter air dried and the biofilm bound dye was eluted in 200 µL ethanol-acetone. A volume of 150 µL of the eluted suspension was moved to a new plate and OD_{595} was determined using a plate reader (FLUOstar Omega, BMG Labtech, Offenburg, Germany). Three wells served as blanks and contained sterile TSB of which the mean value was subtracted from all readings. OD values were averaged in accordance to recommendation.[192]

Biofilm classification

Biofilm production was categorized according to the classification suggest by Baldassarri *et al*.[193] For statistical analysis, this classification was further modified (Figure 18). Control strains were used as references for the different biofilm production categories (Table 5).

Figure 18. *The Baldassarri classification[193] for biofilm production and the modified version used for the analyses of the current study.*

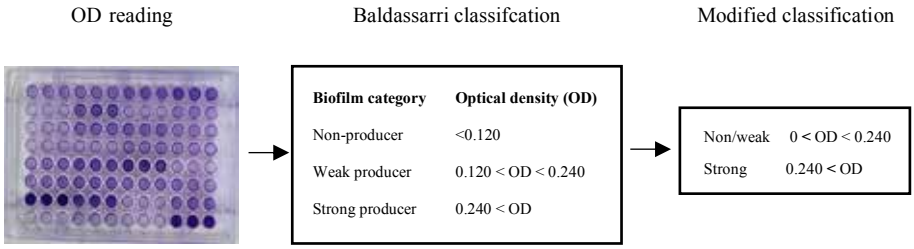

Table 5. *Reference strains for biofilm production.*

Biofilm production category	Reference strain
S. epidermidis	
Non-producer	ATCC 12228 (ica negative)
Strong producer	ATCC 35984
S. aureus	
Non-producer	15981 (ica negative)
Strong producer	15981

Biofilm susceptibility testing: MBEC and MIC

A Calgary Biofilm Device (CBD, MBEC Assay®, Innovotech Inc., Edmonton, Canada), a microtiter plate consisting of 96 wells, was used to grow biofilm (Figure 19).[194, 195] The CBD was combined with an antimicrobial plate of eight commonly used antimicrobial agents in PJI treatment (CML2FNUN: Sensititre™, MA, USA). The Sensititre™ was produced with increasing antimicrobial concentrations based on levels for MIC determination and values above clinical breakpoints (0.25 to 1216 μg/mL) (Paper I, Figure 3).

MBEC was determined according to Zaborowska *et al.* and schematically illustrated in Figure 2 of Paper I.[58] A volume of 150 μL of a bacterial inoculum (10^7 CFU/mL) of each strain in Mueller-Hinton Broth 2 was added in the 96 wells of the CBD and then incubated for 24 h at 37°C on a shaker (125 rpm) for biofilm formation on the CBD-pegs (Figure 19).

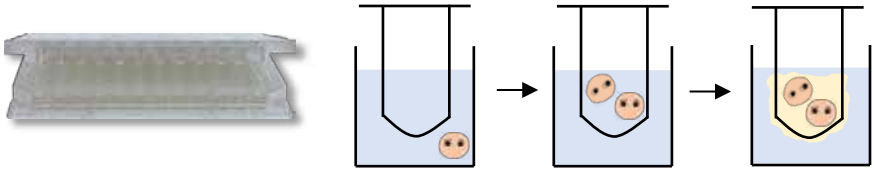

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Figure 19. *The Calgary Biofilm Device (to the left) consists of a lid with 96 pegs and a base with corresponding wells that enables the testing of antimicrobial agents against biofilms. A single peg and well is illustrated to schematically show the adhesion of bacteria from the wells to the peg lids and the formation of biofilm (seen in yellow) on the peg lids.*

Quantification of viable bacteria on the peg (CFU/peg) was performed by removing four pegs with sterile equipment and thereafter washed, vortexed for 1 minute and sonicated for 1 minute (at 40 Hz) to dislodge the biofilm in saline. The dislodged cells were diluted and cultured o.n. on blood agar plates.

For MBEC determination, the peg lids were rinsed with saline and placed in the custom-made Sensititre™ for approximately 20h at 37°C. The peg lids were thereafter rinsed two times, placed in a neutralizing agent and finally sonicated for 1 minute to dislodge the biofilm into the recovery plate wells. After o.n. incubation at 37°C, MBEC was determined visually using the Sensititre™ Manual Viewbox (Figure 20).

MIC was determined using planktonic cultures for all strains, as described by Zaborowska *et al.*[58] A volume of 100 µL containing an equivalent concentration to the CFU/peg for the same strain was added to the wells of the Sensititre™ plate. The plates were incubated for approximately 20h at 37°C. The Manual Viewbox was used to determine the MIC.

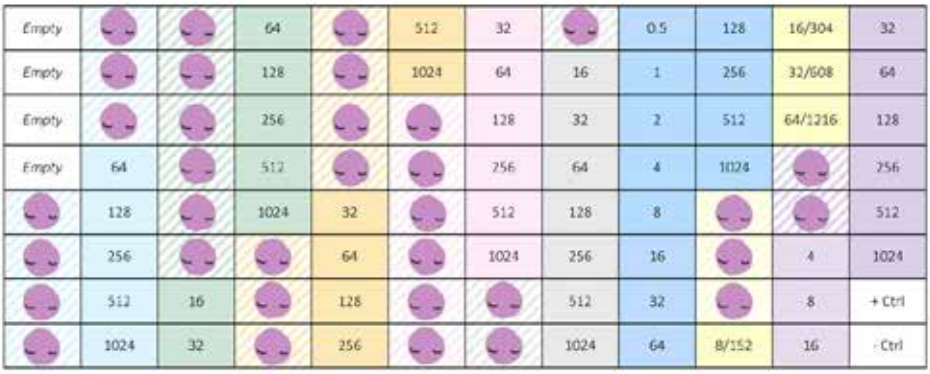

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Figure 20. *An example of the process of determining the MBECs for each strain and all tested antimicrobial agents. The figure shows the antimicrobials and concentrations of the custom-made Sensititre™ plate. Each colour represents a different antimicrobial agent and the numbers reflect the increasing concentrations of each antimicrobial agent. There are four empty wells (left column) and two controls (right column). Once the biofilms have been dislodged in the recovery plate (which does not contain antimicrobial agents) biofilm growth can be determined. The illustration shows the principles of this process where the purple bacteria in the figure represent growth. Using the known concentrations for each well the eradication concentration can be determined (the first concentration at which there is no growth). In the example above, the bacterial strain needs 64 µg/mL of the first antimicrobial (light blue colour) to eradicate biofilm growth.*

Study definitions

Infection resolution was defined as no further suspicion of infection based on clinical judgement, laboratory tests and no further treatment (both antimicrobial and surgical) due to PJI.

Recurrent infection was defined as either a reinfection with an unrelated bacterial strain, or infection relapse *i.e.* the growth of an identical strain.

Symptom onset was defined as the first time a patient contacted the health care system with a suspicion of infection.

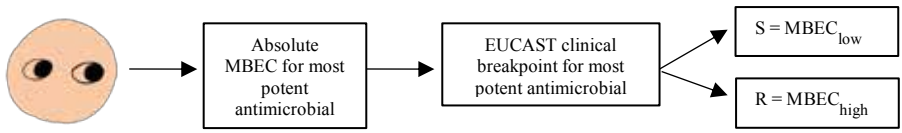
Duration of antimicrobial treatment was defined as the time period between post-operative commencement until cessation of planned therapy, or the date of any further surgery due to PJI.

Surgical treatment was defined as either implant preserving (DAIR, exchange or non-exchange) or implant extracting (any type of revision surgery involving the cup and/or stem).

Antimicrobial susceptibility was determined using the EUCAST definitions and breakpoints for staphylococci (Appendix, Supplementary Table 1).[133] Susceptibility was tested using the MICs and the MBECs for all antimicrobial agents for each strain.

The absolute MBEC values were further dichotomized to high values ($MBEC_{high}$) or low values ($MBEC_{low}$) for the most potent anti-biofilm active antimicrobial given (Figure 21). Rifampicin was considered the most potent antimicrobial in cases where the patient had received polytherapy.

Each bacterial strain was analysed in terms of biofilm production, MICs and MBECs. If several strains caused the same infection each strain was considered as an entity of infection source and were therefore assigned the same clinical outcome.



Linnéa Teljas Puranen/Karin Svensson

Figure 21. *How MBEC degree was assigned to each individual strain based on the most potent antimicrobial agent the patient received.*

Statistical analysis

Descriptive statistics were presented using percentages, means with standard deviations (SD) or standard error of the mean (SEM), medians with the interquartile range (IQR) or mode and range.

Chi-square test was used to analyze the relationship between i) biofilm production (non/weak or strong) and clinical outcome, ii) surgical procedure (implant preservation or extraction) and clinical outcome, iii) MBEC ($MBEC_{low}$ and $MBEC_{high}$) and clinical outcome. Chi-square was also used to compare susceptibility when measured using MBEC. Chi-square is a statistical test used to test for association between two categorical variables *i.e.* qualitative variables, whereof one is independent and the other dependent. For this study, the number of observations exceeded the minimum required (n=20).

One-Sample T-test was used for the evaluation of absolute values (CV OD) of biofilm production intra-species. The One-Sample T-Test was used to compare the means of populations.

Mann-Whitney U test was used for the analyses of i) MBEC/MIC-ratios and clinical outcome, and ii) comparisons of MBECs and MICs for each antimicrobial agent, as these were not normally distributed according to Shapiro-Wilk test. Mann-Whitney U test is used to compare two variables, often non-parametric.

Binomial univariable logistic regression analysis was performed for biofilm production (independent variable) and clinical outcome (dependent variable). Logistic regression indicates the probability that an alternative within a categorical or continuous variable leads to a certain outcome in a dichotomized dependent variable. Odds ratio (OR) are presented with 95% confidence interval (C.I.).

Independent Samples T-Test was used for biofilm production (independent variable) and MBEC/MIC-ratios (dependent variable). This test compares the means between groups in the independent categorical variable on the dependent continuous variable, *i.e.* did the mean MBEC/MIC-ratios for strong biofilm producers differ from the mean MBEC/MIC-ratios of non/weak biofilm producers

One-way ANOVA was used for the analysis of biofilm production (categorical variable) and MBEC/MIC-ratios (continuous variable) for each antimicrobial agent. Levene's test was used to test for homogeneity in variances *i.e.* that variances within each group are equal.

Two-way ANOVA was used to test for interactions between biofilm production (independent variable) and clinical outcome (independent variable) on MBEC/MIC-ratios (dependent variable) for each antimicrobial agent. In other words, the two-way ANOVA analyses the effect of biofilm production on MBEC/MIC-ratios influenced by the clinical outcome, and vice versa.

IBM SPSS Statistics (version 26, IBM corporation, USA) and software R (version 3.6.1, The R project, Vienna, Austria) were used for the statistical analyses. Statistical significance was defined as *p*-value of less than 0.05.

4.2 PAPER II

The Swedish Hip Arthroplasty Register

The Swedish Hip Arthroplasty Register (SHAR) is a nationwide register on primary and revision hip arthroplasty which was started in 1979. Initially it was meant as a study trial to monitor complications after arthroplasty during 1976-1977.[196] Following the study's success, the trial transcended to a continuous prospective multi-centre study *i.e.* a register in which all Swedish orthopaedic units eventually participated. Individual patient data and several parameters associated with implant survival were collected and added on throughout the years. Data such as sex, age, ASA-class, BMI, surgical side, operation unit and implant specific details are collected. The SHAR has a 100% coverage and for 2018 data completeness was 98% for primary THA and 92% for revision THA.[2] Each unit has an assigned contact doctor and contact secretary. Baseline data is inputted by specially trained secretaries at each hospital. Mortality data on patients is obtained using the Swedish Tax Agency which is linked to the SHAR.

The SHAR reports openly on its data and publishes an annual report available for anyone to access on their website (www.shpr.registercentrum.se). Quality measures include reoperations within two years after surgery, re-admission within 30 days after surgery and mortality within 90 days after surgery.

In the SHAR, reoperations are defined as any surgical procedure subsequent and in close relation to the primary THA. Revision procedures are defined as an exchange or extraction of any parts of, or of the entire, prosthesis. The reason for a reoperation is reported to the reoperation database. Medical records of each reoperation are sent to the SHAR for central register inputting to affirm that the reoperation codes are correct.

Study population and data retrieval

The SHAR was used to identify all reoperations due to PJI between 1st January 2009 and 31st December 2016. In order to supplement with data on PJI, report forms were sent out to the SHAR contact doctors at all orthopaedic units in June 2018 (for report form see Appendix, Supplementary Figure 1). Data was retrieved from the participating centres between September 2018 and November 2019. If a centre was interested in participating but was unable to

conduct the journal reviews, KS was granted access to journals first-hand. One centre sent copies of the concerned medical journals for KS to review.

The database containing the supplementary data was merged to the SHAR reoperation database to add on data on previous and subsequent surgery.

Patients were eligible for the current study if they fulfilled the following criteria (study inclusion is illustrated in Paper II, Figure 1):

- A registered DAIR operation for a first-time diagnosis of PJI after primary THA where PJI was defined according to the major criteria of the MSIS definition with further modification to include patients with intraoperative purulence.

Patients were excluded due to the following:

- Treatment with delayed wound closure after DAIR (secondary suturing).
- Concurrent sepsis.
- Bilateral PJI.
- Known endocarditis or known terminal cancer.

Outcome measures

The primary aim of this study was to compare the success rate of DAIR when modular components (femoral head and/or liner) were exchanged (exchange) compared to when they were let be (non-exchange). The primary outcome was defined as any further reoperation due to infection within two years after the first DAIR procedure. The DAIR procedure was considered successful if no subsequent reoperations due to PJI within two years were conducted.

The secondary aim of this study was to compare non-exchange and exchange DAIR in terms of subsequent revision procedures (revision of any bone-anchored implant component *i.e.* the femoral stem and/or the acetabular cup) due to PJI within two years.

Study definitions

Symptom onset was defined as the first time the patient contacted the health care system with a suspicion of PJI. Symptom onset was defined as the date of surgery in cases where patients presented with symptoms immediately after

their operation (typically wound leakage). Symptom onset was set to the first day of the month if the day of symptom onset was unknown but the month and year were reported.

Polymicrobial infections were defined as the presence of more than one bacterial species in the culture results. The sub-species level was not determined for all CoNS and they were therefore regarded in their entity. *Staphylococcus aureus* and *Staphylococcus lugdunensis* were grouped together due to their similar virulence.[197]

Duration of antimicrobial treatment was pre-defined in time intervals (< 4 weeks, 4-8 weeks, 8-12 weeks and > 12 weeks) in the questionnaires. The end date of treatment was either the date of treatment failure (*i.e.* the date for a new reoperation) or the date of treatment cessation. Oral antimicrobials were registered at the date of discharge and any change in antimicrobial therapy was noted. Patients with further reoperations within the same hospitalisation period were registered without oral therapy as this had not been commenced subsequent their first DAIR.

Statistical analyses

Kaplan-Meier survival analysis was used to compare the exchange of modular components to non-exchange in terms of survivorship (defined as no further reoperation) two years subsequent the initial DAIR procedure. Patients were censored at death or new reoperation. Kaplan-Meier survival analysis was also used with revision of bone anchored components as endpoint. Kaplan-Meier is a nonparametric method for the estimation of probable survival for a set time point and plots the survival distribution.

The risk for a new reoperation was calculated using Cox regression analysis comparing exchange and non-exchange DAIR. The following variables were considered potential confounders: age, sex, BMI, method of fixation, bacterial growth and symptom duration from primary procedure and duration from symptom onset to DAIR. ASA-class was not available for the entire cohort, and a sensitivity analysis including aforementioned variables and ASA-class was performed on the cohort in which it was available. Proportional hazard assumption was checked by visually inspecting the Schoenfeld plots. Antimicrobial treatment was not included in the regression analysis due to difficulties in grouping this data. Hazard ratios (HR) are presented with 95% confidence interval (C.I). Cox regression analysis is a type of multivariable regression analysis. Regression analysis can be used for the prediction of the outcome of the dependent variable (exchange/non-exchange DAIR) based on the independent variables (potential confounders).

In a sub-group, data on suppressive antimicrobial therapy and persisting clinical symptoms of infection was available. This group was presented using descriptive data in attempt to obtain the rate of true infection resolution. Infection resolution was defined as no further reoperation, suppressive antimicrobials or clinical signs of infection.

Data analysis was performed using software R (version 3.6.1, The R project, Vienna, Austria).

4.3 PAPER III

The SHAR

This study analysed prospectively collected longitudinal cohort data from the SHAR. For a description of how data collection is conducted within the SHAR please see the mthods description for Paper II (page 50).

Study population

Patients who had received a THA due to osteoarthritis and undergone a one- or two-stage revision procedure due to infection between 1979-2015 were eligible for analysis. Each THA was studied separately in cases of bilateral PJI.

Outcome measures

Re-revision regardless of cause was the primary endpoint. Analysis of re-revision due to aseptic loosening and infection was performed as secondary endpoints.

Study definitions

In the SHAR *revision procedures* are defined as the exchange of parts of or the entire prosthesis alternately, definite extraction of the prosthesis. In this study one-stage revision was defined as exchange of the entire prosthesis and each THR was studied separately in cases when patients had bilateral PJI.

Infection was defined using the code for revision as entered in the SHAR.

Statistical analysis

Demographic data was analysed descriptively using the mean and standard deviation (SD).

Kaplan-Meier survival analysis and Log rank test was used to compare the survivorship between one- and two-stage revision surgery in terms of re-revision. This was done for revision regardless of cause and for aseptic loosening and infection specifically. Truncation was done after 15 years, at this point the number of patients at risk was below 100.

Cox regression analysis was conducted and adjusted for sex, age, diagnosis (primary and secondary osteoarthritis) and method of fixation (cemented or non-cemented). ASA-class and BMI was first registered in the SHAR in 2008. Therefore, this data was not available for the entire study population. A sensitivity analysis was performed using Cox regression adjusted for sex, age, diagnosis, method of fixation, BMI, ASA-class and year of surgery. Hazard ratios (HR) are presented with 95% confidence interval (C.I).

IBM SPSS Statistics (version 22, IBM corporation, USA) was used. Statistical significance was defined as p-value of less than 0.05.

4.4 PAPER IV

Study population

In this study, purposive sampling was employed to capture different perspectives of the study aim.[198] The variables identified as potential contributors to diversity in experience that we used to recruit our study population were: gender, age, level of workplace (county, district or regional hospital), years of experience in arthroplasty surgery and years of experience within PJI. Surgeons with any experience of arthroplasty surgery of the hip or knee were invited to participate. The study had no exclusion criteria.

Eleven heads of department at orthopaedic units in Sweden were approached by e-mail starting October 2017. The units were selected to ensure a variety of surgeon volume. Eighteen prosthetic joint surgeons from nine units participated in the study. Study recruitment ceased once we considered to have reached data saturation *i.e.* the replication or recurrence of data.[199]

The data source for this study was individual interviews. All 18 interviews were conducted face-to-face by the same person (KS) during the period December 2017 to February 2018 at the location of the interviewee's choice. The interviews were conducted in a semi-structured manner using a topic guide list (Appendix, Supplementary Figure 2). Written and oral consent was obtained prior to each interview. Interviews were audio-recorded and were transcribed verbatim by a third part.

Outcome measures

The main outcome of this study was to investigate the experiences and emotional impact of PJI on prosthetic joint surgeons, and identify desired improvements in the management of PJI.

Data analysis

In this study, qualitative content analysis (QCA) according to Graneheim *et al*. was used.[200] Data was processed by listening to, and reading, each interview repeatedly in order to further familiarise with data. Meaning units were identified and extracted from the text in accordance with the study questions. The meaning units were condensed and labelled with a code for further grouping into categories. Themes evolved from the over-arching implication of similar categories. The evolving categories and themes were continuously discussed and contrasted within the research group. The analysis process is schematically illustrated in Figure 22, and exemplified in Paper IV (Figure 1 and Table 2). Quotes were professionally translated by a third part to ensure objectivity.

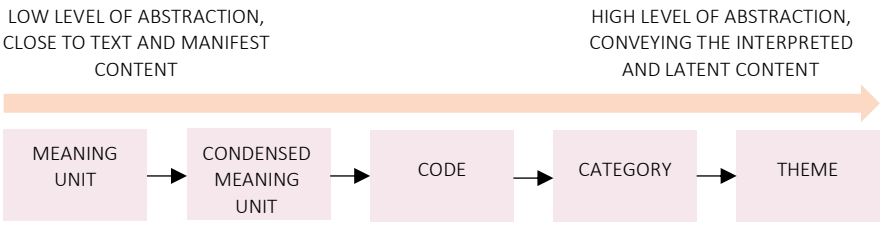


Figure 22. *A schematic overview of the analytical process according to QCA taking the increasing level of abstraction into account for each step. Figure inspired by Erlingsson et al.*[201]

5 RESULTS

5.1 PAPER I

Study population and demography

The study population consisted of 49 patients and 70 bacterial strains (Paper I, Figure 1). The majority of patients were male (67.3%), had a THA (65.3%), had a mild systemic disease (67.3%) and were infected with a monomicrobial infection (69.4%) (Paper I, Table 1). Patients with recurrent infections had a longer duration to symptom onset from index surgery, however, this was not statistically significant. There was a more frequent use of RIF in polytherapy in the patients with resolved infections (n=20) compared to recurrent infections (n=14). Surgical treatment did not associate with clinical outcome (p=0.8). Pre-operative inflammatory markers were similar for patients with resolved and recurrent infections (Paper I, Supplementary material, Table S2).

Biofilm production of the bacterial strains

The majority (n=51, 72.9%) of the bacterial strains were categorised as strong biofilm producers. A greater proportion of strong biofilm producers compared to non/weak producers was observed for all species (*S. aureus*, *S. epidermidis*, and other CoNS) (Paper I, Figure 4A). Further, the number of viable CFU on the pegs of the CBD was similar despite biofilm category (Paper I, Supplementary Table S1).

Biofilm production in relation to clinical outcome

Of the 49 patients, 24 (49%) had recurrent infection (Paper I, Table 1). In the group of patients with recurrent infection the majority (n=22, 92%) had growth of strong biofilm producers. A statistically significant association between recurrent infections and strong biofilm producers, and vice versa, between resolved infections and non/weak producers, was found (p=0.011) (Paper I, Figure 4B and 4C).

A greater probability of infection recurrence was observed in patients who had been infected by strong biofilm producers, with Odds Ratio 5.5 (95% C.I. = 1.65-18.44, p=0.008).

Biofilm production and infection relapse

Bacterial strains had been isolated and saved from subsequent surgery for 12 of the 24 patients with recurrent infection and these were analysed. Six of the 12 patients had a confirmed infection relapse (Paper I, Supplementary material, Table S3). Relapses were more often caused by strong biofilm producers (n=5). Further, they were more common in patients with implant preserving surgery (Paper I, Figure 5A).

Biofilm susceptibility and its relation to clinical outcome

$MBEC_{high}$ was more frequent in patients with recurrent infection and $MBEC_{low}$ more frequent in resolved infections (Paper I, Figure 5B). However, this was not of statistical significance. No statistically significant association between $MBEC_{high}$ or $MBEC_{low}$ and clinical outcome could be observed (p=0.3).

Comparisons of MBEC and MIC showed that the absolute values of MBEC were significantly higher than MIC for all antimicrobial agents (Paper I, Figure 6). For most antimicrobial agents the antibiogram patterns differed when susceptibility was tested according to MIC and MBEC (Paper I, Figure 7), and more strains were categorised as resistant according to MBEC compared to MIC. Oxacillin (OXA) has the most similar susceptibility pattern when comparing MIC and MBEC susceptibility.

The MBEC/MIC-ratios were calculated for each antimicrobial agent to illustrate the increase of antimicrobial dose needed for eradication of biofilm growth compared to planktonic growth. The absolute values for MBEC were divided by the values for MIC. The median MBEC/MIC-ratio was lowest for RIF (ratio: 2) and highest for VAN and FA (ratio: 128) (Paper I, Figure 6). There were some intra-species differences in regard of MBEC where *S. epidermidis* required higher $MBEC_{CIP}$ than other CoNS, and *S.aureus* required highest $MBEC_{OXA}$ compares to *S. epidermidis* and other CoNS (Paper I, Figure 8A).

Other than for CIP, no statistically significant difference could be observed for biofilm production category and MBEC/MIC-ratios. For CIP, the MBEC/MIC-ratios for non/weak producers was 99 compared to strong producers with 360 (p=0.037). When biofilm production was split into further groups (non-, weak, moderate and strong), higher MBEC/MIC-ratios were observed in strains producing biofilm (weak, moderate and strong) compared to non-biofilm producers (Paper I, Supplementary material, Figure S4).

When MBEC/MIC-ratios were compared to clinical outcome, MBEC/MIC-ratios for OXA were significantly higher in recurrent infections compared to resolved infections (p=0.01) (Paper I, Figure 6). No interaction between biofilm production and MBEC/MIC-ratios on clinical outcome was observed.

5.2 PAPER II

Study population

Using the SHAR, 2,571 DAIR reoperations in 1,692 patients were identified for the given study period. The supplementary questions for 1,182 (69.9%) of these patients were collected and 42 of 64 (66%) of the Swedish orthopaedic units participated. After study exclusion, 575 patients were eligible for further analysis (Paper II, Figure 1).

The exchange and non-exchange group had similar demography (Paper II, Table I). Symptom onset from primary surgery differed the greatest where 73.4% of the exchange group had symptoms within 30 days of their surgery compared to 66.8% in the non-exchange group. In regard of surgical technique for DAIR with exchange, the femoral head was exchanged in the majority of cases (n=297, 81.6%) compared to the exchange of both the femoral head and acetabular liner (n=67, 18.4%) (Paper II, Supplementary Table 1).

DAIR with exchange and non-exchange DAIR

In the entire cohort of 575 patients, 195 (33.9%) patients had further surgery after their first DAIR procedure (Paper II, Table 2). The only cause for further reoperation within two years was recurrent PJI. Multiple procedures (>1) were conducted in 111 (19.3%) patients (Paper II, Table 2). It was more common that patients who had undergone non-exchange DAIR were made subject to more than one subsequent procedure (n=57, 27%) compared to DAIR with exchange (n=54, 15%). Furthermore, the mortality rate was 12.8% in the non-exchange group compared to 8.0% in DAIR with exchange.

DAIR with exchange of modular components was more successful than non-exchange. The reoperation rate for DAIR with exchange was 28% compared to non-exchange at 44%. The difference between the procedures was reflected in the Kaplan-Meier implant survival estimate for which DAIR with exchange was 71.4% (95% C.I. = 66.9%-76.3%) compared to non-exchange 55.5% (95% C.I. = 49.1%-62-7%) (Paper II, Figure 2). In a univariable analysis, DAIR with exchange implied a significant risk reduction for further surgery with HR 0.52

(95% C.I. = 0.39-0.68). This risk reduction persisted in the multivariable analysis with HR 0.51 (95% C.I. = 0.38-0-68) (Paper II, Table 3).

Patients with *S. aureus/S. lugdunensis* infections had a higher risk of recurrent infection compared to CoNS (Paper II, Table 3). No other variable was associated with an increased risk for subsequent surgery. Neither was ASA-class in the sensitivity analysis (Paper II, Supplementary material, table 2).

DAIR and subsequent revision of bone-anchored components due to infection

Overall, 92 (47.2%) of the 195 patients had a following revision procedure after their DAIR (Paper II, Table 2). Revision was more common in patients who had undergone non-exchange DAIR (20.4%) compared to DAIR with exchange (13.5%) (Paper II, Table 2). Complete extraction was the most frequent type of revision procedure across both groups. The Kaplan-Meier survival estimate was 86.1% (95% C.I. = 82.4%-89.8%) for DAIR with exchange compared to non-exchange at 78.8% (95% C.I. = 73.3%-84.6%) (Paper II, Figure 3). The risk of revision was lower after DAIR with exchange compared to non-exchange, HR 0.61 (95% C.I. = 0-41-0.92), when unadjusted. Adjusted, there was no statistical significance in risk reduction (Paper II, Supplementary Table 3).

Analysis of true infection resolution

In the sub-group population (n=151) in which detailed information on infection status was available, 83 (55%) of the patients had a resolved infection. DAIR with exchange was more successful with infection resolution in 61.3% of the cases compared to 42.6% in the non-exchange group. Of the non-resolved infections, four (5.8%) patients did not undergo further surgery meaning that the use of reoperation as a marker for recurrent infection failed to capture these (Paper II, Table 4).

Antimicrobial treatment

Patients were given antimicrobial treatment prior to their DAIR procedure in 39% of the cases (Paper II, Table 5). Combinations of RIF in polytherapy were more frequently used in patients in the DAIR with exchange group.

5.3 PAPER III

Study population

A total of 1654 patients were eligible for the study. Demographically, the one- and two-stage groups differed in age, time from primary procedure to revision surgery and follow-up time (Paper III, Table 1).

Distribution of method use

The majority of revision procedures were conducted as two-stage procedures (n=1250) and the remaining were one-stage procedures (n=404). The employment of revision methods changed during the study period where the one-stage procedure was the most common during the first 10 years (used in 59.4% of cases), and the two-stage dominated the last 25 years (used in at least 80% of cases) (Paper III, Table 2 and Figure 1).

Re-revision due to all causes

In the one-stage and two-stage groups 83 (21%) and 259 (21%) were re-revised, (all causes for revision), after their first revision. Unadjusted, the cumulative survival rate was similar in the two groups (p=0.13) with a survival rate of 75 % (±5.4%) and 72% (±3.6%) for the one- and two-stage method respectively (Paper III, Figure 3). Adjusted, there was no difference between the one- or two-stage method, HR=0.9 (95% C.I.=0.7-1.2, p=0.5).

Re-revision due to infection

When analysed specifically for re-revision due to infection, the cumulative survival rate remained similar in both revision groups (p=0.13) (Paper III, Figure 3). The survival rate was 92% for the one-stage group and 89% for the two-stage group. No difference in risk for re-revision could be identified between the two revision methods, HR=0.7 (95% C.I.=0.4-1.1, p=0.2).

Re-revision due to aseptic loosening

For re-revision due to aseptic loosening, no difference in implant survival could be found between the one- and two-stage method (p=0.9) (Paper III, Figure 4). There was no difference in risk for re-revision when comparing the two revision methods, HR=1.2 (95% C.I.=0.8-1.8, p=0.5).

Sensitivity analysis for re-revision due to all causes

In total, ASA-class was available for 466 patients. In this cohort, no difference in re-revision could be found between the two revision methods when ASA-class and year of surgery was added in the regression analysis, HR=0.7 (95% C.I.=0.3-1.6, p=0.4). The distribution of ASA-class and BMI was similar in both groups (Paper III, Table 3).

5.4 PAPER IV

Study participants were between 40 and 74 years old and the majority were male (78%) (Paper IV, Table 1). Several feelings, mainly negative, were reported when surgeons reflected upon how PJI affected them emotionally (Figure 23).

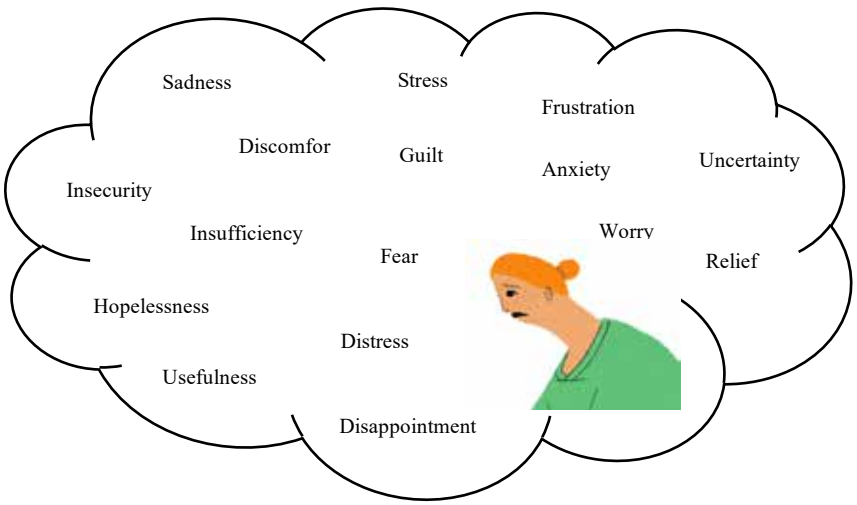


Figure 23. *The feelings reported by surgeons when reflecting upon how PJI affected them emotionally.*

Four main themes were identified in this study: the challenging road towards a diagnosis, tailoring a treatment plan, the relationship between surgeon and patient, and caring for patients with PJI (Paper IV, Figure 2 and 3).

THE CHALLENGING ROAD TOWARDS A DIAGNOSIS

Difficulties in verifying the infection and conveying the diagnosis

”There are many unsatisfied patients with pain. Which one of them have an infection?”

Surgeon (P11)

Low virulent infections were most difficult to detect and diagnose due to diffuse symptoms and inconclusive blood samples. Diagnostic tools were unreliable, and surgeons felt frustrated when their clinical suspicion could not be objectively verified. Improved microbiological methods for determining culture growth contributed to better diagnostics, but also posed a difficulty in determining causative bacteria. This further highlighted the importance of adequate sampling and being able to trust the microbiological department.

”The difficulties arise in low-virulent strains when diagnostic cultures are inconclusive and one is left without aetiology. You then either fumble or wait and repeat the [diagnostic] procedures several times, or you initiate a treatment without valid foundation.”

Surgeon (P15)

Making the decision and conveying it

Deciding upon infection was tough considering the consequences for the affected patient. Surgeons did not unnecessarily want to scare their patient when informing them of suspected PJI and sometimes they withheld how great their suspicion was. Diagnostic uncertainty generated the feeling of frustration and sometimes insufficiency. Thus, although they were aware of the implications for the affected patient, some felt relief once PJI was confirmed.

Managing uncertainty and the emotional impact of diagnostic difficulties

Being responsible for an inconclusive investigation left the surgeon feeling frustrated and insecure. Many relied on their previous experiences, consulted more experienced colleagues or contacted other orthopaedic departments to manage uncertainty. All study participants highlighted the importance of a multi-disciplinary approach with infectious disease (ID) specialists during diagnostics. Surgeons also found it important to involve the patient in the further investigation.

Accepting the diagnosis – a change of attitude

A greater acceptance and awareness for PJI was described today compared to the past. The informants themselves were much more active and persistent in the diagnostics and management of PJI compared to their previous approach to it. However, surgeons admitted that it was difficult to get over the threshold of acceptance of PJI, this was most difficult early on in the surgeon's career. Once over the threshold of acceptance though, surgeons more likely had PJI in mind as a differential diagnosis moving forward.

"It's difficult to accept that something you do can become infected; accepting it is almost like dealing with grief."

Surgeon (P4)

TAILORING A TREATMENT PLAN

Balancing the patient's conditions and needs with treatment options

Several factors were considered when planning treatment. The most important was to patient-centre treatment and create individualized plans. Sturdier evidence and clear treatment algorithms were warranted as treatment opinions could vary within one clinic. Two surgeons described decision-making as rather easy as they felt that treatment was more or less standardized.

Choice of revision method was based on the surgeon's method of preference, the unit's tradition, what the surgeon had been educated in and what he or she thought would give the best end result. All but one said that they preferred and utilized the two-stage method. The surgeon's preferred method was most often used.

"Sometimes I almost immediately feel that it's better for the patient to have a two-stage revision, or at least it makes me feel more secure."

Surgeon (P6)

Many liked the thought of the one-stage procedure but wanted more evidence. The surgeon who used the one-stage method felt it was easier to take care of patients as he/she could offer a less burdensome treatment method.

Planning the treatment and complicating factors

Surgeons could feel stressed by the inability to offer the patient a clear treatment plan early on. Sometimes patients met different colleagues with different treatment opinions. The informants emphasized the need for continuity in order to avoid confusion and patient insecurity.

"This is a patient who is particularly vulnerable and very exposed; a patient like this requires involvement and continuity… The worst thing is when these patients are passed back and forth between colleagues who have different opinions. That creates a huge sense of insecurity."

Surgeon (P1)

Furthermore, lack of time posed a difficulty in planning PJI treatment and led to the re-scheduling of elective surgery to make room for PJI patients. The snowball effect of this was frustrating and stressful. Also, lack of time slots prolonged time to adequate treatment, putting some patients at risk for failed treatment or the development of sepsis.

Everyone agreed on the importance of team work and multi-disciplinary collaboration to optimize treatment. Working together with infections disease (ID) specialists was especially important and considered essential to provide the best possible care. However, mistrusting the ID specialist was reported and one surgeon by-passed his/her local ID specialist and contacted the regional hospital for advice.

"In the past, patients were passed back and forth between the orthopaedic clinic and the ID clinic, as no one wanted to take responsibility for the infection."

Surgeon (P7)

Surgeons felt insecure being responsible for the prescription of antimicrobial treatment due to their interactions with other medications and gruesome side effects. Again, the importance of collaboration with ID doctors was brought forth. One surgeon claimed that patients found the antimicrobial treatment more dreadful than living without a prosthesis. The possibility to give patients prophylactic anti-depressants during treatment was brought forth.

Maintaining the patient's faith in treatment was difficult as surgeons also reported on the fear of persistent infections. Further, the uncertainty of treatment outcome was described as distressing and actual failure was associated with disappointment, worry and frustration.

"When patients suffer mentally it also affects the doctor in the role of being positive, supportive and having a professional approach"

Surgeon (P12)

THE RELATIONSHIP BETWEEN SURGEON AND PATIENT

Preparing the patient for what lies ahead and understanding his or her needs

Despite pre-operative information, surgeons were aware that patients did not expect PJI. They also acknowledged the huge adaption patients needed to go through during treatment and highlighted the need for continuity of a committed and responsive team. Although all surgeons agreed on its importance, continuity was near impossible to achieve because of the rotational nature of the staff schedule.

"Patients are put in a challenging situation when they have been expecting the operation to be successful and it isn't."

Surgeon (P10)

All agreed that it was important that the patient participated in their care and treatment planning. Also, it was important that the patient understood that the infection was not their own fault. Mediating hope but at the same time realistic expectations on subsistence during treatment was described as difficult. The prerequisites for a good patient meeting involved being able to set aside time to listen. However, lack of sufficient time during patient visits aggravated this.

"I think continuity is more important, that the same doctor is responsible for the treatment and the entire process. As far as the patient is concerned, this is far more important than who wields the knife."

Surgeon (P11)

Offering patients the possibility to meet a welfare officer was considered important. Surgeons wanted to support their patients as much as possible and being able to show support gave the surgeon a feeling of being useful. They also wanted to be personal but wanted to be professional at the same time when meeting an upset or sad patient. By referring the patient to a welfare officer the surgeon could protect him- or herself from getting too emotionally involved.

"There's plenty of scope for feelings of guilt for both the patient and the doctor"

Surgeon (P4)

The impact of the patient – surgeon relationship

Surgeons described a special type of relationship with PJI patients since they got to know them and their related rather well. Finding solace in the patient meeting was described, if the surgeon had a good relationship with their patient. Many patients showed an understanding for the multi-factorial genesis in PJI, however, some blamed their surgeon for it. Some patients requested referrals to the regional hospitals as they believed that their surgeons were better.

Surgeons felt sad and disappointed when one of their "own" patients was infected. They often felt they had done everything in their power to prevent PJI. A couple of surgeons described PJI in their "own" patient as a personal failure and a defeat. Some worried about how to maintain their patient's trust in the event of PJI.

Taking care of a referred patient was easier as surgeons did not need to feel as guilty or feel that they had made a bad decision about an operation that had failed. However, the surgeon could feel worried that he or she would not be as committed when taking over someone else's patient as he or she did not have an existing relationship with that patient.

"It's slightly easier to take over other people's patients, as you know that you don't need to feel guilty about being involved in something that went wrong."

Surgeon (P17)

CARING FOR PATIENTS WITH PJI

The feeling of guilt

Many brought up the feeling of guilt and felt accountable for PJI describing the feeling of personal failure. Surgeons were aware of the multi-factorial causes of PJI but as one surgeon said: "you take the blame anyway". Patients and their related could perceive PJI as the surgeon's failure. The accusative attitude was sometimes difficult to manage and when in despair patients could take it out on the surgeon. In such situations, surgeons desired support from their colleagues. However, most often, the patients did not seek a scapegoat.

"What I sometimes find most difficult is relatives who are very obstinate and somewhat accusatory when there's a feeling that it's our fault... What did you do wrong, have you made a mistake?"

Surgeon (P1)

Surgeons said that it was important to be unpresuming and scrutinize one's role in the process. Some meant that PJI was inevitable. Surgeons questioned themselves, ruminated on cases, tried to identify what they could have done better and reflected upon the cause of PJI cases, even at home, but not to the extent that it affected their ability to sleep. At times the surgeon could feel worried if her or she got a feeling that he or she could have done something better.

"It is a difficult diagnosis and you find yourself ruminating a bit about your patients with prosthetic joint infections all the time"

Surgeon (P18)

Coping with difficult feelings and the need for emotional support

Surgeons found it important to learn how to emotionally deal with complications in order to prevent burn-out. This became easier with experience. Surgeons highly valued the emotional support they received from their colleagues. Being part of a social environment open for discussions to avoid dealing with PJI cases alone was described as important. One surgeon had experienced handling PJI on his or her own and felt that this had been very difficult. Many felt that the collegial support was sufficient and sufficed as debriefing. However, some, mainly at the regional hospital, desired structured support with the possibility for external support and reflected upon the lack of support available for doctors, *e.g.* that debriefing opportunities were not given to doctors after adverse events, but were offered to other health care staff. One surgeon described how he/she shut down emotionally so that the situation would not get too personal. Further, the importance of multi-disciplinary collaboration was mentioned by all study participants. Also, for support and for educational reasons, it was considered good that a team consisted of surgeons with a mix of experience.

"Having a good relationship to your colleagues, helping each other out and talking to each other about complications is the salvation. The support you get from your colleagues makes the work situation much more sustainable."

Surgeon (P9)

Linnéa Teljas Puranen/Karin Svensson

Figure 24. *The importance of a multi-disciplinary collaboration, discussing cases with colleagues and being able to turn to experienced colleagues for advice was highlighted by study participants (from the left: clinical microbiologist, infectious disease specialist, orthopaedic surgeon 1, orthopaedic surgeon 2, experienced prosthetic joint surgeon 1, experienced prosthetic joint surgeon 2.*

Acceptance of PJI was most difficult early on in the career. At the beginning of their career surgeons were more inclined to self-blame, consider PJI as "hopeless", and reported on the difficulty in realizing the magnitude of PJI. They also mentioned troubles sleeping and worried about treatment choices and not being able to help their patient. With experience it became easier to manage patients with PJI as the surgeons knew roughly how the outcome would be and could rely on their previous experiences of PJI and better trust their judgement. However, experienced surgeons could also feel worried.

"The more experienced you are, the more frightened and more careful you are when you meet an infected patient"

Surgeon (P11)

MOVING FORWARD

The organization of PJI management differed at the surgeons' units but several structural improvements were mentioned as suggestions on facilitating factors during management (Paper IV, Figure 4).

To detect PJI surgeons desired standardized follow-up of patients; clear referral paths for GPs; better educated GPs, medical locums, junior doctors and emergency room doctors. Surgeons were concerned about the change of expertise in the hospital's emergency room as it nowadays most often was staffed by emergency doctors and junior doctors.

Surgeons wished for an even better collaboration between colleagues, committed ID specialists and the microbiological laboratory. Surgeons who worked at units without joint out-patient appointments with ID specialists wanted such a set-up.

Some surgeons discussed centralizing the care of PJI, meaning that it would maybe make the surgeons who work there much better experienced. In turn, other surgeons would then be able to consult them for help in the management of PJI. With a dedicated center, inexperienced surgeons would not need to deal with PJI and thereby not need to feel worry or a sense of personal failure otherwise associated with PJI. However, there was a fear that well-functioning smaller centres would lose their abilities to treat PJI.

Sometimes patients were kept at the hospital ward for a long time, often due to intravenous antimicrobial treatment. Administering antibiotics at home was described as a solution to this problem.

At smaller hospitals the geographical distances from patient to hospital could be very big and made it harder to follow the patient after discharge from the hospital. One surgeon highlighted the wish for better follow up routines in such cases.

Many felt that it was difficult to maintain continuity with today's organization of the health care system. Some felt that there was not always enough understanding from the clinic or health care system for PJI. The surgeon had to work hard to be able to schedule PJI patients and sometimes persuade the ward staff that the patient needed a longer in-house stay. At clinics where PJI was prioritized which made it easier for the surgeon.

There was a need for more time to manage PJI patients. Fully-booked appointment schedules and operation schedules made it difficult and stressful for the surgeons to find the time for PJI patients. It was described as difficult and challenging to keep focus and maintain an optimal standard when the surgeon had to work after hours on PJI cases. Sometimes the lack of time meant that the surgeon could not think through the management plan thoroughly enough which sometimes led to hasty decisions.

As mentioned, many felt that the support from their colleagues was sufficient. However, some wished for more structured support and having set times in the schedule for case discussions was brought up as a desired for improvement.

The lack of evidence for new methods was described as problematic as they were sometimes introduced in a non-evidence-based matter. Surgeon was worried that the companies behind the technological advances did not understand the full problem of PJI. Also, as a surgeon it felt impossible to understand which systems were the best

ADDITIONAL RESULTS

Surgeons felt that they were better at registering procedures in the SHAR nowadays leading to an increased trust for reports on infection. Further, improved diagnostic methods led to better detection of PJI, also contributing to more reliable statistics. However, this also meant that it made it difficult to compare incidence rates over the years.

6 DISCUSSION

6.1 PAPER I

Biofilm production and clinical outcome

In the current study, presence of a strong biofilm implied a greater risk of, and was associated with, treatment failure. In contrast, non/weak biofilm production was associated with infection resolution. This is the first study to investigate the influence of biofilm production on clinical outcome, *i.e.* infection status, in a study cohort of only PJI patients. In a non-orthopaedic setting the effect of biofilm production on clinical outcome is ambiguous. Biofilm production in *S. aureus* causing bacteraemia has not been associated with poor clinical outcome (bacteraemia, endocarditis or death).[202] However, biofilm forming strains have been reported more common in patients with persistent infections,[203] and another study linked biofilm production to persistent skin and soft-tissue infections in trauma injuries in military staff.[204] Within orthopaedic infections, strong biofilm has been associated to greater treatment failure. Morgenstern *et al*. investigated biofilm production caused by *S. epidermidis* after fracture osteosyntheses and PJI, and concluded that strong biofilm production gave a lower rate of treatment success compared to non-biofilm producers.[205] In their study, non-biofilm production was associated with cure rates of 85% whereas the strongest biofilm producers had a cure rate of 60%. A lower cure rate was also found by Post *et al*. in orthopaedic device-related infections caused by strong biofilm producers compared to non-producers.[206] Furthermore, Zaborowska *et al*. reported on a worse clinical outcome in percutaneous orthopaedic implant infections caused by strong biofilm producers.[58] Overall, the studies on biofilm production in relation to clinical outcome are difficult to compare to one another as factors such as inclusion of bacterial species, biofilm quantification methods, type of infection, definitions for biofilm production and outcome definitions differ. Nonetheless, the current study adds on to research suggesting that biofilm production has an influence on clinical outcome and should be assessed in the management of PJI.[206-208]

The majority (73%) of bacterial strains in the current study showed strong biofilm production ability. The ability of staphylococci to produce biofilm has previously been reported.[127, 206, 207] Biofilm production was evaluated per

species to identify whether biofilm production was greater in *S. aureus*, *S. epidermidis* or the other CoNS species. Strong biofilm producers were more frequent than non/weak producers across all three species groups. In the group of other CoNS (*n*=8), of which there were five *S. capitis*, there were no non/weak producers. This may be a random finding, but *S. capitis* has recently been suggested as an emerging nosocomial pathogen in PJI displaying biofilm production abilities.[209]

The association between biofilm production, MBEC and clinical outcome

The primary and secondary outcome of the current study was to evaluate the relationships between biofilm production, MBEC and clinical outcome. It can be hypothesized that MBEC could be used as a surrogate marker for biofilm production (Figure 25). The current study could establish an association between biofilm production and clinical outcome. However, no association could be found between biofilm production and MBEC, or MBEC and clinical outcome.

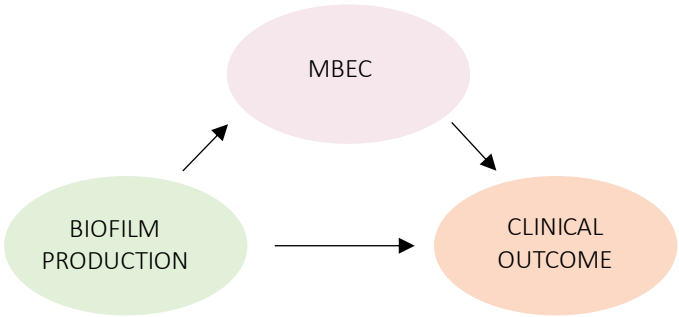


Figure 25. *The hypothesized relationship between biofilm production, MBEC and clinical outcome.*

The absence of an association between MBEC and clinical outcome could be explained by two factors. Firstly, MBEC for the most potent antimicrobial administered was not available for all cases. The MBEC of seven cases could not be compared to clinical outcome due to this missing data, limiting the study sample size. Secondly, the assignment of several of the bacterial strains from the same infection to the same clinical outcome, despite intra-species variations of MBEC, may further obstruct an identification of association.

Biofilm susceptibility

Antimicrobial concentrations in the tissue of the affected joint are unknown and there is a risk that treatment guided with MIC leads to sub-inhibitory antimicrobial concentrations in tissue. Mlynek *et al.* found that the exposure of MRSA to sub-MICs of amoxicillin induced surface adhesion and biofilm production.[210] Further, bacterial strains were up to 8,192 times more resistant to antimicrobials when grown in biofilms compared to their planktonic state in the present study. This finding confirms previous research reporting on a greater resistance of biofilm versus planktonic when comparing MBECs to MICs.[56-58, 134, 207, 208] This implies that MIC-guided antimicrobial treatment reflects the planktonic state of bacteria but does not consider susceptibility when bacteria are adherent and grown in biofilm. This further suggests that MICs may be insufficient in guiding antimicrobial treatment in biofilm-associated infections, which should be considered when administering antimicrobial treatment.

Patients in the current study were treated with intravenous vancomycin (mono- or polytherapy) in the majority (71%) of cases. However, in the current study, vancomycin was also associated with the greatest median MBEC/MIC-ratio. $MBEC_{VAN}$ was greater than MIC_{VAN} for 77% of the strains. The resistance to vancomycin in biofilm- producing staphylococci has previously been confirmed in a study where 93% of biofilm producers were non-susceptible.[208] Rifampicin in combination therapy was the most common oral antimicrobial treatment, used in 69% of cases. In terms of susceptibility, rifampicin was the most susceptible option when comparing MBEC/MIC-ratios as 46% of $MBEC_{RIF}$ were equivalent or lower than MIC_{RIF}. Thus, our results confirm rifampicin as the best oral option.[32, 211] The high MBEC/MIC-ratios and the antibiogram patterns for both vancomycin and rifampicin may further indicate that treatment guided by MIC is insufficient.[212]

The concentrations of antimicrobial agents needed to eradicate bacteria using doses guided by MBEC could in many cases imply toxic levels in human tissue. As such it may not be a useful addition in regards of dosage guidance. However, using MBEC as a tool to evaluate the empiric biofilm susceptibilities of causative bacteria may, nonetheless, be advantageous in the early decision-making on surgical options.

Cell numbers were equal in the starting bacterial inoculums used for MIC and MBEC determination. Therefore, the higher resistance of MBECs cannot be explained by a high cell count as biofilm production was not dependent of

inoculum size. Instead, the actual switch of growth into a state of biofilm explains the greater resistance, also suggested by Zaborowska *et al*.[58]

C-reactive protein and biofilm production

Patients with recurrent infection had a higher median CRP compared to patients with infection resolution. CRP has previously been suggested as a good surrogate marker for the size of bacterial infectious dose which in turn may affect the efficacy of antimicrobial treatment.[38] Although the range of CRP (2-450) was greater in patients with strong biofilm producers compared to non/weak (3-170), the median remained similar between the groups. CRP over 115 mg/L is associated with failure in DAIR treatment,[38, 154] however, it is unknown if failure is due to biofilm production and whether CRP is associated with biofilm. Further studies are needed to establish the relationship between CRP and biofilm production.

Strengths, limitations and methodological considerations?

This study is the first to evaluate staphylococcal biofilm in a cohort of only PJI patients in relation to clinical outcome. It employs a method for detection of biofilm (CV) which is easily adaptable in clinical laboratories whilst both time- and cost efficient. Further, it confirms that biofilms are more resistant to antimicrobials when MBEC is used compared to MIC which may be an important clinical factor when deciding upon antimicrobial treatment. The lack of association between MBEC and clinical outcome may be due to sample size.

The storage and transportation of the bacterial strains may have affected their virulence properties. Bacterial strains were stored at -80 °C and should tolerate 1-10 years in these conditions whilst maintaining their virulence factors.[192] The different phase variants of biofilm are noteworthy when preparing staphylococcal inoculum. There are several ways to measure biofilm biomass, the current study used CV which is commonly used, [213] however the metabolic activity of the biofilm was not evaluated and could be considered a good supplement in further studies on biofilm susceptibility. However, in a clinical setting the detection of whether biofilm is present or not and its metabolic state in the patient is unknown and for this CV can be used on its own. Manual reading of the OD is user dependent and an automatic reader may minimize analyst bias.

The results of the current study could have been affected by another classification of biofilm production such as using the Stepanovic *et al*.[192] classification instead of Baldassarri *et al*.[193] Further, Post *et al.* defined patients as cured if they were infection free at a defined follow-up time regardless of

whether multiple surgical procedures had been conducted along the way.[206] Such a definition may have altered our results. We have used the clinical breakpoint designed for MIC for both MIC and MBEC. However, there is no clinical breakpoint for MBEC, nor a standardized test medium, perhaps due to differing nutritional needs to stimulate biofilm growth *in vitro.*

MBEC can vary slightly in definition but, defined as the complete biofilm bactericidal concentration, additional measurements of CFU counts need to be done as there is a lower limit in detection level of viable cells in our model.[214] In our model the biofilm-coated pegs were exposed to the antimicrobial agents for 18-20 h and thereafter exposed to a neutralizing agent during 24 h in which any viable cells were able to grow. In that aspect, the MBEC values we determined should be the correct eradication values if no turbidity was measured. Both MIC and MBEC values were determined by visual inspection of the first non-turbid concentration, makes them equivalent and comparable.

An alternative model of analysis could have been the employment of a worst-case model in which the strain with greatest biofilm production was selected for further analysis. However, regarding the infection as an entity of all the strains found in the same samples, our approach may be justified as there may be synergistic effects contributing to infection.[54] Hence, it would be interesting to further elucidate the relationship between biofilm production, MBEC and clinical outcome (Figure 25) in another cohort including only single strain infections and in which MBEC to the administered antimicrobial treatment was available for all infections.

The findings of the current study should be interpreted in the light of its *in vitro* setting. Although the CBD is an acknowledged model of biofilm quantification, the peg lids are not comparable to prosthetic material and the test mediums do not reflect the *in vivo* setting. Several actions can be taken to further mimic the *in vivo* conditions of the host tissues and immune response such as coating of the pegs and the use of medium resembling host conditions. The use of simulated synovial fluid as test medium may be a good alternative and has been found to better stimulate biofilm growth and maturity compared to TSB and serum.[127] Such actions may enhance the models and contribute to a greater transferability.

Clinical implications

The current study reports on an increased risk of infection recurrence in the presence of strong biofilm producers. Thus, additional reproducible methods of biofilm evaluation, such as the microtiter plate test (crystal violet), may facilitate the routine diagnostics of PJI. Biofilm production may have a

predictive value but the association of biofilm production on clinical outcome needs to be further evaluated in larger study cohorts.

6.2 PAPER II

Exchange or non-exchange?

The overall success rate of both DAIR methods combined was 61.1% which lies within the span of previously reported numbers of 26.9-87%.[15, 34, 137-139, 141] DAIR with exchange had a higher success rates than non-exchange DAIR and implied a significant risk reduction for further surgery. The current study is the largest study on first-time PJI after primary THA and its result confirms research supporting DAIR with exchange.[40, 136, 137, 140] There may be rare situations when exchange cannot be conducted due to surgical difficulties. However, considering the significant risk reduction for further surgery when using DAIR with exchange, it should be employed whenever possible.

The demography of the two treatment groups was similar and could not explain the difference in success rates. However, there was a greater proportion of patients with symptom onset within 30 days of their primary procedure in the exchange group (73.4% compared to 66.8% in the non-exchange group). This may influence the greater success rates of DAIR with exchange, as DAIR is recommended within 30 days of initial arthroplasty,[123] but does not fully explain it. Furthermore, time to symptom onset was not a significant confounding variable using multivariable regression analysis. Time to onset of symptoms is theoretically an important factor in terms of biofilm establishment and has been reported a potential indicator of treatment failure, where late infection defined as two years after the initial procedure has been associated with treatment failure.[7] However, time to symptom onset may not affect treatment outcome,[141] which supports our findings.

Anti-biofilm active therapy, *i.e.* rifampicin in polytherapy, was more common after exchange. We cannot explain the reason for this. However, it may impact the success rate in patients undergoing DAIR with exchange as DAIR combined with rifampicin in polytherapy is more successful than other antimicrobial therapy.[211] Length of total antimicrobial therapy differed in the two treatment groups. This may also affect treatment success. However, the descriptive data on antimicrobial treatment in this study should be interpreted with caution. Duration of antimicrobial treatment was pre-defined (Appendix,

Supplementary Figure 1) and we only accounted for antimicrobial treatment in patients who had not undergone further surgery before hospital discharge.

Another confounder in the success of DAIR, in theory explained by biofilm formation, may be the duration of symptoms to surgery. In the current study a cut-off of seven days was chosen, as less than seven days symptom duration is associated with better outcome.[137] No difference in risk for further surgery was identified based on symptom duration. Duration of symptoms is an equivocal factor, but it is recommended that DAIR should be performed within either seven,[7] or 21,[142] days of symptom onset. Symptom duration of more than seven days is associated with DAIR failure.[7] In the current study, a further analysis for symptom duration <21 days and ≥21 days was conducted. However, no difference in risk could be found.

Mortality was higher in the non-exchange group (12.8%) compared to the exchange group (8.0%). Non-exchange DAIR may be used in patients where more extensive surgery may not be considered suitable. Therefore, it was somewhat surprising that the distribution of age and ASA-class were similar between both treatment groups. However, the difference in mortality may indicate that patients selected for non-exchange had a greater morbidity or frailty, making the surgeon more inclined to choose a less extensive procedure such as non-exchange DAIR. Even though ASA-class can be used as a measure of comorbidity and predictor of mortality,[215] it does not consider frailty, the assessment is user-dependent and the classification is vague enough to allow for several interpretations. Furthermore, there was a greater percentage of missing ASA-class in the non-exchange group.

DAIR and revision of bone-anchored components due to infection

The secondary outcome of this study was to analyze the risk of revision of bone-anchored components due to infection, as this is a resource demanding procedure with considerable impact on the patient's quality of life. A lower percentage of patients undergoing DAIR with exchange had a subsequent revision due to infection (13.5%) compared to the non-exchange group (20.4%). However, this was not significant in the regression analysis, maybe due to a small sample size. Surgeon preference and other factors influencing the choice of revision subsequent a single DAIR are unknown and our result should be interpreted considering this uncertainty. The impact of a prior DAIR on the success of a subsequent two-stage revision is contradictive with reports on similar success,[216] and lower success[217] rates compared to patients who undergo staged revision without a prior DAIR.

Bacterial growth

The type of bacteria may influence treatment results after DAIR. However, this needs further elucidation. Some studies have reported on an association between CoNS and treatment failure,[7, 38] whilst the growth of *S. aureus* has been identified as a risk factor for treatment failure.[154] In the current study, *S. aureus/S. lugdunensis* implied a greater risk for additional surgery compared to PJI caused by CoNS. Biofilm growth is proposed to be a reason for DAIR failure,[60] this needs further evaluation in combined *in vitro* and *in vivo* studies.

Polymicrobial infections may be more difficult to treat due to possible inter-microbial synergistic effects and the need for broad antimicrobial treatment.[54, 218] The overall rates of polymicrobial infection for the entire study cohort was 31.3%, which could have influenced the overall success rates. A previous study has reported on rates of polymicrobial infection similar to ours at 38.3%,[38] whereas others reported a lower share (5.5%-13.1% polymicrobial).[7, 10, 219]

Strengths, limitations and methodological considerations

This is the largest multi-centre cohort study to evaluate the success rate of DAIR in first-time PJI after primary arthroplasty. The current study involved a retrospective retrieval of data from medical records to gather more information on each reoperation. The reporting of data considered the suggested "core outcome set" needed for standardizing DAIR research,[137] but did not include all host status factors, antimicrobial susceptibility or the delivery of local antimicrobials.

The data collection form did not include information on infection resolution. The end-point of the current study was additional surgery due to PJI and not infection resolution. Infection resolution was described for a subset of patients in which information on this information could be obtained. In this subset of patients (n = 151), 4 (5.8%) patients had recurrent infection but did not undergo further surgery. Hence, using reoperation as a measure of infection recurrence captured 94% of all cases. Although this is not valid for the entire study population, reoperations can be considered a reasonable way of studying recurrent infection.

The current study did not take surgeon experience into account. This may affect the results of DAIR. In one study on DAIR of the hip, surgery performed by trained hip surgeons showed a greater chance of infection resolution.[141] DAIR with exchange of modular components may require a greater surgical experience and therefore suggest the presence of a hip surgeon. Further, the

DAIR procedures were not performed according to a standardized protocol and as the majority of cases were cemented THA, the liner was not exchanged.

The definition of a successful DAIR varies and some studies evaluate its success after multiple consecutive DAIR procedures.[34, 40, 220] Considering multiple DAIR procedures as a successful therapy would improve the overall success rates of the current study. Allowing for two consecutive DAIR procedures would increase the overall success rate from 61.1% to 80.3%. It is yet unclear how many DAIR procedures are acceptable before resorting to revision of bone-anchored components. In a meta-analysis success rates improved when multiple debridements were performed, however, this did not have statistical significance.[137]

Clinical implication

The significantly improved success rate compared to non-exchange DAIR supports the utilization of DAIR with exchange. DAIR with exchange should be conducted whenever possible in attempt to secure the greatest chances for infection resolution. Furthermore, our material indicates that success rates increase when multiple consecutive DAIR procedures are conducted. A cut-off for how many consecutive DAIRs are reasonable was not evaluated in the current study, but at least a second DAIR may be justified if the first one fails. However, this needs further evaluation.

6.3 PAPER III

Re-revision after one- or two-stage revision

The overall re-revision rates for both methods were 21% in the current study. No increased risk for re-revision due to any cause, or specifically due to infection or aseptic loosening, could be identified when comparing the one- and two-stage methods. This further supports that there may not be a difference in infection resolution between the two revision methods.[147, 148, 221, 222]

There was a difference in age between the patients in the one- and two-stage group. Patients in the one-stage group were older than in the two-stage group. This could possibly reflect an unwillingness in surgeons to make elderly patients subject to two surgeries.

Further, type of fixation differed between the groups. Cemented fixation was used to a greater extent during the primary revision procedure in the one-stage

group. This may be due to the age difference as older patients generally receive cemented implants. However, in our study the influence of cemented versus uncemented fixation is difficult to evaluate. The reason being that the type of cement used is not always known and we lack information on use of local treatment of antibiotic loaded collagen, calcium sulphate pellets or cement beads, which could have influenced the rate of infection resolution.

Strengths, limitations and methodological considerations

This is the largest national observational study on risk for re-revision between the one- and two-stage procedure for PJI. A limitation in this study is the lack of data on microbiological details and antimicrobial therapy. Unfortunately, such data is not available in the SHAR and there are no nationwide registers we could have collaborated with to retrieve this information. In two-stage revision, staphylococci are associated with a greater risk of recurrent infection.[223] In one-stage revision, enterococci have been found associated with re-revision.[224] The lack of microbiological data also obstructs our ability to verify whether PJI patients have been diagnosed correctly. Cases diagnosed as aseptic loosening may be incorrect. Numbers from recent studies on aseptic revisions report that 7-10% are septic and thereby wrongly diagnosed.[122, 225]

Further, the only variables available on patient related risk factors were ASA-class and BMI. These were not available for all cases as they were first registered in the SHAR from 2008 and onward. To investigate the influence of BMI and ASA, a separate sensitivity analysis was performed in which we could not find a difference in risk for re-revision. Also, the study period stretched over 36 years in which several changes in surgical technique, operative hygiene, microbial and antimicrobial development have occurred. We included year of revision in the sensitivity analysis to address this and could not identify a significant difference in risk for re-revision between the one- and two-stage group.

Although nationwide, the current study has not been able to capture all revisions and re-revisions due to PJI for the study period. A validation of SHAR data from 2005 to 2008, revealed that 78% of the revisions due to PJI was reported.[226] In addition, it should be noted that our study did not capture cases of recurrent infection not treated with further surgery. Hence, there may have been cases of recurrent infection where patients were not made subject to further surgery. As patients in the one-stage group were older it could be assumed that further surgery was abstained to a greater extent in this group.

Addition of microbiological and patient related risk factors would have added to the strength of this study. It is, however difficult to study infections using

the SHAR without complement from another data source.[227] On the other hand, the use of register data enables large study cohorts in which "trends" may be identified, that could be explored in further research. As such this study adds on to existing research and emphasizes the need to further elucidate whether the one- or two-stage procedure is superior to the other.

Clinical implications

Several questions regarding the choice of optimal revision strategy are yet unanswered and need further evaluation. The current study supports the use of one-stage revision as a viable option in PJI treatment. However, the aforementioned limitations call for further research to explore if our observations remain valid when considering microbial growth, patient selection and infection resolution.

6.4 PAPER IV

The emotional impact of PJI on surgeons

The emotional spectrum of PJI on study participants was largely consistent with previous reports on emotional responses to adverse events.[177, 228] Surgeons reported on a four-phase emotional response as identified by Luu *et al*. (Figure 26).[186] The phases being i) an emotional reaction to failure, ii) an experience of chaos and scrutiny of one's contribution to the adverse event, iii) reflection on what one can learn from the event, iv) the prolonged and cumulative effects of one's emotional response on one's personal and/or professional identity.

The current study illuminates the negative emotional impact of PJI on prosthetic joint surgeons. This confirms previous findings of the impact of PJI on surgeons.[177] Surgeons interviewed in our study were aware of the many possible causes leading to PJI and some felt it was irrational that they blamed themselves for the infection. Mallon *et al*. too reported on the accountability surgeons felt, but also that surgeons described PJI as inevitable and that they did not need feel at fault for it.[177] However, there is a report on 80% of infections being related to surgery and 20% related to non-surgical factors,[86] and self-scrutiny was reported in our study.

Figure 26. *The four-phase emotional response in surgeons in the current study, as suggested by Luu et al.*[186]

Being recognized as one of the most successful types of surgery, arthroplasty surgery may generate another set of expectations and involve a greater disappointment from both patient and treating surgeon when it fails. Orthopaedic infections, especially PJI, have gained a lot of attention during the past years in regards of diagnostics and treatment. Faivre *et al.* investigated burnout nationwide amongst French orthopaedic surgeons and traumatologists and found that 39% reported burnout symptoms.[229] In addition, 8% reported on suicidal thoughts. Further, 43% stated they would not recommend their children to follow their career path. Keeping in mind responder bias (response rate 23%), the study reports on alarming numbers of psychological ill-being. Another study in orthopaedic residents identified medical errors as contributor to burnout.[230] The current study did not explore burnout (emotional exhaustion, depersonalization and low sense of personal accomplishment) as such, but no clear signs of it were identified during the interviews. It should also be noted that surgeons reported on a positive emotional impact when they were able to help their patient and when treatment had been successful. They also described finding solace in a good doctor-patient relationship and appreciated the support they received from their colleagues.

Although the present study is on PJI we believe that the results may be applicable on surgeons involved in other types of postoperative infections. The magnitude of at which adverse events emotionally affect surgeons in other fields has previously been described.[180-182, 185, 186, 228, 231]

Support needs during the management of PJI

In the current study, and a UK-based study,[177] working with PJI in a team-based manner was reported as the best measure of professional support. High treatment success has been suggested dependent on multi-disciplinary collaboration in PJI cases.[232] Further, Swedish surgeons regarded the support they received from colleagues as the best type of emotional support. Mallon *et al*. described a need for open and regular discussions on adverse, and this too was desired by Swedish surgeons.[177] The need for support and the possibility for discussion has also been emphasized in studies on the emotional response to adverse events within other surgical fields.[186, 228] Furthermore, there seems to be lacking opportunity for surgeons to receive emotional support and discuss adverse events and improved emotional support systems have previously been warranted.[182, 186, 228]

Although surgeons working at county or district hospitals reported conferring with their colleagues and with the regional hospitals on PJI cases, surgeons working at a regional hospital were more prone to wish for improved peer support. They desired regular debriefings or the possibility to talk to an external professional to a greater extent than surgeons at non-regional hospitals. The fact that complicated cases are referred to the regional hospitals may in part explain this. Further, the surgical teams may be bigger at a regional hospital which may affect the unity of the group. Nonetheless, the findings among UK and Swedish arthroplasty surgeons should encourage health care organizations to offer the possibility of structured support and look over possibilities to unburden, and facilitate for, surgeons during PJI management.

The doctor – patient relationship

Surgeons felt worse when "their" patient got infected in contrast to taking over "someone else's" infected patient. Some also worried about maintaining the patient's trust. This worry was confirmed in a study in which patients reported on losing faith in their surgeon once infected.[6] Andersson *et al.* confirmed the surgeon's feeling of patients blaming them for the infection, describing a bitterness towards doctors.[5] Further, patients report on feeling insecure during the management of PJI,[5] which may be a reflection of the insecurity in management reported by surgeons in the current study.

Based on our interviews, we do not think that PJI needs to be diagnosed by a colleague to ensure objectivity. However, since the most important factor facilitating the surgeon both emotionally and practically was being able to discuss PJI cases with a colleague orthopaedic surgeon, that may be an incentive to have a colleague involved in the process of diagnostics. Our study was based in Sweden where a lot of work has been done to bring awareness to infections, also the hospital system is not very hierarchical, which may influence a greater openness and reduce factors leading to denial. In other countries with other cultures, there may be a greater risk for subjectivity and denial. Further, the impact of the doctor-patient relationship may influence treatment choice. This was not explored in the current study, but Ryan *et al.* suggested that patients from outside hospitals were more likely treated with implant extracting procedures.[219] This finding may further support the need for collaboration in PJI cases.

Our study may draw attention to the influence on the physician's well-being of the doctor-patient relationship. Perhaps, in knowing that other surgeons are affected and are negatively impacted when "their" patient gets a PJI the individual surgeon will not feel as lonely.[186] This may lead to a more open discussion and awareness among colleagues, which should have a positive effect on the surgeon's well-being. Further, it is of importance to increase the education of patients in order to highlight the severity and reality of PJI.

There are studies reporting on the patient experience of not being taken seriously by their doctors when they present with diffuse PJI symptoms.[1, 5, 6] Surgeons were aware of this in our study. A possible reason may be lack of knowledge in PJI within the medical profession. This was brought forth during the interviews of the current study. Furthermore, another reason to why patients feel they are not taken seriously may be surgeon denial. However, surgeons witnessed on a change of attitude in the management of PJI where Swedish surgeons today seemed less likely to deny PJI.

Andersson *et al.* reported that some patients did not regard their doctors as a source of support, whereas some did.[5] Emotional intelligence has been proposed an important factor in the doctor-patient relationship. Previous research suggests that orthopaedic surgery residents demonstrate low emotional intelligence and that surgeons need further education on this.[233] In the current study, all surgeons were perceived as emotionally intelligent, both in how they managed their own feelings but also in their understanding of the patient's emotions.

Strengths, limitations and methodological considerations

The current study is the first to explore the experiences and the emotional impact of PJI in Swedish surgeons. Further it has identified desired improvements that may facilitate the management of PJI for the involved surgeons (Paper I, Figure 4). These need to be evaluated for their efficacy.

The current study is based on reflections on PJI cases. The negative impact of PJI may have become even more pronounced if interviews were conducted in connection to a PJI case or if relatively inexperienced surgeons were interviewed.[186, 228, 231] The study population was purposively selected for its diversity to capture as many perspectives as possible. Therefore, we did not strive for proportionality to the population of hip and knee arthroplasty surgeons in Sweden. However, in Sweden, 19.7% of orthopaedic surgeons are female which reflects nicely in our study population (22%). The over-representation of male surgeons may risk that certain perspectives important to female surgeons were not captured. Further, females are more motivated to discuss adverse events.[234] In our material there were no obvious differences in male and female reflections on PJI. This is in accordance with previous research on male and female surgeons reflecting on adverse events.[186]

It is difficult to objectively prove saturation and, in our study, we may have come across new perspectives had we continued our data collection. Therefore, based on our sample size, we cannot claim that no new perspectives can be captured as this is unknown.

In qualitative research there are several concepts of which trustworthiness can be discussed. According to Graneheim *et al*. trustworthiness is built on credibility, dependability and transferability.[200] The credibility of a study concerns how well data and analysis reflect the study aim. To address this, we used purposive sampling and discussed data within our study group of persons with different experiences of PJI. Furthermore, the selection of meaning units was discussed between AEA and KS to ensure a well-chosen data extraction. Quotes from interviewees, translated by a third part, were also intertwined in our text. Sending our results to randomly selected study participants was also done to confirm credibility.

The dependability of a study addresses how data may change over time, perhaps due to data collection stretching over a longer period, or how the researcher approaches data during the "maturation" of his or her analytical process. In our study, data was collected during a short period of time (3 months). There was a consistency in KS approach to data and, as mentioned, the process of QCA was continuously discussed within the study group.

According to Graneheim *et al.*, it is up to the individual reader to assess the transferability.[200] Cultural and health care organizational differences may limit the transferability of our study. The impact on surgeons may be different in countries where surgeons may face lawsuits following adverse events.[235] We believe that our results can transfer to other systems and cultures similar to Sweden, *i.e.* Northern Europe. This is strengthened by the fact that, despite differences in both culture and health care systems, our study findings are largely consistent with the UK-based study conducted by Mallon *et al*.[177]

Clinical implications

The results of this study will most probably not have a direct effect on treatment outcomes. However, hopefully it will put light on the importance of discussions, sharing experiences and knowledge on PJI between colleagues. Doing so should not only create a sense of support for the individual surgeon but may also serve as a base for education. Knowing that surgeons find it important to work in teams may improve, coordinate or standardize care models, which in turn may lead to a positive effect on both treatment outcome and health care economics. Previous studies claim that a multi-disciplinary approach is necessary for improved treatment outcome,[236] and in regard of surgeon well-being health care organizations should consider regular debriefing possibilities for their staff.

6.5 GENERAL DISCUSSION

Selection of patients for primary arthroplasty

Surgeons reported on being more restrictive in their selection of patients for primary arthroplasty after managing PJI cases (**Paper IV**). This was not explored further, but the correct selection of patients may in theory be an important preventive measure for PJI. Many risk factors have been identified (page 11) and it is recommended that these should be considered carefully prior to primary arthroplasty.[28, 237]

Further research is warranted to evaluate the effect of optimization of modifiable risk factors and how the selection of patients may influence PJI incidence to further elucidate the importance of patient-related risk factors. Also, the astounding lack of evidence in perioperative factors such as airflow and perioperative disinfectants needs to be addressed in further evaluation.

Diagnosing PJI

Surgeons felt that the diagnostics could be difficult and that diagnostic tests were unreliable (**Paper IV**). Intra-operative cultures were considered the ultimate proof of infection (**Paper IV**), and in **Paper II**, 143 (18%) patients were excluded from the analysis due to negative culture growth. Considering the proportion of patients with negative growth in **Paper II**, there is a likelihood that some patients in **Paper III** were culture-negative. Another study on revisions due to PJI identified culture-negative samples in 41% of PJI cases.[144] On the other hand, negative culture growth does not rule out the possibility of infection. To increase detection rates, sonication,[58] polymerase chain reaction (PCR),[238] or whole-genome sequencing can be used. Further, storage and transportation of samples may impact culture growth. Another important factor is the use of antimicrobials prior to surgery. It is important to establish routines in how negative cultures should be managed to facilitate diagnostics. Surgeons desired better diagnostic tools, introduced in an evidence-based manner (**Paper IV**), and such a tool may be the use of biofilm measurements and MBEC susceptibility testing (**Paper I**).[54]

Although not a diagnostic tool confirming PJI, the use of biofilm production measurement, and perhaps MBEC, may aid the surgeons and ID specialists in their treatment decisions. This has also been suggested by Saeed *et al*.[54] As the presence of strong biofilm producing staphylococci was associated with infection recurrence (**Paper I**), the introduction of biofilm OD measurements in routine clinical practice may influence treatment setups. Confirmation of a strong biofilm producing bacteria may suggest that surgical treatment need be more "aggressive". This needs further evaluation.

Considering preferences and patient risk factors in the treatment setup

In this thesis none of the studies focused on the patient perspective, which is a weakness, but beyond the scope of this thesis. However, there are both qualitative and quantitative studies available on patient experiences and physical function after PJI treatment. Hence, in **Paper IV** we asked surgeons on their take on the patient experience. Surgeons agreed upon the importance of involving their patient in treatment decisions. Shared decision-making may alleviate the surgeon from feeling full responsibility and coheres with person centred care.

It is unknown to what extent patient risk factors affect treatment outcome in reoperations due to PJI. Kheir *et al.* found that previous DAIR, previous myocardial infarction or revision surgery were the three most important risk factors for failed reoperation due to PJI.[239] Previous surgery

has been reported a risk facture for failed treatment in other studies.[224, 240] In **Paper II**, no patient risk factors could be identified in regard of treatment failure when using either DAIR method. However, this study only included primary arthroplasties, and neither **Paper II** or **III** evaluated myocardial disease. The conclusion of **Paper II** and **III** is that further research is warranted to establish which patient factors may make a patient eligible to one or another surgical treatment.

Microbial factors

Polymicrobial infections have been associated with a higher failure rate after DAIR.[38] This was not confirmed in **Paper II**. However, in this study we did not have access to the antibiogram of the causative agents and therefore there may have been an under-reporting on the number of polymicrobial infections considering intra-species variations. In **Paper I**, 31% cases were polymicrobial, but interestingly there was a greater number of polymicrobial cases in cured infections (36%) compared to recurrent infections (25%).

Previous research has shown that there is a higher risk of failure after DAIR in cases where many culture results are positive.[38, 154] Tornero *et al.* discuss the possibility that many positive cultures may imply a higher infectious dose and thereby cause a more aggressive infection.[38] We did not study this in **Paper I**, since the starting bacterial inoculum added to the CBD and microtiter plate test was the same for all the strains, and then they exhibited their different biofilm production abilities on the plastic surfaces.

Surgical treatment

For DAIR, the results of **Paper II** support an exchange of modular components, and coheres with previous research. To date, it is suggested that the removal of modular components means better chances of biofilm eradication, and in turn better chances for outcome success. However, there is no study confirming this. Scanning electron microscopy has confirmed biofilm growth on prosthesis components *in vivo*.[52] The components of a hip prosthesis in patients with PJI have been examined and it is reported that adherence of bacteria is greatest on the polyethylene liners.[241] The removal of components should therefore theoretically imply a more extensive clean-out. In turn, the extraction of a prosthesis performed during one- or two-stage surgery implies an even greater chance of biofilm eradication, which may be why these methods are superior to DAIR in terms of infection resolution.

The importance of biofilm eradication for successful treatment outcome is further supported by **Paper I**. In addition to the greater risk of infection

recurrence in infections caused by strong biofilm producers, infection relapses were more common in patients treated with implant preserving surgery (5 of 6 relapses, 83%). However, the sample size of relapses was small and therefore conclusions should be drawn with caution. Nonetheless, relapses highlight the importance of meticulous surgery regardless of whether patients are treated with implant preserving or implant extracting procedures.

Another study on growth of *S. aureus* in stage one and stage two of two-stage surgery reported on relapses of *S. aureus* in 7.5% of cases and observed a greater resistance, measured in increases of MIC, in strains cultured from stage two.[164] These results underline both the importance of meticulous surgery during stage one in terms of a persisting species, and also that bacteria exposed to antimicrobial agents may pick up resistance genes. In patients where bacteria have not been completely eradicated during treatment, there is a risk that they persist as asymptomatic biofilm or as small colony variants inside other cells.[242]

Antimicrobial treatment

In **Paper II**, 39% of patients had received antimicrobial therapy prior to their DAIR procedure. Due to the efforts to increase awareness of PJI management (**Paper IV**), this number would perhaps be different if the study were to be conducted on patients later than 2009-2015.

Translational research

In vitro models aim to mimic *in vivo* conditions, however, there are several interactions that cannot be reproduced *in vitro* that may have a significant influence on clinical presentation and outcome. The CBD model used in **Paper I** does not mirror the surface properties of a prosthetic implant or human tissue. Neither does the model consider the nutritional environment of the implant interface or the interactions with the host immune system.

Power problem

Due to their multi-factorial nature, and relatively low incidence rate, large datasets are desired when studying PJI. The ideal studies are prospective, multi-centred studies consisting of large study cohorts. This requires nationwide and, or, international collaborations in study setups. Another alternative to address the power problem is conducting individual participant data pooled analyses or using the national joint registers.

Infections in the national registers

Several register-based studies have been performed to analyse different aspects of PJI. Revision rates, incidence rates, surgical procedures and risk factors have been studied in national datasets [19, 22, 82, 243-245]. However, infections are of a multi-factorial character and currently, national joint registries alone do not provide adequate data for a comprehensive approach to infection research.[227] The inconsistency in data collection and definitions of infection in the registers further aggravate comparisons of PJI within registers. Infection burden has also been suggested to be underestimated in national joint registers. [4, 14]

In the registers, infections are reported as revision procedures. It is therefore important to mention that patients with infections who are not subject to revision or other reoperations are not captured within the registers. Further, the definition of infection is inconsistent across the registers, and revision can be defined as all procedures manipulating, exchanging, or removing prosthesis parts. Some registers categorize the procedures and report on them accordingly, others do not make distinctions between the procedures.

The registers report on completeness of registered data in their annual reports but not specifically on completeness of reported infection procedures. Validation of data reported on infection to the registries is important in order to maintain a high data quality. Validation studies of the Danish and Swedish arthroplasty registers have shown an under reporting of PJI. [226, 246] Gundtoft *et al.* calculated the incidence of PJI using the Danish National Arthroplasty Register (DHR) reported that the incidence of PJI was 40% lower using the DHR compared to their algorithm based on multiple sources.[247] An underestimation of the incidence of PJI has also been suggested in the Finnish Arthroplasty Register.[17]

Studies reviewing the sensitivity in capturing reoperations for PJI and capturing PJI are presented in Table 6. Definitions of time period for incidence rates or reoperation rates vary for the studies. Minor wound revisions and salvage procedures risk not being registered, and implant preserving reoperations risk not being reported or may be omitted in the register. [4, 14, 248]

Table 6. *Studies on the capture rate of PJI in national joint registers.*

Study	Register	Reoperation rate in register	Reoperation rate from other source	Register sensitivity
Zhu *et al.*[14]	New Zeeland Joint Register	0.67%	1.07% (hospital discharge records)	63%
Jämsen *et al.*[4]	Finnish Knee Register	0.77%	0.89% (Finnish Patient Register)	87%
Lindgren *et al.*[226]	The Swedish Hip Arthroplasty Register	1.30%	(Swedish Prescribed Drug Register)	67%
Gundtoft *et al.*[249]	The Danish Arthroplasty Register	Not stated	National Register of Patients, medical records*	67%

*and supplementary information from prescription, microbiology and biochemistry databases

The national registers have an enormous strength in that they provide an opportunity to conduct research on big populations. This is crucial to be able to monitor infections, study incidence rates, changes in incidence rates and surveil trends in which further scientific studies should be performed to validate and explain the register findings.

Addressing the limitations in national joint registries

It may be difficult to reach consensus on how to report on infections within registers. It is important to be able to compare annual statistics within a register and therefore it may be difficult to change current definitions. However, a harmonization of reporting would facilitate international comparisons and collaboration studies across the registers. Therefore, there is a need to agree upon certain variables of infection interest that are adopted into all registers.

In the meantime, collaborative studies using register linking may be an alternative to obtain necessary data. This method has been adopted by Gundtoft *et al*. as Denmark offers a unique possibility for supplement on microbial growth via their national microbiological register.[249] Holmberg *et al*. collected medical records to retrieve pathogenic information and this method was also employed in **Paper II**.[250]

7 CONCLUSIONS

- **Paper I** Patients infected by strong biofilm producing staphylococci have up to 5 times greater risk recurrent infection than when infected by non/weak producers. Biofilm measurements should be considered in routine clinical practice as the presence of strong biofilm producing bacteria may indicate the need for more aggressive surgical therapy.

- **Paper II** Using DAIR with the exchange of modular components results in reduced risk of further reoperations due to infection and should be employed in all patients eligible for DAIR.

- **Paper III** The risk for re-revision is similar for the one- and two-stage procedure. This supports the use of the one-stage method, but needs further evaluation in future studies.

- **Paper IV** Prosthetic joint surgeons experience a negative emotional impact when managing PJI. Facilitating factors such as peer support and multidisciplinary approaches were identified as the most important coping strategy. The current study reports on further improvements desired by surgeons working with PJI. The results and suggestions on improvement may transfer onto surgeons in other medical fields managing postoperative infections.

- A multidisciplinary approach in research and clinical management are necessary factors for future progress in the treatment of PJI (**Paper I** and **Paper IV**). This has been brought forth in previous publications, and may also be true for other orthopaedic infections, or medical device-related infections in general.

Linnéa Teljas Puranen

Figure 27. *Multidisciplinary team from multiple disciplines working together to discuss clinical cases and collaborative research work. From the left: clinical microbiologist, ID specialist, orthopaedic surgeon 1, orthopaedic surgeon 2, experienced prosthetic joint surgeon 1, experienced prosthetic joint surgeon 2, microbiologist and biomaterial researcher.*

8 FUTURE STUDIES AND PERSPECTIVES

The current studies have led to new research questions, planned add-on work and further projects.

Paper I

- The current study was limited to first-time infection of total arthroplasty of the hip or knee. Staphylococci from reoperations due to infection of other orthopaedic implants (hemi-arthroplasties) and not limited to first-time infections have also been analysed. In addition, molecular microbiological analyses of the strains were performed and this additional data will be compared to clinical outcome (infection resolution/recurrence).
- A prospective study is under planning to evaluate whether MBEC can be used as a surrogate marker for biofilm susceptibility in a clinical setting.

Paper II

- The database created for Paper II offers a unique opportunity to further evaluate different aspects of the DAIR procedure. We are in the process of merging it with the Swedish Drug Database (Läkemedelsregister) to obtain a more accurate outcome parameter and to improve our analysis of optimum treatment for infection resolution.
- Delayed wound closure was used at some orthopaedic units during the study period. A study on evaluating the success rates of this surgical method in terms of further reoperations or revision surgery is planned.

Paper III

- The research group is involved in a prospective randomised controlled trial in a multi-centre setting which was initiated and set up by the INFORM group.[151] This study is the first of its kind to investigate whether there is a superiority in either the one- or two-stage method, but with focus on patient reported outcome measures. Data analysis is in process and the manuscript is planned for submission in 2020.

In general, much can be done to improve the research possibilities within, and management of, orthopaedic infections. Some of the current limitations have been mentioned in this thesis including the difficulties in conducting comprehensive infection research using national joint registers and the difficulties in translational research.

- There is a need to further establish the mechanisms of pathogenesis in orthopaedic infections. Acquiring a greater knowledge on the mechanisms of pathogenicity is essential to generate new treatment alternatives. Several basic improvements that may facilitate research on pathogenic factors could be to establish routines for the management of intra-operative samples.
- In regard of biofilm, there is a need to develop clinical breakpoints for susceptibility testing of antimicrobial agents on biofilms. Further, developing clinically available techniques for establishing the presence, and pathogenicity, of biofilms using surrogate markers or imaging techniques is warranted.
- It is important to evaluate whether the virulence properties of microorganisms can be associated to biomarkers as this would facilitate the diagnosis and further management of PJI.
- The influence of patient factors needs to be further studied in order to improve the selection of patients for arthroplasty surgery and to identify whether patient factors impact the treatment of PJI.
- There is a need to establish a standardized way of reporting on PJI with defined outcome measures in order to increase comparability and improve the possibilities of metanalyses and register-based research to increase study populations.

9 RELATED PROJECTS NOT INCLUDED IN THIS THESIS

- Bargon R, Bruenke J, Carli A, Fabritius M, Goel R, Goswami K, Graf P, Groff H, Grupp T, Malchau H, Mohaddes M, Novaes de Santana C, Scott Phillips K, Rohde H, Rolfson O, Rondon A, Schaer T, Sculco P, Svensson K General Assembly, Research Caveats: Proceedings of International Consensus on Orthopedic Infections
  Journal of Arthroplasty, 2019;34(2S):S245-253.e1

- Seth Caous J, Fridell Y, Svensson K, Malchau H, Ahlstrom L, Grant P
  Instrument tables equipped with local laminar airflow units reduce bacterial contamination during orthopedic surgery
  In manuscript

- The INFORM study group
  One-stage or two-stage revision surgery for prosthetic hip joint infection: a randomised controlled trial.
  Study protocol available[151]

- PRISS expertgrupp 2019
  Mohaddes M, Svensson K, Stefánsdóttir A, Rydén C, Andersson I, Tammelin A, Gustafson P
  Riskfaktorer för ledprotesrelaterad infektion samt optimering av patient inför ledprotesoperation
  PRISS Slutrapport 2019
  www.lof.se/wp-content/uploads/Riskfaktorer-samt-optimering.pdf

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APPENDIX

Supplementary Table 1. The EUCAST definitions on breakpoints for staphylococci and the antimicrobials tested in the study.[133]

Antimicrobial agent		**MIC breakpoints** *(mg/L)*	
		S ≤	R>
Ciprofloxacin	*S. aureus* CoNS	0.001 0.001	1 1
Clindamycin		0.25	0.25
Fusidic acid		1	1
Linezolid		4	4
Oxacillin	*S. aureus* CoNS	2 0.25	2 0.25
Rifampicin		0.06	0.5
Trimethoprim/sulfamethoxazole		2	4
Vancomycin	*S. aureus* CoNS	2 4	2 4

Supplementary Figure 1. The report form that was sent out for supplementary on infection data on a patient level to all orthopaedic units in Sweden.

Social security number	
Date of reoperation *(year-month-day)*	
Reoperation due to infection *Sequence number according to SHAR*	
Number of culture samples *How many samples were obtained during the arthrocentesis/operation?*	*Preoperative:*
	Peroperative:
Number of positive samples for each microbe *e.g.: 3 staphylococcus aureus, 2 CoNS*	*Preoperative:*
	Peroperative:
Onset of symptoms *When did the patient contact health care for the first time? (year-month-day) If the date is unclear, please state month and year (e.g. 2015-10-?)*	
Antimicrobials prior to surgery? *(yes/no)*	
Antimicrobial agent 1 *Which type(s) of intravenous antimicrobials did the patient receive?*	
Antimicrobial agent 2 *Which type(s) of antimicrobial agents were prescribed at discharge?*	
Change of antimicrobial agents *Was the antimicrobial therapy changed after discharge?*	
Duration of antimicrobial therapy *How long did the patients receive antimicrobial treatment? Choose the best alternative.*	< 4 v 4 – 8 v 8 – 12 v > 12 v
Additional comments	

Supplementary Figure 2. The protocol used as a topic guide list for the interviews conducted in Paper IV.

Semi-structured protocol
The interview starts off with brief information about the interview setup and that the audio-records and interviews are stored unidentified and that no one outside of the study group can access them. Participants are asked once again to consent to their partaking in the study.

Aim: To acquire an understanding for how orthopaedic surgeons perceive and experience the management of PJI, the emotional impact of it and identify areas of improvement.

- What experience do you have of revision surgery due to PJI of the hip?
- How many years have you worked with PJI of the hip?
- Do you have a method of preference (one- or two stage revision) and if so, why?
- Which difficulties do you encounter in managing deep PJI?
- Do you feel that there are any difficulties in the diagnostics of PJI, if so, what are they?
- Which difficulties do you encounter when setting up a treatment plan?
- How do you reason when planning treatment?
- How do you feel about choosing a treatment plan?
- Which patient factors may make you prone to choosing one treatment alternative rather than another?
- Which are the strengths/weaknesses in current care and management of PJI patients?
- How does the patient group affect you emotionally?
- How is it to meet patients with PJI, how does it affect you?
- How does it affect you when one of your patients gets a PJI?
- How do you manage the difficulties you encounter when managing PJI?
- Do you receive any support, and if so, what type?
- Is there any type of support you and your colleagues may need?
- What do you think is a good means of support?
- Based on your experiences, which aspects of management and care of PJI patients need improvement?
- Which are your suggestions to facilitating the management of PJI?
- Can you see any specific areas of management, care and organization that imply a threat to the patient's security?
- Which improvements have contributed to improved diagnostics and eased management of PJI during your career?
- How do you keep yourself updated on PJI management?
- What do you think are the most important factors to facilitate the patient experience of PJI?
- Is there anything you would like to add or anything else you think we should cover?