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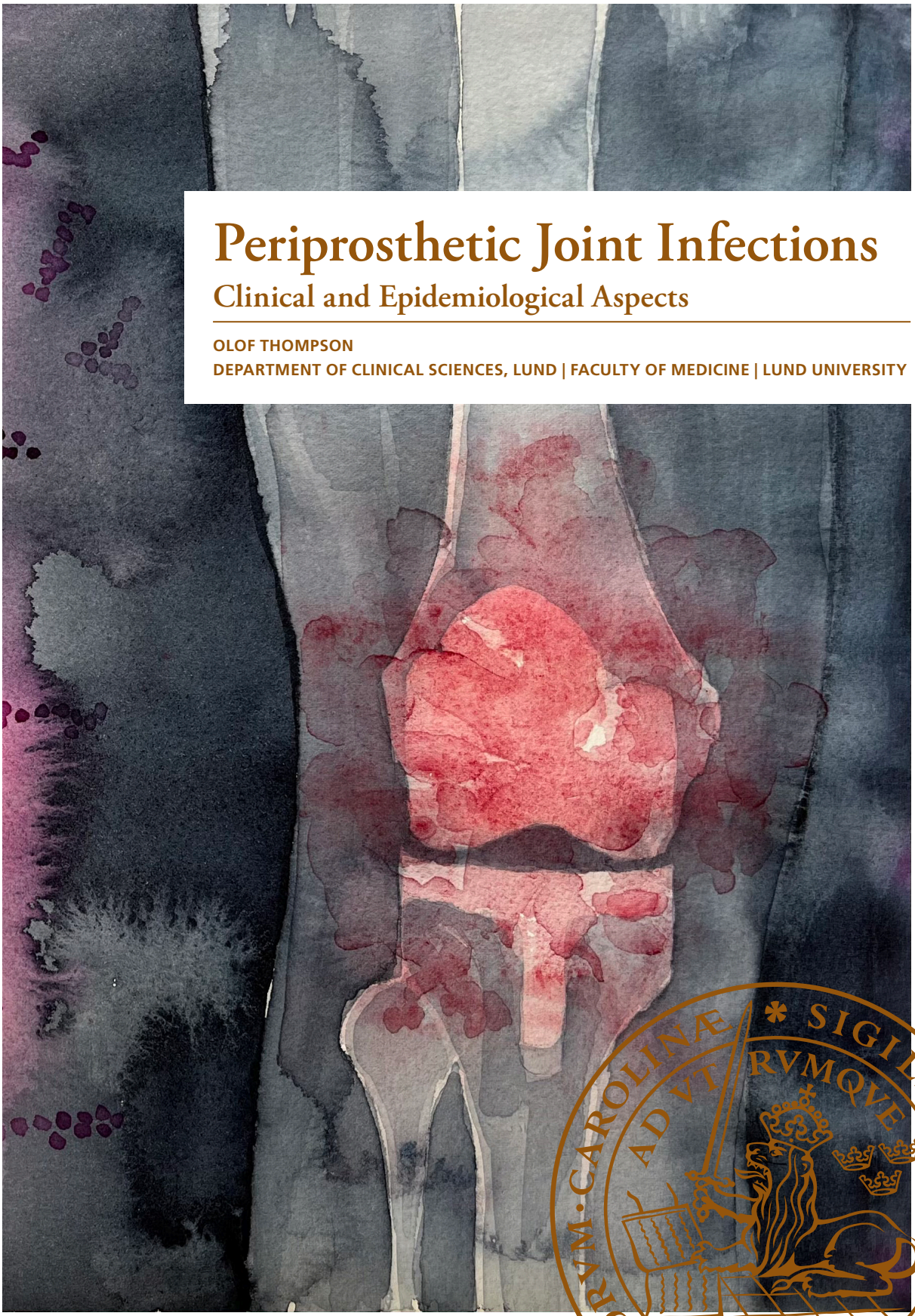

Periprosthetic Joint Infections

Clinical and Epidemiological Aspects

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Olof Thompson

LUND
UNIVERSITY

DOCTORAL DISSERTATION
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Abstract

Periprostheteic joint infection (PJI) is a rare complication of arthroplasty with severe consequences for the affected patients. PJI most often necessitates additional surgery and prolonged courses of antibiotic treatment, leading to worse functional results and increased societal costs. Evaluating treatment of PJI as well as preventive efforts are essential to increase our understanding of PJI and to enable improved approaches in the future.

In this thesis four studies covering different aspects of PJI are included. PJIs caused by streptococci and enterococci were investigated in papers I and II, respectively. Patients in Skåne with growth of either streptococci or enterococci in sterile cultures from prosthetic joints were included and data from the medical records were reviewed retrospectively. The aim was to describe the affected populations, surgical and antimicrobial treatments and treatment outcome. Paper I showed that streptococcal PJIs were often acute hematogenous infections treated with surgical debridement. Successful outcome was achieved in 89% of cases. Paper II showed that enterococcal PJI were often early postoperative infections in elderly fragile patients, where enterococci were found as a part of a polymicrobial flora. Overall cure was reached in 67% of cases. However, when complete cure, defined as preservation of a functional joint and eradication of infection, was the treament intention, this was achieved in 80% of cases.

In paper III the effect of a national infection control programme on the incidence of PJI after primary total knee arthroplasty (TKA) was evaluated. Through matching of 45,438 primary TKAs from the Swedish Knee Arthroplasty Register to the Swedish Prescribed Drug Register, 2505 TKAs were identified as having received ≥28 days of continuous antibiotic treatment within 2 years of TKA. Subsequent review of medical records identified 644 PJIs, giving a cumulative 2 year incidence of 1.45%. PJI incidence rates were similar during both time-periods.

In paper IV mortality of patients with PJI after primary TKA was compared to patients without PJI using data aquired in paper III and mortality data from the tax agency. Results showed a significantly increased mortality for PJI patients in both short- and long-term.

This thesis shows that patients with streptococcal PJI have a relatively good prognosis. Patients with enterococcal PJI, on the other hand, are challanging to cure. However, the results do suggest acceptable success rates for a subset of enterococcal PJI-patients where complete cure is a viable option. Further, this thesis shows that incidence rates of PJI were similar before and after a national project to reduce infection rates. The lack of effect of the prevention programme, however, remains to be explained. Patients undergoing primary TKA with PJI have a higher mortality rate than non-infected patients. This effect remains long-term, indicating that mortality is not related to PJI alone, perhaps reflecting a general frailty in the PJI population.

Key words prosthetic joint infection, arthroplasty, *Streptococcus*, *Enterococcus*, register, mortality

Classification system and/or index terms (if any)

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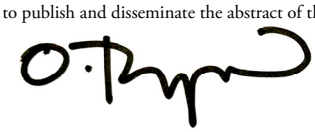
Signature  Date 2022-08-23

Periprosthetic Joint Infections

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And all this science

I don't understand.

It's just my job five days a week.

Elton John "Rocket Man"

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Original papers

I. Lam A, Rasmussen M, **Thompson O**. Successful outcome for patients with streptococcal prosthetic joint infections – a retrospective population-based study. *Infect Dis (Lond.)*. 2018;50(8):593-600. doi:10.1080/23744235.2018.1449961

II. **Thompson O**, Rasmussen M, Stefánsdóttir A, Christensson B, Åkesson P. A population-based study on the treatment and outcome of enterococcal prosthetic joint infections. A consecutive series of 55 cases. *J bone Jt Infect*. 2019;4(6):285-291. doi:10.7150/jbji.35683

III. **Thompson O**, W-Dahl A, Lindgren V, Gordon M, Robertsson O, Stefánsdóttir A. Similar periprosthetisc joint infection rates after and before a national infection control programme: a study of 45, 438 primary total knee arthroplasties. *Acta Orthop.* Epub 2021 Sep 17. doi: 10.1080/17453674.2021.1977532

IV. **Thompson O**, W-Dahl A, Stefánsdóttir A. Increased short- and long-term mortality amongst patients with periprosthetic knee joint infections. [Submitted] 2022.

Thesis at a glance

	QUESTION	METHODS	RESULTS	CONCLUSIONS
I	What is the treatment outcome of streptococcal PJI? Is DAIR an adequate treatment option in streptococcal PJI?	Retrospective analysis of 83 cases in Skåne 2011-2015.	Cure was achieved in 89% of cases. When DAIR treatment was primarily chosen, cure was achieved in 84% of cases.	The success rate for streptococcal PJI is high. DAIR treatment is an adequate option in selected cases.
II	What is the treatment outcome of enterococcal PJI?	Retrospective analysis of 55 cases in Skåne 2011-2015.	Overall cure rate was 67%. When cure was intended this was achieved in 80% of cases.	Prognosis for enterococcal PJI is not so poor when cure is intended
III	What is the incidence of PJI within 2 years of primary TKA? Did PRISS reduce the incidence of PJI after primary TKA?	Linking of the national Swedish registers SKAR and SPDR. Review of medical records.	Cumulative incidence of PJI was 1.44% before PRISS and 1.46% after PRISS.	Similar incidence rates of PJI before and after PRISS
IV	Is PJI within 90 days of primary TKA associated with an increased mortality rate? Have morality rates been affected by changes in treatment practices?	Patients from paper III with PJI within 90 days of primary TKA compared to patients without PJI regarding mortality.	Mortality rates at 1 and 5 years were 2.6% and 15.7% for patients with PJI and 0.8% and 7.1% for patients without PJI. Mortality rates were similar across treatment methods.	Patients with PJI have an increased mortality rate compared to patients without PJI. Treatment strategy had no apparent effect on mortality.

Abbreviations

AAHKS	American association of hip and knee surgeons
ALBC	Antibiotic loaded bone cement
ASA	American society for anesthesiologists
BMI	Body mass index
CFU	Colony forming units
CI	Confidence interval
CoNS	Coagulase negative staphylococci
CRP	C-reactive protein
DAIR	Debridement, antibiotics, and implant retention
EBJIS	European bone and joint infection society
FDG	Fluor-deoxy-glucose
GBS	Group B streptococcus
Hb	Haemoglobin
HPF	High power fields
HR	Hazard Ratio
ICM	International consensus meeting
IDSA	Infectious disease society of America
IL-6	Interleukin-6
LAF	Laminar air flow
LE	Leukocyte esterase
MBBC	Minimum biofilm bactericidal concentration
MBEC	Minimum biofilm eradication concentration

MIC	Minimum inhibitory concentration
MRSA	Methicillin resistant *Staphylococcus aureus*
MSIS	Musculoskeletal infection society
OA	Osteoarthritis
OR	Operating room
PET	Positron emission tomography
PJI	Periprosthetic joint infection
PMMA	Polymethyl methacrylate
PMN	Polymorphonuclear cells
PRISS	Prosthesis related infections shall be stopped
RCT	Randomized controlled trial
SAB	Staphylococcus aureus bacteraemia
SD	Standard deviation
SHAR	Swedish hip arthroplasty register
SKAR	Swedish knee arthroplasty register
SPDR	Swedish prescribed drug register
THA	Total hip arthroplasty
TKA	Total knee arthroplasty
VRE	Vancomycin resistant enterococci
WBC	White blood cells

Introduction

The ability to substitute a damaged joint with a mechanical prosthesis is a major medical achievement that enables vast improvements in quality of life through increased mobility and pain reduction.

The introduction in the late 1950s of polymethyl methacrylate (PMMA, bone cement) as fixation and of high-density polyethylene as a bearing surface paved the way for the modern era of arthroplasty. Beginning in 1962, with the pioneer hip replacement innovations by Charnley, and continuing through the 1970s, with a furious development of different knee prostheses, joint replacement procedures have helped millions of people worldwide.[1,2]

Osteoarthritis is the dominating indication for arthroplasty and has been for many years, comprising ~65% of hip and ~97% of knee arthroplasties. Fracture treatment is the second leading cause for hip arthroplasty (~26%), and for this reason the incidence of hip arthroplasty is somewhat higher than knee arthroplasty (146 vs. 114 per 100,000 inhabitants in 2020).[3] Other indications for arthroplasty, including inflammatory joint disease, post traumatic osteoarthritis, osteonecrosis, and tumours, make up only a minor part of the implants.

It is projected that the ageing population and obesity epidemic will increase the incidence and prevalence of osteoarthritis leading to a continued increase in the need for arthroplasty, possibly reaching a plateau in the coming decade.[4-6] Estimates point towards 40,000 total hip and knee arthroplasties annually in Sweden (Figure 1) and more than 4 million in the USA by 2030.[4,5,7]

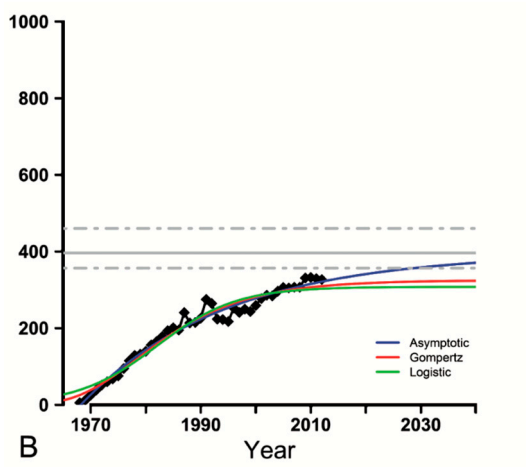

Figure 1. Recorded and projected incidence of total hip arthroplasty per 10^5 Swedish residents aged 40 years or older, 2013-2030. From Nemes et al. 2014.[4] Licensed under CC BY-NC 4.0. For more information see https://creativecommons.org/licenses/by-nc/4.0/. Available at https://doi.org/10.3109/17453674.2014.913224

As with all surgery, complications do occur. The leading cause for revision surgery within 2 years of implantation is deep infection involving the prosthesis. Other reasons for revision surgery include aseptic loosening, instability (knee) and dislocation (hip).[3]

Periprosthetic joint infections

Introduction, epidemiology & magnitude of the problem

Periprosthetic joint infection (PJI) has been a dreaded complication since arthroplasty was introduced in the 1960s. Initial infection rates were high and treatment options were often limited to complete removal of the implant combined with long courses of antibiotics.[8]

Infection control measures have therefore been an important part of arthroplasty since the beginning. Early focus on the environment in the operating room (OR) have developed into the rigorous holistic approach employed today, aiming at optimization of all components of patient care. Routines now include patient selection, optimization of medical conditions, skin care, preoperative preparation, choice and timing of prophylactic antibiotics, operative procedures, operating room environment, postoperative care, wound dressing, follow up and early contact in cases of suspected infection. With these measures infection rates have dropped and are estimated at 0.5-1.6%.[9-15] Incidence rates of PJI are, however, difficult to estimate. Variations in definition, diagnosis and lack of systematic registrations contribute to the uncertainty of estimates. Arthroplasty registers, often focusing on revisions, have been shown to underestimate infection rates since not all PJIs are subjected to revision surgery and not all revisions are reported.[11,16] Recent reports have indicated rising trends of PJI incidence,[15,17,18] but adequate surveillance is lacking.

However, with a projected continued increase in the number of arthroplasties, the total number of prosthesis related infections are also expected to rise.[7,19,20] Given the high cost for an infected arthroplasty this will put financial strain on health care systems. Septic revisions are estimated to cost 2.5-4 times as much as primary surgery or revision for other causes,[21,22] and with estimated increases in PJI volumes this is projected to cost $1.85 billion per year in the USA alone (Figure 2).[19] Prevention of PJI is considered the main realistic option for cost reduction and would of course also benefit patients through subsequent reductions in morbidity and mortality.[20,21]

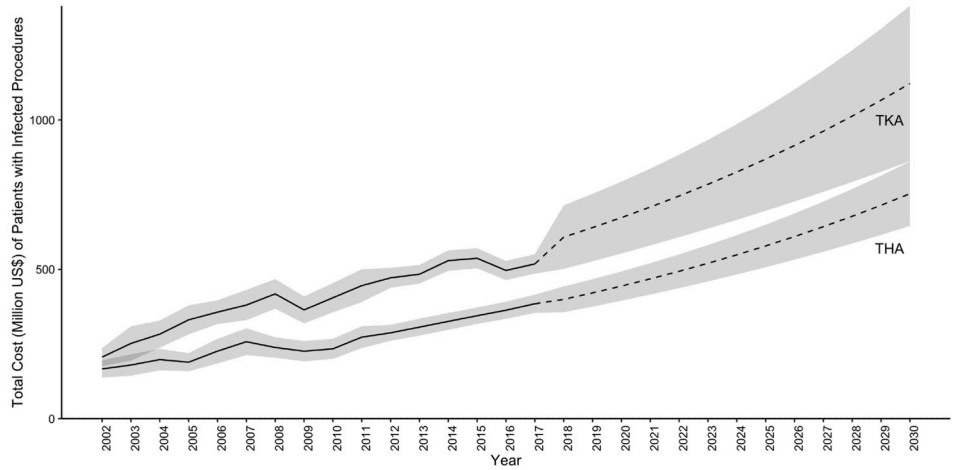

Figure 2. Historical and projected cost of PJI-related revision THA and TKA in the USA 2002-2030. The dashed lines represent projected cost and the shaded area represent the 95% CIs. PJI, periprosthetic joint infection; THA, total hip arthroplasty; TKA, total knee arthriplasty. From Premkumar 2021. [19] Reprinted with permission from Elsevier. Available at https://doi.org/10.1016/j.arth.2020.12.005.

Diagnosis

Clinical signs

The clinical picture associated with PJI is highly variable and dependent on several factors such as the virulence of the causing agent, the type of joint, duration of infection (early, delayed, late), and the immunological status of the host. Clinically, a few different syndromes are identified, depending on the route of acquisition (exogenous or haematogenous) and virulence of the infecting organism.

Exogenous acquisition can occur during surgery by contamination of the implant or the exposed surfaces of the wound, or in the immediate postoperative period before wound closure. In acute postoperative infections local inflammatory signs (erythema, delayed wound healing, wound discharge) dominate the picture, whereas high fever and systemic inflammation is less frequent.[23] Chronic PJI generally originates from perioperative inoculation of low-virulent bacteria such as coagulase negative staphylococci (CoNS) and *Cutibacterium acnes*, causing slowly developing symptoms that are easily missed. Clinical signs are chronic pain and joint stiffness. Signs of implant loosening can be visible on the x-ray. Spontaneous drainage through a sinus

tract communicating with the joint is not seldomly seen. Systemic inflammatory markers, like erythrocyte sedimentation rate (ESR), can be slightly elevated.

Haematogenous PJI can occur at any time, even years, after implantation. Beyond the postoperative period, PJI with acute onset usually originates from haematogenous seeding. Symptoms are characterized by severe joint pain, frequently accompanied by fever, and elevated systemic inflammatory markers (C-reactive protein, white blood cell count).[23-25] Bacteria of low virulence, i.e., viridans streptococci, can also cause haematogenous PJI, though usually with a slow chronic development.

Clinical classification

An earlier classification system, based on pathogenesis, classified infections as early (exogenous perioperative seeding of high virulent bacteria) within 3 months, delayed (exogenous perioperative seeding of low virulent bacteria) between 3-24 months and late (hematogenous seeding of bacteria) if more than 24 months had passed from implantation.[26] This classification has now been replaced to better harmonize with recommendations for clinical management. Classification of PJI is presently done with special focus on symptom duration which is used as a surrogate marker for biofilm maturation. This allows for differentiation between infections that are possible to cure with debridement and retention of the prosthesis, and infections where implant removal is a prerequisite for cure.[27]

- *Early postoperative PJI*: Manifestation of infection within 1 month of implantation.
- *Chronic PJI*: Symptom duration >3 weeks.
- *Acute hematogenous PJI*: Symptom duration <3 weeks beyond the postoperative period in a previously well-functioning implant.

Hematogenous PJI is predominantly associated with *S. aureus* bacteraemia (SAB), with a risk of 20-40% of developing PJI, particularly during the first year after implantation and when SAB is community acquired.[25,28,29]

Definitions of PJI

Accurate diagnosis of PJI is a clinical challenge. This is illustrated by the many different diagnostic definitions that have been developed during the last decade. Definitions are partly overlapping but differ in the inclusion and evaluation of available diagnostic tests. No definition has yet been unanimously adopted by clinicians and researchers as the

gold standard. The fact that many infections are caused by commensal skin flora, in other circumstances often interpreted as contamination, coupled with the existence of culture negative PJI can cause substantial headache for the clinician. There is also much at stake, with treatment being both expensive, resource demanding and cumbersome. Many of the clinically problematic situations arise in patients with a possible chronic, low grade PJI, where signs and symptoms are less prominent. Differentiating between infection and no infection in these cases often involves deciding whether to remove the prosthesis or not. This decision has grave consequences for the patient and as no single test can clarify these situations, several scoring systems have been developed by different organizations, using a combination of clinical findings, biochemical tests, microbiology, and radiology (summarised in Table 1 and Figure 3). All the definitions have their own inherent weaknesses and, for the most part, lack validation.

Table 1. Definitions of PJI according to different criteria. Adopted from Parvizi 2011, Osmon 2013, Parvizi 2014, Shohat 2019.[30-33]

MSIS 2011	IDSA 2012	ICM 2013	ICM 2018
≥ 1 Major criterion **OR** 4/6 Minor criteria	≥1 Criteria	≥1 Major criterion **OR** 3/5 Minor criteria	≥ 1 Major criterion **OR** ≥6 p = Definitive PJI 3-5 p = Possible PJI <3 p = Not PJI
Major: 1. Sinus tract 2. ≥2 positive cultures* Minor: 1. ESR > 30mm/h AND CRP > 10mg/L 2. Elevated synovial WBC 3. Elevated synovial PMN% 4. Purulence in the affected joint 5. 1 positive culture* 6. Histology ≥ 5 neutrophils in ≥ 5 HPF	1. Sinus tract 2. Purulence surrounding the prosthesis 3. Histology with acute inflammation 4. ≥2 positive cultures*	Major: 1. Sinus tract 2. ≥2 positive cultures* Minor: 1. Elevated CRP **AND** ESR 2. Elevated synovial WBC **OR** positive LE 3. Elevated synovial PMN% 4. Histology >5 neutrophils per HPF 5. 1 positive culture*	Major: 1. Sinus tract 2. ≥2 positive cultures* Minor: 1. Elevated serum CRP **OR** D-dimer (2p) 2. Elevated ESR (1p) 3. Elevated synovial WBC **OR** positive LE **OR** positive alpha defensin (3p) 4. Elevated synovial PMN% (2p) 5. Elevated synovial CRP (1p) 6. 1 positive culture* (2p) 7. Positive histology (3p) 8. Purulence (3p)

ESR, Erythrocyte Sedimentation Rate; CRP, C-reactive protein; WBC, White blood cell count; PMN%, Percentage polymorphonuclear cells; HPF, High-power fields (magnification x 400); LE, Synovial leukocyte esterase test; PJI, Periprosthetic joint infection; *Sterile cultures from synovial fluid or per-operative tissue biopsies.

The Musculoskeletal Infection Society (MSIS) published a first set of criteria in 2011,[30] using a scoring system with "Major" and "Minor" criteria akin to the Duke's criteria used for infective endocarditis. The proposed definition was intended as a gold standard for clinical use, surveillance, and research purposes. The MSIS definition acknowledge that PJI may be present even if minor criteria are not met. This definition

has been widely used in research publications but suffer from a lack of sensitivity of low-grade infections.

In 2013 the Infectious Disease Society of America (IDSA) published their set of guidelines on PJI,[31] including a new set of diagnostic criteria and subsequent treatment recommendations. Although easy to use, these criteria had low precision, relied heavily on intra-operative findings, and did not provide substantial guidance in clinically tricky situations.

The International Consensus Meeting on orthopedic infections (ICM) in 2013 assembled many delegates from different countries, including orthopaedic surgeons, microbiologists, and infectious disease specialists. Many topics were discussed, and a revised version of the MSIS criteria received support from 85% of delegates.[32,34] In 2018, during the second ICM convention, a new scoring system was proposed but received only 68% support from attendees.[33] An attempt at validation of these criteria, with comparisons of MSIS and ICM 2013-definitions was published in 2018.[35] In this validation the ICM 2018 definition reached a sensitivity of 97.7% vs. 79.3 for the MSIS and 86.9% for the ICM 2013 definitions. Specificity was 99.5% for all three definitions.

The latest addition to the flora of diagnostic criteria is the European Bone and Joint Infection Society (EBJIS) definition, published in 2021(Figure 3).[36] The EBJIS fit a new system, based on previous literature, that uses a "traffic light" approach with three possible outcomes: PJI confirmed, PJI likely or PJI unlikely. This definition acknowledges the difficulty in making a definitive diagnosis in the clinical situation. The EBJIS definition remains to be validated.

From a scientific standpoint, the lack of a widely accepted diagnostic standard precludes comparison between studies, procedures, and outcomes. Evaluation of algorithms for diagnosis and treatment has also been hampered by this lack.

For the clinician, the overriding priority is for diagnostic criteria to be helpful in clinical day to day decision making. Tests that are readily available, easy to interpret and accurately identifies infected cases without overdiagnosing infection are therefore important.

	Infection Unlikely (all findings negative)	Infection Likely (two positive findings)[a]	Infection Confirmed (any positive finding)
Clinical and blood workup			
Clinical features	Clear alternative reason for implant dysfunction (e.g. fracture, implant breakage, malposition, tumour)	1) Radiological signs of loosening within the first five years after implantation 2) Previous wound healing problems 3) History of recent fever or bacteraemia 4) Purulence around the prosthesis[b]	Sinus tract with evidence of communication to the joint or visualization of the prosthesis
C-reactive protein		> 10 mg/l (1 mg/dl)[c]	
Synovial fluid cytological analysis[d]			
Leukocyte count[c] (cells/µl)	≤ 1,500	> 1,500	>3,000
PMN (%)[c]	≤ 65%	> 65%	> 80%
Synovial fluid biomarkers			
Alpha-defensin[e]			Positive immunoassay or lateral-flow assay[e]
Microbiology[f]			
Aspiration fluid		Positive culture	
Intraoperative (fluid and tissue)	All cultures negative	Single positive culture[g]	≥ two positive samples with the same microorganism
Sonication[h] (CFU/ml)	No growth	> 1 CFU/ml of any organism[g]	> 50 CFU/ml of any organism
Histology[c,i]			
High-power field (400x magnification)	Negative	Presence of ≥ five neutrophils in a single HPF	Presence of ≥ five neutrophils in ≥ five HPF
			Presence of visible microorganisms
Others			
Nuclear imaging	Negative three-phase isotope bone scan[c]	Positive WBC scintigraphy[j]	

Summary Key

a. Infection is only likely if there is a positive clinical feature or raised serum C-reactive protein (CRP), together with another positive test (synovial fluid, microbiology, histology or nuclear imaging).

b. Except in adverse local tissue reaction (ALTR) and crystal arthropathy cases.

c. Should be interpreted with caution when other possible causes of inflammation are present: gout or other crystal arthropathy, metallosis, active inflammatory joint disease (e.g. rheumatoid arthritis), periprosthetic fracture, or the early postoperative period.

d. These values are valid for hips and knee periprosthetic joint infection (PJI). Parameters are only valid when clear fluid is obtained and no lavage has been performed. Volume for the analysis should be > 250 µL, ideally 1 ml, collected in an EDTA containing tube and analyzed in <1h, preferentially using automated techniques. For viscous samples, pre-treatment with hyaluronidase improves the accuracy of optical or automated techniques. In case of bloody samples, the adjusted synovial WBC= synovial WBC $_{observed}$ – [WBC $_{blood}$ / RBC blood x RBC $_{synovial\ fluid}$] should be used.

e. Not valid in cases of ALTR, haematomas, or acute inflammatory arthritis or gout.

f. If antibiotic treatment has been given (not simple prophylaxis), the results of microbiological analysis may be compromised. In these cases, molecular techniques may have a place. Results of culture may be obtained from preoperative synovial aspiration, preoperative synovial biopsies or (preferred) from intraoperative tissue samples.

g. Interpretation of single positive culture (or < 50 UFC/ml in sonication fluid) must be cautious and taken together with other evidence. If a preoperative aspiration identified the same microorganism, they should be considered as two positive confirmatory samples. Uncommon contaminants or virulent organisms (e.g. *Staphylococcus aureus* or Gram negative rods) are more likely to represent infection than common contaminants (such as coagulase-negative staphylococci, micrococci, or *Cutibacterium acnes*).

h. If centrifugation is applied, then the suggested cut-off is 200 CFU/ml to confirm infection. If other variations to the protocol are used, the published cut-offs for each protocol must be applied.

i. Histological analysis may be from preoperative biopsy, intraoperative tissue samples with either paraffin, or frozen section preparation.

j. WBC scintigraphy is regarded as positive if the uptake is increased at the 20-hour scan, compared to the earlier scans (especially when combined with complementary bone marrow scan).

Figure 3. The European Bone and Joint Infection Society (EBJIS) criteria for suspected periprosthetic joint infection. From McNally 2021.[36] Reprinted with permission from the authors. Available at https://doi.org/10.1302/0301-620X.103B1.BJJ-2020-1381.R1

Some common ground between definitions can be detected: all agree that a sinus tract communicating with the prosthesis is evidence of infection, as are ≥2 positive cultures from periprosthetic tissue or synovial fluid (although most also agree that growth in a single specimen of a highly virulent bacteria, such as *S. aureus*, should be regarded as an infection). Histology consistent with acute inflammation, generally defined as ≥5 neutrophils per high power field (x400 magnification) is also regarded as pathognomonic but is not routinely performed in Sweden, possibly due to lack of pathologists. Other tests are valued slightly differently between definitions and cut-offs for inflammatory markers (e.g., CRP and synovial WBC) differs.

Biomarkers

Arthrocentesis of the affected joint is recommended in all diagnostic algorithms. This allows for synovial fluid to be sent for leukocyte count, microbial cultures, and PCR-analysis as well as analysis of several biomarkers. I will briefly describe a few of the biomarkers having been of interest in recent years. It is important to note that sensitivity and specificity calculations are highly dependent on the standard against which it has been measured. In many cases the MSIS PJI definition have been used (with a known lack of sensitivity in itself), but others have used local definitions, culture positivity or the level of some other biomarker as a reference. This makes comparison of available data quite difficult.

Table 2 Sensitivity of synovial biomarkers for PJI. Adapted from Lee 2017.[37]

Synovial test	Sensitivity, % (95% CI)	Specificity, % (95% CI)
CRP	85 (78-90)	88 (78-94)
Leukocyte count (WBC)	89 (86-81)	86 (80-90)
PMN%	89 (82-93)	86 (77-92)
Alpha defensin	97 (93-99)	96 (94-98)
Leukocyte esterase	77 (63-87)	95 (86-98)
IL-6	81 (70-89)	94 (88-97)
Culture	62 (50-74)	94 (91-96)

CRP, C-reactive protein; PMN%, percentage polymorphonuclear cells; IL-6, interleukin-6

C-reactive protein (CRP) is an acute-phase protein produced in the liver. Serum-CRP is a standard biomarker for systemic inflammation, not specific for infection. In low-grade infections the serum-CRP levels may be normal, and an elevated level is not in itself evidence of PJI.[38] It has, however, been suggested that a serum-CRP >10 mg/l

is sufficiently specific for infection if no other cause for inflammatory activation is present (e.g., inflammatory joint disease, gout, early post-operative period).[36,38-41]

Since CRP functions as an activator of the complement system, increased levels at the inflammatory site, compared to systemic levels, would be expected. Synovial CRP has been evaluated for PJI in several studies and has high sensitivity and specificity.[42-45] Concordance with serum levels is, however, also high, why the additional value of synovial CRP is questionable.

The *synovial leukocyte count* (WBC, white blood cell count) and percentage polymorphonuclear cells (PMN%) have been thoroughly studied in the PJI setting, [45-49] and is included in most diagnostic definitions. Established cut-off values for WBC fall between 1,500 and 3,000 cells/μL for chronic PJI and >10,000 cells/μL for acute PJI.[30,34,36] A PMN% >65% is suggestive of infection[46,48] and a level of >80% is considered definitive evidence of infection in the EBJIS definition.[36] Inflammatory joint disease and other inflammatory conditions, such as crystal arthropathy, may also increase the synovial WBC, which necessitates clinical judgement in these situations.[36] Although generally considered reliable, the studies validating synovial WBC and PMN% were done using manual cell counts. Automated cell counters may perform less well in the PJI setting, which has raised concern over the risk of overdiagnosing infections with automatic systems.[50]

Leukocyte esterase is an enzyme secreted by activated neutrophils. It is used in everyday care on urine samples to demonstrate the presence of neutrophils in urinary tract infections. The test is easily performed with a simple and cheap colorimetric test strip. Its usefulness in the diagnosis of PJI has been evaluated in several studies with sensitivity ranging from 66% to 93% and specificity from 81% to 100%.[51-54] If blood is present in the synovial fluid the test strip can become unreadable, which hampers its usefulness. By centrifuging the sample before analysis this can be overcome, though possibly affecting sensitivity.[55]

Alpha-defensin is an antimicrobial peptide secreted by neutrophils and macrophages with activity against bacteria and fungi. The level of alpha-defensin can be measured through an ELISA (enzyme-linked immunosorbent assay) or qualitatively through a lateral flow test. Reports have demonstrated high levels of sensitivity (97% to 100%) and specificity (85% to 100%) for the ELISA in hip and knee PJI.[41,54,56-58] The lateral flow test has lower sensitivity (54%-84%) while maintaining high specificity (>95%), possibly making it more suitable as a confirmatory test.[41,59,60] A possible role for alpha-defensin could also be in cases where antibiotics have been administered since this does not seem to affect the sensitivity of the test.[57] Price is an issue with

the alpha-defensin analysis since test kits are expensive compared to some of the other available tests.

Interleukin-6 (IL-6) is a cytokine produced by macrophages and monocytes to stimulate the immune response. It is an unspecific marker of inflammation and has been evaluated for PJI diagnosis in both serum and synovial fluid. No optimal cut-off levels have been determined and there is considerable variability between publications. In serum sensitivity ranges from 49% to 97% and specificity from 58% to 91%.[61-63] In synovial fluid sensitivity ranges between 60% to 90% and specificity from 86% to 100%.[56,62,64,65]

Histopathology

Frozen or paraffin section histopathology on perioperative tissue biopsies is used internationally and considered a valuable part of the diagnostic work-up in PJI. Acute inflammation in the tissue is highly specific for PJI, though sensitivity is lower.[66] Different cut-offs have been proposed, the most common being ≥ 5 neutrophils in 5 high power fields (HPF; x400 magnification). Sensitivity may benefit from a lower threshold or by the use of histochemistry for better detection of neutrophils.[67] The use of histopathology is dependent on trained pathologists, which is a lacking resource in Sweden. It is, therefore, not routinely used.

Imaging

A plain radiograph of the affected joint is always recommended as a first line diagnostic procedure to visualize the state of the implant, signs of prosthetic loosening or other problems such as fractures.[68] Early radiographic abnormalities of the implant is more often caused by an infection than late abnormalities.[69]

Other imaging techniques are of less clear value. Three-phase bone scintigraphy depicts osteoblast activity. Any type of bone remodelling will therefore show on the scan, such as post-operative bone formation or aseptic loosening, reducing its usefulness within 2-5 years of implantation. A negative bone scintigarphy, however, has a high negative predictive value.[68] White blood cell (WBC) scintigraphy is of higher value in the first few years after implantation, where a positive result is suggestive of infection, especially if combined with a bone marrow scintigraphy. WBC scintigraphy also has a high negative predictive value.[70] Fluor-deoxy-glucose positron emission tomography (FDG-PET) has unclear diagnostic value at this point since standardized criteria for interpretation are lacking in the setting of PJI.[68]

Cultures

Microbiologic sampling is a cornerstone in the diagnostic work-up and positive cultures remain a major criterion in most definitions. Cultures from both synovial fluid and tissue are recommended. Drago, et al. recently published a summary of procedures for microbiological sampling.[71] Culture results and antimicrobial susceptibility testing are also essential for adequate antibiotic treatment.

Synovial fluid collection is done by sterile arthrocentesis of the affected joint, guided by ultrasound or x-ray if needed. Culture of synovial fluid in aerobe and anaerobe blood-culture bottles increase both sensitivity and specificity compared to conventional agar.[72] If the obtained volume is small (1-3 ml) a paediatric blood-culture bottle is suitable. A negative synovial fluid culture does not exclude PJI, but a positive finding is highly suggestive of infection.[73,74] Concordance with per-operative tissue cultures can be poor, especially for low-virulent bacteria and chronic infections why judicious interpretation of the results is necessary. [75]

Tissue cultures can be obtained preoperatively through percutaneous tissue biopsy or, more frequently, during surgery. Percutaneous biopsies do not have better sensitivity and specificity than synovial fluid culture [41] and are, therefore, not generally recommended. In select cases with unclear diagnoses, dry synovial punctures or negative synovial cultures, this modality can, however, be useful.

Collection of periprosthetic tissue biopsies per-operatively is recommended in all algorithms for diagnosis and treatment of PJI. Tissue specimens should be obtained from areas with macroscopic signs of inflammation and each biopsy taken with a new set of clean instruments.[71] 5 biopsies has been the standard since 1981, when Kamme and Lindberg described their method for PJI diagnosis in hip arthroplasty revisions,[76] though later authors claim that 4 biopsies produces optimal balance between sensitivity and specificity.[77,78] Inoculation of tissue in blood culture bottles improves sensitivity and detection time compared to conventional agar and broth media.[79] Incubation times of 5-7 days for aerobic and 14 days for anaerobic cultures are recommended.[71]

Sonication of explanted prosthetic material can increase the chance of a positive culture, particularly in chronic infections and when prior antibiotics have been administered.[80] Sonication is performed to disrupt the biofilm on the prosthetic surface, dislodging adherent bacteria and enable cultivation. The explanted material is submerged in fluid in an ultrasound bath and the resulting fluid is then cultured, with or without preceding centrifugation. Due to the risk of contamination of the prosthesis during explantation quantitative evaluation of sonication cultures is recommended. A

cut-off of >50 colony forming units (CFUs) per millilitre of (non-concentrated) sonication fluid has been proposed as evidence of infection.[36]

Microbiology

In most cases bacteria are responsible for PJI. Gram-positive bacteria dominate, with staphylococci being the predominant genus. *S. aureus* and CoNS can be found in 55-60% of all PJIs, with *S. aureus* being more prevalent in early and haematogenous infections. *Enterococcus* species and *Streptococcus* species are both found in 8-14% and enterobacterales in 4-10% of PJIs. Among anaerobes *Cutibacterium acnes* (formerly *Propionebacterium acnes*) is the most common species, isolated in 4-8% of infected arthroplasties.[16,81,82] Polymicrobial infections account for 19-31% of PJIs and are more common in the early postoperative period.[83] Culture negative cases are found in some 5%.[81] As for most other infections, differences in microbiological pattern exist between countries, primarily regarding antimicrobial resistance.[84] In Sweden pronounced antimicrobial resistance is rare with a very low frequency of methicillin resistant *S. aureus* (MRSA). Methicillin resistance is, however, common in CoNS and has been increasing since the 1980s.[82] Fungal PJI, although unusual, accounts for 0.2-2% of PJIs, usually involving *Candida* species.[85]

Staphylococci

Staphylococci are aerobic Gram-positive bacteria that are part of the normal flora of the human skin. Clinically staphylococci are grouped depending on coagulase production. *S. aureus* is the only pathogen in the coagulase positive group. *S. aureus* is highly virulent and a frequent cause of many types of invasive disease, such as skin- and soft tissue infections, endocarditis, blood stream infections and osteomyelitis. In Sweden some 30% are susceptible to penicillin and the rate of methicillin resistance is low.[86,87] The CoNS consists of many different species with less virulence than *S. aureus*. They are most often nosocomial pathogens associated with a compromised host or a foreign material, such as intravascular catheters or orthopaedic implants.[88] Species identification has become widely available in recent years through matrix-assisted laser desorption ionization time of flight (MALDI-TOF). *S. epidermidis* is the CoNS responsible for most PJIs, with other species such as *S. caprae*, *S. simulans* and *S. capitis* also represented.[89] *S. epidermidis* are frequently resistant to multiple antibiotics and have the ability to form biofilm.[90] *S. lugdunensis* is a CoNS with clinical traits resembling those of *S. aureus* being increasingly recognized as a cause of PJI.[91]

Streptococci

Commensal colonisers of the human oral cavity and gastrointestinal tract, streptococci are Gram-positive, facultative anaerobic bacteria. Taxonomy is complex and traditional clinical division is done by visual assessment of the haemolytic ability into α and β-haemolytic strains. β-haemolytic streptococci are further characterized by surface antigens into Lancefield groups A-G. Lancefield groups are still relevant in clinical practice although species determination is standard procedure nowadays. *S. pyogenes* (group A streptococci, GAS) is highly virulent, being responsible for severe infections such as necrotizing fasciitis. *S. dysgalactiae* subsp. *equisimilis* (group C or G streptococci, GCS/GGS), is closely related to *S. pyogenes* and produce similar clinical entities.[92] *S. agalactiae* (group B streptococci, GBS) are commensals of the female genital tract, though carriage among elderly of both sexes is also common.[93] GBS is a dreaded cause of neonatal sepsis but also cause invasive disease in adults.[94] It is also the most commonly isolated streptococcal species in PJI and has been associated with poor outcome.[95,96] α-haemolytic streptococci, sometimes referred to as viridans group streptococci (VGS), are diverse and contain many different species that are important causes of dental caries and endocarditis.[97] Streptococci are generally highly susceptible to penicillin, with exceptions primarily among VGS species *S. mitis* and *S. salivarius.*[98]

Enterococci

Enterococci are Gram-positive facultative anaerobe commensals of the human intestine, normally constituting a minor proportion of the gut microbiome. Exposure to antibiotics, however, facilitates enterococcal colonization. Enterococci tolerate harsh conditions and a wide range of temperatures. They can survive on surfaces for long times and frequently colonize the hospital environment.[99] Nosocomial spread of enterococci is an increasing problem internationally and enterococci are second only to staphylococci as aetiologic cause of catheter related blood stream infections.[88]

Two enterococcal species are responsible for most of the clinical infections, *E. faecalis* and *E. faecium*. Enterococci have natural resistance to several common antibiotics such as penicillin, cephalosporins and clindamycin. *E faecalis* is generally susceptible to ampicillin but *E. faecium* often displays extensive antimicrobial resistance. An increasing nosocomial problem is vancomycin resistant enterococci (VRE), where very limited treatment options remain.[100]

Biofilm

The formation of bacterial biofilm is an important part of biomaterial associated infections such as PJI. The biological properties of bacteria living in a biofilm differ substantially from the properties of planktonic bacteria. Knowledge of these properties is essential to the understanding of foreign body infections such as PJI. Though we have ample reason to believe that *in vitro* biofilms behave quite differently from biofilms in the complex *in vivo* environment, laboratory studies have given many clues on formation of biofilms and specific properties of the inhabiting bacterial colonies. Specifics of the biofilm formation process are species dependant and much of the complexity remains to be investigated. Though simplified, the process is generally described in four steps. *First*, bacterial inoculates not immediately killed by the host immune response passively adhere to the foreign body surface through non-specific electrochemical forces, like hydrophobicity, and active attachment through specific adhesins. *Second*, bacteria proliferate and accumulate in multiple layers attached to each other and switch to the biofilm phenotype, producing a protective extracellular matrix. *Third*, maturation of the biofilm ensues where the surrounding matrix thickens. Tolerance to antimicrobials increase due to impaired diffusion through the matrix and differentiated physiological activity of the microbes, leading to reduced metabolic activity in the deep layers and the development of dormant bacteria, so called persister cells.[101,102] Mature biofilms are complex environments where microbes can take on properties similar to multi-cellular organisms. Signalling peptides mediate cell-cell communication, "quorum sensing", that control the size and proliferation of the bacterial population. In the *fourth*, and final, stage dispersion of the biofilm is induced, leading to detachment of bacterial colonies ready to re-enter the planktonic phase and restart the process.[103] Neutrophils seem unable to penetrate an established biofilm, rather surrounding it, giving rise to a chronic inflammatory response.[102] It has also been suggested that granulocyte function is impaired in the presence of a foreign material decreasing their killing ability.[104]

The time it takes for a mature biofilm to form is not completely understood. Simple methods to assess biofilm formation and maturation in clinical practice are lacking. Therefore, this is not routinely done. In clinical studies a rapid decline in success rate with implant retention after more than 3-4 weeks of infection has been seen.[105,106] This is possibly dependant, at least in part, on the maturation process of the bacterial biofilm. Time is therefore used as a crude proxy for biofilm maturation in clinical practice and is an essential component of the clinical evaluation.

Management

General considerations

Early diagnosis and successful outcome of the first treatment intervention are important components of PJI management. Since diagnosis is challenging, early referral to a specialized centre with a multidisciplinary team is recommended.[107] Failed treatment increases the risk of damage to bone and soft tissues, aggravating the integrity of the joint and leading to decreased chances of cure and a worse functional outcome.[27,108]

Resolution of the infection always requires treatment with a combination of surgery and antibiotics. A multidisciplinary approach is therefore key to finding the best treatment for the individual patient, taking different aspects of the problem into account: status and stability of the implant and surrounding soft tissue, virulence and antimicrobial susceptibility of the infecting microorganism, over-all health, and preference of the patient. In most cases, the treatment goal is to cure the infection, although sometimes, only keeping it in check is the appropriate strategy. Cure is not a realistic option for all patients, why clinicians need to determine whether a curative or palliative strategy is the appropriate choice for the individual patient.

Outcome

In the clinical situation cure can mean very different things to different patients. This means tailoring the best suited treatment to reach that individual goal for each patient.

Defining cure scientifically is thus not self-evident, and different studies have defined successful outcome in different ways, complicating comparisons. A Delphi-based multidisciplinary expert panel proposed cure after PJI treatment to be defined as:

1) Microbiological and clinical eradication of infection.
2) No subsequent surgical intervention for the same infection.
3) No PJI-related mortality.

However, the dimension of functional outcome was not covered by this definition.[109] The question was discussed at the 2018 international consensus meeting resulting in a complicated recommendation of outcome reporting including functional integrity of the joint.[107] In this thesis PJI-cure has generally been defined as eradication of the infection with a functional prosthesis in place at time of follow up.

Treatment strategies

Surgery, with the goal to remove as much of the infected tissue as possible and to reduce the bacterial load and amount of biofilm is an integral part of PJI treatment. It can be performed as an implant preserving debridement or by exchanging the implant in one- or two stages. Existing recommendations and treatment algorithms are largely based on local practice and expert opinion. [27,31] As a general rule, the least invasive surgical approach that cures the infection should be chosen.

To optimize chances of a correct aetiological diagnosis (which is crucial for successful antimicrobial treatment), antibiotics should be withheld until surgery unless a life-threatening septic condition is present. Prophylactic antibiotics are, however, recommended (in procedures where a prosthesis is retained or implanted) and have a negligible effect on culture yields while protecting the implant from a new infection.[110,111] After surgery systemic antibiotics are administered intravenously awaiting culture results and clinical signs of infection control, normally 1-2 weeks. Oral treatment (if possible) is often started at discharge and continued for 6-12 weeks depending on treatment strategy, which are briefly described below and in Figure 4.

Debridement, antibiotics, and implant retention (DAIR), also referred to as irrigation and debridement (I&D), is recommended in acute early postoperative (<1 month of implantation) and acute hematogenous (symptom duration <3 weeks) PJI if the implant is stable, soft tissues are in good condition (i.e., no fistula or periprosthetic abscess), and the pathogen is susceptible to anti-biofilm antibiotics.[31,112] This procedure enables cure of the infection without removal of the implant. Debridement should be performed through open arthrotomy with thorough removal of all infected and necrotic tissue and followed by irrigation.[113] Exchange of modular parts is associated with better prognosis.[114] Arthroscopic debridement has no place in PJI management and is associated with increased risk of failure.[112,113]

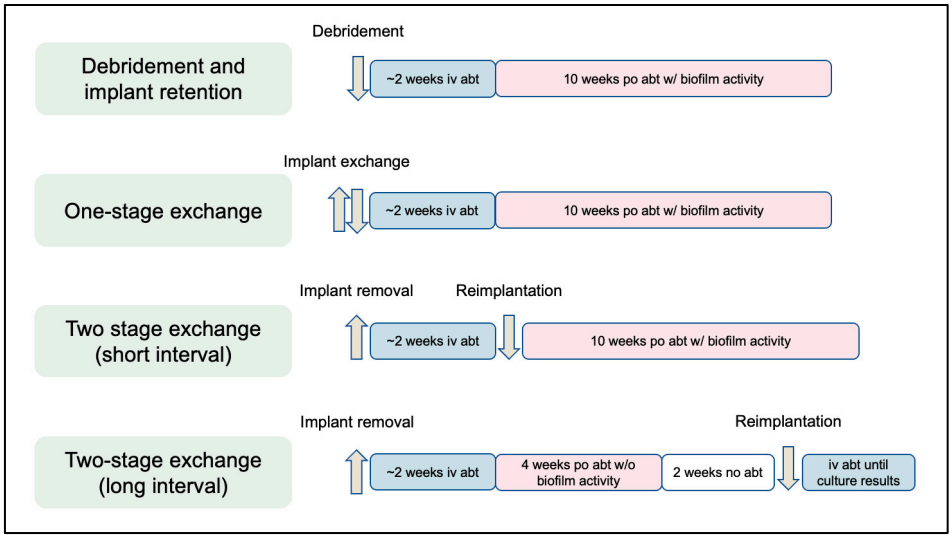

Figure 4. Schematic overview of treatment strategies for PJI. Adapted from Zimmerli 2015.[27]
iv, intravenous; po, per oral; abt, antibiotic therapy; w, with; w/o, without

Time limits for the DAIR strategy are derived from Zimmerlis randomized trial on rifampicin treatment where no patients had symptom durations exceeding 21 days.[105] No comparative studies on extension of the 4-week postoperative time limit exists, though 3 months was previously suggested, with a 4-week limit on symptom duration. [26,115] There is general agreement that debridement should not be delayed (e.g. by waiting for culture results) once reasonable suspicion of the diagnosis has been established.[112] Symptom duration is known to be an important factor for successful outcome and symptom duration >7 days and ≥21 days has been associated with lower infection control rates.[116-118] Symptom duration, however, can be difficult to assess in the immediate postoperative period, where postoperative pain and surgery induced inflammation cloud the picture. It is reasonable to argue that implant age is not the crucial factor, but rather the age of the infection with ensuing tissue damage and maturation of the microbial biofilm. This is supported by observational data showing similar outcomes for DAIR procedures performed within 1 month of implantation compared to 2-3 months. [96,114,119]

After surgical debridement intravenous antibiotics are administered for 1-2 weeks. The aim is to reduce the bacterial load and the number of planktonic bacteria. Initial empiric treatment should provide coverage of known and suspected aetiologies and should be tailored to the culture results as soon as they become available. Switch to oral treatment with biofilm activity is made when the wound is dry and there are clinical signs of infection control. Duration of antibiotic treatment has been an ongoing

discussion for several years. Earlier recommendations of 3 months for hip and 6 months for knee infections lack empirical support.[26,31] Several observational studies have shown similar results with shorter treatment durations[120] and a small Spanish randomized controlled trial (RCT) reported promising results comparing 8 weeks vs. 3-6 months with rifampicin and levofloxacin after DAIR for acute staphylococcal PJI.[121] Most recently, however, a French RCT compared 6 vs. 12 weeks of antibiotics following surgery for PJI and recorded higher failure rates in the 6-week group. The difference was most prominent among DAIR treated patients.[122] In Sweden 12 weeks of total antibiotic treatment is currently recommended and has been for several years.[123]

Outcome after DAIR varies widely between studies and comparisons are difficult due to heterogeneity of patient selection, treatment durations, and outcome definitions. A meta-analysis of observational studies performed between 1983 and 2017 included 4897 PJIs treated with DAIR.[118] They found an over-all pooled success rate of 61.4%, or 75.4% when only including hips and knees. Studies performed before 2000 had lower success rates than later studies. More recent work has demonstrated success rates around 80% for early PJIs treated with DAIR.[119,124-126] Substantially worse success rates, between 46-67%, have recently been reported for late acute (hematogenous) PJIs.[25,127,128]

One-stage exchange of the implant has been locally favoured in some European centres (most notably the Endo-clinic in Hamburg, where 85% of exchange procedures for PJI are done as a one-stage exchange)[129] while being used very little in the USA. Surgically, the method includes extensive debridement of the affected bone and soft tissue, resection of the implant and removal of all bone-cement. After sterile redraping and new instrumentation, reimplantation is performed with the appropriate antibiotic-loaded bone cement.[130] Benefits from only one procedure are earlier return of mobility, as well as reductions in postoperative morbidity and overall cost.[131] In selected patients with chronic PJI of known aetiology and sensitivity to antibiotics with biofilm acting properties or excellent bioavailability, this treatment option has been shown to be a viable alternative.[132] There are, however, no strict exclusion criteria for one-stage exchange, though patients with on-going sepsis, extensive soft tissue or bone damage or PJI due to highly resistant microbes may not be suitable for this strategy.[131] Surgery is followed by antibiotic treatment, preferably with biofilm activity. Evidence is lacking for optimum treatment duration; in Sweden 12 weeks is recommended, though 4-6 weeks may suffice.[122,123,132,133] Success-rates after 1-stage exchange are generally high, being reported to between 88%-94%.[131,134-137]

Two-stage exchange has long been regarded the "gold standard" for treatment of PJI. In this strategy the prosthesis is resected along with all infected tissue and, usually, replaced by a temporary spacer of antibiotic loaded bone cement. After a period of antibiotic treatment, subsequent implantation is performed. Traditionally, duration of antibiotic treatment is 6 weeks, though 4 weeks may be equally effective.[31,138,139] Biofilm active antibiotics are usually not necessary since all foreign materials have been removed surgically. Cessation of antibiotics is followed by a 2 week "drug holiday" before proceeding to reimplantation. The drug holiday is supposed to allow for any residual infection to be captured by tissue cultures taken during reimplantation. Systemic antibiotics (directed towards initial pathogen(s)) are usually administered post-operatively awaiting culture results. If the cultures are negative, treatment is stopped, otherwise directed treatment with biofilm activity is given for an additional 3 months. Evidence supporting the clinical benefit of the drug holiday is lacking,[140] and one study even demonstrated an association with higher rates of relapse compared to continuing antibiotics until reimplantation.[141] Optimal timing for reimplantation has not been determined and inflammatory markers provide little guidance.[142,143] Alternative regimens are also employed, using a short 2-4-week interval between ex- and implantation, followed by 6-12 weeks of biofilm active antibiotics.[26]

Cure rates around 90% or more have been reported for two-stage exchange procedures.[122,136,137,144] This may be an overestimation, since some patients never make it to the second stage, though not reported as failures.[145] The proportion of patients not completing stage two within 12 months of explantation has been reported to be >50%.[146] Controlled trials comparing different surgical treatment strategies for PJI are lacking. Study protocols for two randomized controlled studies comparing one- and two-stage exchange have been published, but no results from these trials have yet been presented.[147,148]

Salvage procedures may be necessary in cases where infection control is otherwise difficult to obtain or when joint preservation does not improve the functional outcome. Resection of the arthroplasty without reimplantation can be performed to enable healing of the infection. In knee-PJI a subsequent arthrodesis will allow weight bearing. Amputation is a last resort in desolate cases.

Non-surgical treatment can be an option for selected patients where complete cure is not realistic or where surgery is not possible (e.g., due to comorbidity or advanced age). The aim will then be controlling the infection, rather than eradicating it, by means of long-term suppression with antibiotics. This strategy comes with inherent risks of drug

toxicity and progression of the infection despite treatment. Selection of resistant bacteria is also an issue to consider. Despite these consideration, suppressive treatment is sometimes employed, and prolonged infection control can be achieved in 50-90% of patients.[149,150]

Antibiotics

Antibiotic treatment of PJI comes with a special set of considerations. Apart from results from standard susceptibility testing, the clinician must also consider the ability of the antimicrobial agent to penetrate bone as well as its biofilm activity. Bone consists of ~70% inorganic (hydroxyapatite) matrix and ~30% organic tissue, with only 1-2% being bone cells.[151] Bone is thus a heterogenous tissue where it is reasonable to believe that neither antibiotics nor infecting bacteria are evenly distributed. Additionally, studies on antibiotic bone penetration present considerable heterogeneity due to methodological differences in sampling, preparation, and analysis.[152,153] Bone involvement is common in chronic infections making this aspect important when choosing therapy. The fact that biofilm embedded bacteria become metabolically inactive ad to the complexity.[101] Persister cells have a decreased susceptibility to many antibiotics, especially those acting mainly on dividing cells (i.e. cell wall active antibiotics), leading to a 100-fold increase in minimum bactericidal concentration.[154-156] These factors need to be taken into account by the clinician when choosing the appropriate treatment.

Rifampicin (rifampin) is a semisynthetic antibiotic discovered in the 1960s. Rifampicin inhibits bacterial RNA-synthesis and is an essential drug in the treatment of tuberculosis and other mycobacterial infections. It is also effective against staphylococci and other Gram-positives and has a proven effect on bacteria embedded in biofilm.[157] Bone penetration is considered to be reasonable with serum/bone-concentration ratios between 0.1-0.5.[152] These properties make rifampicin pivotal in the treatment of early and hematogenous PJI. Due to the low resistance barrier (a single point mutation is all it takes for resistance to develop) rifampicin cannot be used alone and must therefore always be combined with a suitable companion-drug. Side effects are often manageable, including nausea, liver toxicity and rash. Serious side effects (severe liver toxicity, bone marrow suppression) are rare but motivate regular monitoring during treatment. The main issue with rifampicin treatment is drug-drug interactions. Rifampicin is a powerful inducer of cytochrome p450-enzymes responsible for metabolization of many pharmaceutical drugs and interactions are therefore a common issue that must be considered. Other rifamycins with more favourable toxicity- and interaction-profiles are available and although *in vitro* efficacy

on staphylococci seem equal, clinical data for these agents are lacking.[158] There is no consensus on the optimal time for initiating rifampicin therapy. In the RCT by Zimmerli et al.[105] rifampicin was started immediately after surgery, which is debatable. Arguments against immediate initiation focus on the risk for emergence of resistance when the bacterial load is high, which could give rise to rifampicin resistant superinfections. For this reason, rifampicin is nowadays often started when the wound is dry and the infection is under control.[106]

Fluoroquinolones interact with bacterial DNA-synthesis and have a broad antibacterial spectrum with bactericidal activity, also in biofilms. They have good oral bioavailability and penetration to bone.[152,153] Fluoroquinolones are primarily used in PJI treatment as companion drugs to rifampicin and have a documented effect on outcome.[159] In Sweden ciprofloxacin is most widely used in PJI. Internationally, levofloxacin is often used though moxifloxacin generally has lower minimum inhibitory concentration (MIC) for Gram-positives. Interaction with rifampicin, lowering the moxifloxacin serum concentration has raised concern, though (limited) clinical data suggest equal efficacy.[160] Side effects include QTc-prolongation and tendinopathy. Recent findings associate fluoroquinolone use with increased risk of aortic aneurysm or dissection and has led to recommendations on avoiding use when possible.[161] Alternatives in the PJI setting, however, are few and often less effective, leaving the treating physician with limited options.

Beta-lactam antibiotics (e.g., penicillins and cephalosporins) exert bactericidal activity through inhibition of cell wall synthesis. Penetration into bone is lower than for quinolones and activity in biofilm is poor.[152] In Sweden cloxacillin is the recommended prophylactic antibiotic in arthroplasty and the preferred (initial) antibiotic for most invasive infections by *S. aureus*. Streptococci and enterococci are treated with penicillin (G and V) and/or ampicillin/amoxicillin. Main benefits include high tolerability, low toxicity, and favourable ecological profile.

Glycopeptides are a growing class of antibiotics with effect on Gram-positive bacteria. Systemic treatment with glycopeptides is only available through i.v. administration. Vancomycin has been used for more than 50 years and is the standard antibiotic in treatment of methicillin resistant staphylococci and is often mixed in bone cement for local prophylactic use in arthroplasty. Its usefulness systemically is limited by toxicity, the need for therapeutic drug monitoring, and poor bone and tissue penetration. The recently introduced novel lipoglycopeptides (i.e., dalbavancin and oritavancin) have more favourable toxicity profiles, good penetration to bone, and very long half-lives (for dalbavancin almost 400 hours), giving them ideal properties for outpatient use.[162] Initial studies on dalbavancin use in orthopaedic infections are promising, but more studies are needed.[163,164] *In vitro* activity of dalbavancin on biofilm has

been demonstrated, although it is not clear if this is also the case *in vivo*.[165-167] Dalbavancin seems to prevent emergence of rifampicin resistance when the 2 drugs are combined.[165]

Daptomycin is a cyclic lipopeptide for with bactericidal activity on Gram-positive bacteria, including resistant strains such as MRSA and VRE. Daptomycin is only available as an i.v.-formulation. Penetration to tissue and bone is good and daptomycin has effect on both planktonic and biofilm embedded bacteria.[153] The bactericidal effect is concentration dependent and in PJI dosing 6-12mg/kg once daily is recommended, depending on target MIC.[168] Combination with rifampicin seem to increase the effect in biofilm.[169] Side effects include muscle toxicity and eosinophilic pneumonia and should prompt termination (or switch) of treatment.

Clindamycin is a protein synthesis inhibitor with effect on many Gram-positive and anaerobic bacteria. It is generally considered to have a good capacity to penetrate bone, though in reality only slightly higher than cephalosporins, with a serum/bone ratio of 0.21-0.45.[151] In PJI clindamycin is mainly used as an oral companion drug to rifampicin. However, rifampicin-clindamycin interactions may result in suboptimal serum concentrations and use of clindamycin (+rifampicin) has been associated with increased failure rates.[170] High doses should therefore be administered to optimize concentrations in this setting.

Fusidic acid has been used for many years in oral and topical formulations. It inhibits protein synthesis and is mainly active on Gram-positive bacteria. Recent years have seen a renewed interest in fusidic acid to treat MRSA infections. Fusidic acid was never introduced in the US and resistance levels are therefore very low there compared to the 10% seen in Europe.[171] *In vitro* effect in biofilm has been demonstrated for fusidic acid combined with linezolid and daptomycin. [172] Combination with rifampicin has been used in PJI with adequate effect.[173,174] However, pharmacological studies showing drug-drug interactions going both ways have raised concern regarding this combination.[175,176]

Linezolid is a bacteriostatic agent active against Gram-positives and belonging to the oxazolidinones. Oral availability is excellent and bone penetration is good.[153] Use is hampered by a repelling toxicity profile, including irreversible neuropathy and myelosuppression, especially with prolonged courses of treatment. Biofilm activity is probably low, although enhanced when combined with rifampicin.[155,156,172] Combination with rifampicin, however, leads to reduced serum concentrations, further complicating use. Clinical data is heterogenous, which precludes drawing of general conclusions.[170,177,178]

Aminoglycosides (i.e., gentamicin, tobramycin, and amikacin) act through binding to the bacterial ribosome, having a concentration dependent bactericidal effect. Aminoglycosides vary somewhat in microbiological spectrum but exhibit effect on both Gram-negatives and Gram-positives. Bone penetration is reasonable.[153] When used systemically, nephro- and ototoxicity demand vigilance and motivate regular monitoring of serum concentrations. Systemic aminoglycosides have predominantly been used in PJI as adjunctive agents in combination therapy. In enterococcal PJI addition of an aminoglycoside did not, however, provide better outcome but led to increased risk of ototoxicity. [179] In arthroplasty an aminoglycoside is often mixed in the bone cement for local prophylactic effect. High rates of aminoglycoside resistance among CoNS responsible for PJI have been reported.[82,180]

Prevention

The prevention of PJI remains a top priority in arthroplasty There is an abundance of literature identifying various risk factors for PJI and optimization regarding all aspects, pre-, per-, and post-operatively is considered a prerequisite for successful prevention. Some measures have a proven efficacy (such as ultra-clean air and prophylactic antibiotics), while providing evidence for the efficacy of many other measures (e.g., optimization of co morbidities and skin decolonization) have been difficult. Factors affecting the risk for development of PJI after total joint arthroplasty can be divided into three categories: patient-related, operating room environment and surgical factors and are briefly described below.

Table 3. Modifiable risk factors for periprosthetic joint infections. Modified from Cizmic 2019,[181] Kunutsor 2016,[182] and Adeli 2012.[183]

Patient related	Operating room environment	Surgical factors
Active infection	Air quality	Antibiotic prophylaxis
ASA-class >2	- Minimizing personnel and traffic	Antibiotic loaded bone cement
Diabetes mellitus	- Ventilation	Surgical technique
Anemia	- Covering attire and face masks	Postoperative wound care
Immunosuppression	General hygiene and sterility	
Obesity	Instrument preparation	
Smoking	Skin disinfection and draping	
Alcoholism	Hair removal	

Patient-related risk factors

Optimization of modifiable risk factors is regarded as an essential part of the preoperative planning, though prospective data supporting preventive efficacy is largely lacking. Appropriate screening is recommended for all patients using, for example, questionnaires and clinical examination.

Active infection is a well-established risk factor for PJI. That ongoing infection in the current joint is a risk factor is self-explanatory. However, also infections in other sites (skin infections, urinary tract infections) entail an increased risk for PJI and should be managed before arthroplasty.[181,184]

ASA-class (The American Society of Anaesthesiologists physical status classification) is a crude estimate of comorbidity and has been used globally for many years in preoperative assessments of patient health. Despite its simplicity, ASA-class has been associated with postoperative complications in different fields.[185] In arthroplasty ASA-class >2 has been uniformly associated with increased risk for PJI in several studies.[186-188]

Table 4. American Society of Anesthesiologists physical status classification system. From Bjørgul 2010.[185]

ASA-class	
1	A normally healthy patient
2	A patient with mild systemic disease
3	A patient with severe systemic disease that limits activity but is not incapacitating
4	A patient with an incapacitating systemic disease that is a constant threat to life
5	A moribund patient who is not expected to survive 24 hours with or without treatment.

Diabetes mellitus has been a known risk factor for postoperative complications for years. It is considered a strong risk factor for PJI and the association between diabetes and increased risk for PJI has been well described.[182,187] There is, however, conflicting evidence, pointing towards diabetes not being a direct risk factor but rather a proxy for other, more severe, comorbidities.[189] The role for perioperative glucose control and diabetes management around the time for surgery remain unclear but optimization is nevertheless recommended and uncontrolled diabetes is considered a contraindication for elective arthroplasty.[181]

Many c*omorbidities* have also been associated with PJI: ischemic heart disease, congestive heart failure, chronic obstructive pulmonary disease, cirrhosis of the liver, chronic kidney disease, cancer, and psychiatric disorders to name a few.[9,13,186,190-192] Since there are few downsides to optimization of patient comorbidities most

would recommend it, though it's still an open question whether optimization can reduce the actual risk of PJI.

Immunosuppression is not uncommon among arthroplasty patients, of which some suffer from autoimmune conditions, such as rheumatoid arthritis. Increased risk of infection is a well-known side-effect for most immunosuppressant substances. Detailed guidelines for management of immunosuppressive therapy in adjunction with arthroplasty have therefore been developed to balance the risk of PJI against pausing or modifying the immunosuppressive treatment.[193]

Preoperative anaemia (for females: Hb <120, and males: Hb <130) is associated with increased risk of surgical site infection and PJI, as well as other postoperative complications, such as cardiovascular events. [194] It is not clear whether the anaemia in itself is responsible for the increased risk. Blood transfusion, which of course is more common among patients with preoperative anaemia, is also a risk factor for infection. It remains unclear if preoperative management of anaemia, with iron substitution for example, is beneficial for the risk of infection.[193]

Smoking is a strong risk factor for surgical site infections and PJI as well as for other surgical complications and readmissions after surgery.[195,196] Smoking cessation has been proven to reduce postoperative complications after surgery including wound healing problems, although not specifically the risk for PJI.[197,198] Patients should be offered counselling and qualified assistance with cessation for at least 4-8 weeks preoperatively.[199]

Obesity is a recognized risk factor for PJI and the risk seems to gradually increase with rising BMI and is markedly elevated in patients with morbid obesity (BMI >40).[200] The American Association of Hip and Knee Surgeons (AAHKS) recommend delaying arthroplasty in patients with morbid obesity, as other complications also become more common and functional benefits seem less clear.[201] It is also important to consider BMI when dosing prophylactic antibiotics to avoid suboptimal concentrations in obese patients.

Alcoholism is associated with increased rates of postoperative complications in many types of surgery, which has been demonstrated in several studies,[202] and in arthroplasty alcohol abuse has been identified as a risk factor for PJI.[184,203] Although it has not been proven that abstinence reduces the risk for PJI, it has been shown that 1 month of preoperative abstinence reduces the risk for postoperative complications.[204]

Male sex is a non-modifiable risk factor for PJI. Men are reported to have a relative risk of 1.36 to develop PJI as compared to women.[182] The reason for this has not been

determined. The gender-association appears to be less strong in arthroplasty of the hip than in the knee.

Age is a (non-modifiable) factor that does not seem to be associated with increased risk of PJI, although some uncertainty remains.[182,193] Most reports include age as a continuous variable and the existence of a non-linear relationship cannot be entirely excluded.

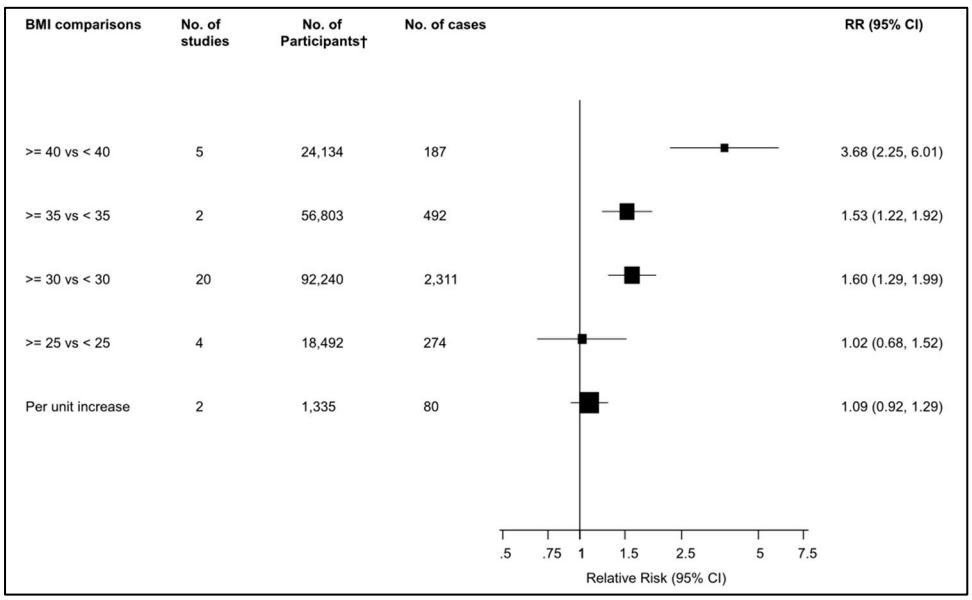

Figure 5. Body mass index comparisons and risk for periprosthetic joint infection. From Kunutsor 2016[182] Licensed under CC BY-NC 4.0, https://creativecommons.org/licenses/by-nc/4.0/. Available at https://doi.org/10.1371/journal.pone.0150866.

Operating room environment

The OR environment is a complex system with many components. People working in the OR interact with each other and with the physical environment, architectural conditions, technical systems, ventilation, and equipment. It was demonstrated by Charnley already in the 60s that meticulous control of these factors can have excellent effect on decreasing infection rates.[8] Most postoperative infections in arthroplasty are caused by skin commensals, originating from the patients' own skin flora or from the surrounding.

Preoperative decontamination at home, using chlorhexidine-based soaps is widely recommended. It reduces the bacterial load on the skin and is considered a cost-effective measure with very few adverse effects.[199,205,206] Some evidence for the efficacy in PJI prevention has been presented, though not entirely conclusive.[207] Skin disinfection with alcohol-based chlorhexidine antiseptics of the surgical field is likewise recommended.[208]

Air borne microbials in the operating room have been proven to be an important source for surgical site contamination.[209] Air quality has therefore been a focus of great interest for many years. Microbial contamination of the OR air can be measured by air sampling and expressed in colony forming units per cubic meter (CFU/m^3). Air sampling, however, is neither standardized nor routinely performed and clear correlations between CFU-levels and infection rates are lacking. Current Swedish recommendations state that <5 CFU/m^3 should be achieved in arthroplasty, whereas the WHO recommend <10 CFU/m^3.[210,211] Ventilation, behaviour and clothing all affect the OR air quality. Through the years there has been much debate on ventilation. It has been difficult to determine the effect of different modes of ventilation on PJI risk since many factors contribute to air quality as well as to the development of postoperative infection. Laminar air flow systems have, however, become more and more common over the years. Supporting this development is a recent study where lower rates of infection related revisions from hospitals using high-volume laminar air flow was found.[212] The same research group have, however, also showed, through a series of experiments, that ultra-clean air (<10 CFU/m^3) can be achieved through correct behaviour and the use of correct apparel.[213] It is well known that traffic in the OR (people coming and going, doors opening and closing) disrupt air flow and draw less clean air from adjacent rooms into the OR, leading to higher CFU-levels. Use of correct fabrics and clothing reduce the amount of skin flora from the OR personnel that contaminate the OR air.[209,211] Traffic should therefore be at a minimum during arthroplasty, and strict protocols regarding materials and clothing should be employed.

Surgical factors

Systemic prophylactic antibiotics are strongly recommended in arthroplasty and have been proven to reduce postoperative wound infections in arthroplasty by 80%.[214] Since the target organisms are skin commensals, predominantly staphylococci, the recommended substance in Sweden is cloxacillin, though internationally cephalosporins are often recommended. Timing is important to achieve optimum tissue concentrations. Based on the short half-life of recommended β-lactam-

antibiotics, the first dose should be given 30-60 minutes before incision.[215-217] The choice of prophylactic antibiotics should also take into consideration the local resistance pattern and any host-related factors (such as colonization of MRSA). Clindamycin is often administered to patients with a stated penicillin allergy but has been associated with an increased risk for infection-related revision, when compared with cloxacillin.[218] Penicillin allergy should therefore prompt a thorough evaluation. Most patients with a stated penicillin allergy do not, in fact, have a true allergy and can safely be given a cephalosporin after evaluation.[219,220]

Antibiotic loaded bone cement (ALBC) has been routinely used in arthroplasty for many years to prevent PJI. Chiu, et al. reported reduced rates of deep infections when using ABLC in a small RCT of TKA in a high-risk population of diabetics.[221] Lower infection-related revision rates with use of ABLC have also been reported in register based studies.[17,222] There is, however, some controversy, regarding the efficacy of ABLC in PJI prevention. Aspects regarding cost, selection of antimicrobial resistance and the risk for negative impact on the mechanical strength of the bone cement also need clarification. Hopefully some of these issues can be resolved by a register based RCT that has been launched by the Norwegian Arthroplasty Register that is currently running.[223]

The PRISS project

Between 2009-2012 the PRISS project (Prosthesis Related Infections Shall be Stopped) was implemented throughout Sweden. The project was sponsored by Löf, the Swedish patient insurance, and was a collaborative effort by several professional organizations (including the Swedish Orthopaedic Association, Swedish Association for Infectious Disease Specialists and Swedish Association for Infection Control), and all orthopaedic units, public and private, that performed hip and knee arthroplasty participated (n=72).

The main goal was to cut the frequency of prosthesis related infections by half and secondary goals were increased awareness of infection risks and a better understanding of the actual infection frequency.

PRISS was implemented using a method including self-assessment and external audit of experts appointed by the respective professional organizations. Results of the project revealed that procedures varied widely among participating units and many measures to increase patient safety were implemented.[224]

Registers

The Swedish Knee Arthroplasty Register

The Swedish Knee Arthroplasty Register (SKAR) was founded in 1975 by the Swedish Orthopaedic Association (SOF) and was the first national arthroplasty register in the world. Arthroplasty of the knee was a relatively new treatment at the time and provided only to patients with severe disability. It was deemed impossible for the individual surgeon to determine optimal surgical technique and choice of implant due to a constantly changing flora of implants and scarcity of the literature. With data aggregated on a national level it would be possible to compare methods and implants, with the aim of identifying inferior techniques and implant designs.[225]

Since the start the SKAR has collected data prospectively on primary and revision knee arthroplasties performed at public and private arthroplasty units. Although participation is voluntary, all units that routinely perform knee arthroplasty report to the SKAR and validation of the register shows a 97% completeness regarding primary TKAs. Until December 2020 the SKAR had collected data on 314,702 primary knee arthroplasties and 29,208 reoperations or revisions.[3,226]

Focus of the SKAR has been revisions, defined as exchange, removal, or addition of at least one of the components of the prosthesis, and revision frequencies have been included in the yearly reports since the start of the register. Reoperations, that is other surgeries not defined as revisions (e.g., arthroscopy or debridement for PJI without exchange of the tibial insert), were registered if reported, but were not systematically collected before 2014. The minimal initial dataset of the SKAR was expanded in 2009 to include ASA class, BMI and data regarding anaesthesia, operating time, and prophylactic antibiotics. In later years patient related outcome measures (PROMs) have also been added to the SKAR.

In 2021 the SKAR was merged with the Swedish Hip Arthroplasty Register to form the Swedish Arthroplasty Register.

The Swedish Prescribed Drug Register

The Swedish Prescribed Drug Register (SPDR) was established in 2005. Data on all dispensed prescriptions for the entire population is collected through automatic transfer of digital records from public and private pharmacies. Participation is mandatory and data loss is presumably zero. Collected variables include drug name, substance, dosing, prescription time, amount prescribed, amount collected, prescribing physician and

instructions for use. The SPDR does not, however, contain information regarding drugs sold without prescriptions, “over the counter”, or drugs used in hospitals.[227] In this thesis, the SPDR was used to identify patients at high risk of PJI through prolonged use of outpatient antibiotics. Systemic antibiotics are not sold without prescription in Sweden. The SPDR, therefore, captures all prescribed outpatient antibiotic treatments. Treatment given entirely in the hospital would, however, be missed by the SPDR since hospitals consumption is not included in the register.

Aims and rationale

Overall aims

The main purpose of this thesis was to fill the gaps in our understanding of certain less well investigated aetiologies in the context of PJI, to increase our knowledge of the incidence and surgical treatment of PJI of the knee and investigate its impact on survival.

Specific aims

Paper I

To describe the patient population affected by streptococcal PJI in Skåne, the different treatment choices and to analyse the outcome.

Paper II

To describe the patient population of enterococcal PJI regarding demography and co-morbidities. To investigate the treatment alternatives and outcome.

Paper III

The primary aim of this study was to evaluate the effect of the PRISS project on the incidence rate of PJI following primary TKA, by calculating the cumulative incidence rate before and after PRISS. Secondary aims were to evaluate time to diagnosis, primary treatment method, and PJI registration in the SKAR.

Paper IV

To estimate the mortality rate of patients diagnosed with PJI within 90 days of primary TKA, and, more specifically, to ascertain whether patients with PJI had a higher mortality rate compared to patients without PJI. We hypothesized that improvements in treatment practices of PJI during later years would have a positive effect on mortality rates. A secondary aim was, therefore, to compare mortality rates between time-periods and between surgical treatment methods.

Overall rationale

The most common aetiology of PJI, *S. aureus* and CoNS, have received a lot of research attention through the years. Principles of surgical and antimicrobial PJI-management have also, to a high degree, been based on findings from studies on staphylococci. There is, therefore, a need for studies on PJIs caused by less common aetiologies.

PJI is a rare complication of arthroplasty. Diagnosis of PJI is elusive and diagnostic criteria have changed over the years. All these factors make PJIs difficult to study. National arthroplasty registers are well suited to capture low-frequency complications but generally underestimate PJI rates. There is, therefore, a lack of accurate estimates of PJI incidence rates.

Specific rationale

Paper I

Streptococci are the second most common genus to cause PJI but have not been thoroughly investigated in the PJI context. Presentation, treatment, and outcome of streptococcal PJI vary widely across the few published studies. Though most streptococci are highly susceptible to treatment with penicillins, optimal choice and duration of treatment remain to be defined. Knowledge on outcome of different surgical strategies is scarce.

Paper II

Few studies on enterococcal PJI exist. Based on a few relatively small case series with poor treatment results, enterococcal PJI have come to be considered as difficult to treat.

Treatment algorithms therefore primarily advocate use of two-stage exchange procedures for these infections in favour of DAIR treatment.

Paper III

Intense labour has been directed towards prevention of PJI worldwide. In Sweden, the nationwide PRISS project was aiming to reduce infection rates by half. Incidence rates of PJI are, however, difficult to measure and arthroplasty registers are inherently prone to underestimation. Therefore, no accurate estimates of PJI rates were available for evaluation of PRISS when the project was implemented.

Paper IV

Previous studies on mortality in the PJI population usually focus on certain surgical interventions, emanate from single centres, or include a mixture of periprosthetic infections of the hip and knee. A few recent studies on mortality after PJI of the hip, using data from large cohorts exist, but large studies on mortality after PJI of the knee are scarce. The benefit of different treatment strategies on survival is largely unknown.

Patients and Methods

Study design

	I	II	III	IV
Design	Retrospective population based case series	Retrospective population based case series	Register based retrospective observational cohort study	Register based retospective observational cohort study
Population	Patients with streptococcal PJI in Skåne 2011-2015 (n=83)	Patients with enterococcal PJI in Skåne 2011-2015 (n=55)	Patients undergoing TKA 2007-2008 and 2012-2013	Patients undergoing TKA 2007-2008 and 2012-2013
Outcomes	Descriptions of population and aetiology Surgical and antimicrobial treatment Cure from infection	Description of the population Surgical and antimicrobial treatment Cure from infection	Incidence of PJI Surgical treatment methods Time to diagnosis Infection registration of the SKAR	Mortality rate with or without PJI within 90 days
Data collection methods	Review of medical records	Review of medical records	Data from SKAR and SPDR. Review of medical records	Cohort from III and data from SKAR
Data analysis	Mann-Whitney U Chi-square	Student's t-test Mann-Whitney U-test Fishers' exact test Kaplan-Meier survival curves	Cumulative incidence calculation Cox-regression analysis	Kaplan-Meier survival curves Cox regression analysis

Papers I & II

Population and patient selection

For papers I and II patients were identified through the database of Clinical Microbiology, Skåne. Between Jan 1st 2011 and Dec 31st 2015 all adult patients with positive cultures from sterile tissue or synovial fluid growing streptococci or enterococci were included if an orthopaedic implant was present in the affected joint. Records from

included patients were reviewed retrospectively. In **paper I** 83 patients with streptococcal PJI were included and in **paper II** 55 patients with enterococcal PJI were included.

Patients treated partly outside of Skåne were excluded to minimize selection bias.

Definitions

Diagnosis of PJI was defined as ≥2 samples from periprosthetic tissue or synovial fluid with growth of identical species of bacteria in culture or PCR. For highly virulent strains of streptococci (β-haemolytic streptococci), one positive culture was deemed sufficient, as was monomicrobial growth of enterococci in a single sample. Clinical signs and symptoms of infection (eg, joint swelling, pain, discharge, fistula, intraarticular pus, or fever) were also needed for inclusion.

A PJI episode was defined as the period of time ranging from diagnosis to the end of antimicrobial therapy. All surgical interventions during this time were considered part of the same episode.

Cure was defined as eradication of infection (no signs or symptoms of infection) with an implant in place at a minimum of one year after end of the episode.

Failure was defined as permanent removal of the prosthesis, amputation, relapse (growth of the same bacteria), death of infection or chronic antimicrobial suppression therapy.

Statistics

Students' t-test and Mann-Whitney U-test were used for normally and non-normally distributed continuous variables respectively. Categorical variables were analysed using the Pearson's Chi-square-test or Fisher´s exact test. The cumulative probability of cure was estimated using the Kaplan-Meier survival method (log-rank test). Statistical significance was set at $p \leq 0.05$.

Paper III-IV

Population and patient selection

For **paper III** linkage of two national registers, the SKAR and the SPDR was performed. To evaluate the PRISS project, two time periods were selected: before (2007-2008) and after (2012-2013) implementation of the project. All patients undergoing primary TKA during these time periods were included (n=45,438 TKAs). Based on the clinical

experience that most PJI patients receive long courses of outpatient antibiotic treatment, the SPDR was used to identify patients having more than 28 days of continuous treatment with antibiotics within 2 years of TKA, leaving 2505 cases for final review. For each case a questionnaire was sent to the primary operating unit for retrospective review of the medical records (Figure 6). Information regarding presence of PJI was obtained along with additional information regarding diagnosis, aetiology, treatment and follow up.

The incidence rate was calculated by dividing the number of PJIs with the total time at risk during the first 2 years postoperatively. Patients were followed until death, migration, reoperation for other causes than infection or a maximum of 2 years. The 2-year cumulative incidence rate was then obtained by multiplying the incidence rate by 2 years and presented in percentage with 95% confidence interval (CI). Cox regression was used to assess the hazard ratio (HR) for PJI between the periods and included age, sex, diagnosis (dichotomized on osteoarthritis (OA) or not), and fixation of the TKA (cemented or uncemented) in the final model.

For **paper IV** the cohorts with and without PJI from **paper III** were used. In cases with bilateral TKA only the first was included, or in case of PJI, only the infected TKA. Data on mortality was obtained through the SKAR, which is updated daily and automatically from the Swedish population register.

Patients diagnosed with PJI within the first 90 days postoperatively were included and compared to patients with no PJI. The intention was to capture predominantly early postoperative PJIs and to exclude low-grade chronic infections and haematogenous PJIs. Based on the previous study (III), improvements in surgical management were clearest in this group.

Statistics

Incidence of mortality was assessed at 1-, 2-, 5- and 10-years using Kaplan-Meier analysis and visualized through Kaplan-Meier curves, with log-rank test comparing the groups. Hazard ratios (HR) were calculated in the whole cohort using Cox regression adjusting for sex, age, indication (dichotomized into osteoarthritis or not) and period for primary surgery. A subgroup analysis of the 2012-2013 cohort was performed adding ASA-class and BMI to the previous Cox regression model. Proportional hazards assumption was assessed visually using a log (-log) plot.

Figure 6. Picture of the questionnaire used in paper III.

LOF Svenska knäprotesregistret

Questionnaire regarding patient with suspected periprosthetic joint infection

Primary clinic: prefilled
Personal registration number: prefilled
Date for primary surgery: prefilled **Side:** prefilled
Participant study no.: prefilled

1. Has this patient, *within 2 years of primary surgery*, had a **DEEP PERIPROSTHETIC** joint infection in the knee in question?

Yes, deep periprosthetic infection of the knee in question.

If YES, please answer all the questions in the questionnaire.

Yes, but the infection occurred after reoperation/revision for other causes than infection
(ie. instability, patellar problems or fracture)
- date for re-operation: _____
- cause of re-operation: _____

NO, but treated for a superficial wound infection (*no further information required).*
NO, no knee-related post-operative infection.
DON'T KNOW. The follow-up took place at **another hospital** or **clinic**
-At what hospital/clinic can information be found regarding potential prosthesis-related infection?

_____

If any of these alternatives: proceed to signature on page 2

If the patient had a **deep periprosthetic joint infection**, please answer questions 2 to 6:

2. CLINICAL INFORMATION

a. date for diagnosis: _____

b. which of the following signs of infection were present at the time of diagnosis?

- Fistulation	yes	no	don't know
- Pus in the joint	yes	no	don't know
- Systemic inflammation (ie fever el. leucocytosis)	yes	no	don't know

c. CRP at diagnosis_____ mg/L (*if information is lacking, just put "?"*)

Svenska knäprotesregistret
Remissgatan 4, Wigerthuset, plan 2
Skånes Universitetssjukhus
221 85 Lund

TURN!

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3. REOPERATIONS
State all re-operations performed in an operating theater due to deep periprosthetic joint infection.

Arthroscopic lavage	date:_____
Debridement **with** exchange of tibial insert	date:_____
Debridement **without** exchange of tibial insert.	date:_____
One-stage revision	date:_____
Extraction of prosthesis	date:_____
spacer implanted	
no spacer	
Re-implantation (stage 2 in 2-stage procedure)	date:_____
Artrodesis	date:_____
external fixation	
internal fixation	
Amputation	date:_____
Other surgery:_____	date:_____

Not reopererated for prosthetic joint infection (*the patient had prosthetic joint infection but was not operated*)

4. DIAGNOSTICS & MICROBIOLOGY:

a. Culture on synovial fluid:	no. of cultures ____	no. of positives ____
b. Tissue cultures peroperatively:	no. of cultures ____	no. of positives ____
c. PCR-analysis (tissue and/or synovial fluid):	no. of cultures ____	no of positives ____

d. Identified **etiology** (one or more): **Attach copies of culture results!**
1. _____
2. _____
3. _____

5. FOLLOW UP
a. Date for termination of antibiotic treatment: _____
b. Date for latest follow up: _____
c. Infection clinically cured on latest follow up?
yes no don't know

6. OTHER information that you think would be of value for the study: _____
_____
_____
_____

Reviewer:
Date: _____
Name: _____
Mail: _____
Phone number: _____

General methodological considerations

Experimental and observational studies

Fortunately (though not for the researcher), PJI is a rare occurrence. PJI is also a heterogenous entity, comprised of infections in different types of prosthetic joints by many different microbes (sometimes simultaneously) during different time periods after surgery. Subsequently, the clinical presentation varies substantially. These factors make the collection of prospective data very challenging.

Clinical studies can be performed in two fundamentally different ways: as experimental or observational studies. In experimental studies the researcher assigns the intervention or exposure in a random or non-random fashion to evaluate its effect on the outcome of interest. When random assignment is used it's called a randomized controlled trial (RCT). The randomization process is used to eliminate bias when assigning the intervention and to minimize group differences regarding unknown confounders. RCTs are held as the best way to evaluate the efficacy of an intervention.[228] An RCT needs to be of sufficient size to detect a clinically important difference, making sample size, or power, calculations very important. Many interventions have small to moderate effects on outcome, necessitating inclusion of a large number of study participants to be able to detect this effect. For these reasons RCTs are cumbersome, time consuming, and expensive to perform. The experimental design can also have an impact on the generalizability of results to other populations. Study participants are often quite different from patients the clinician face in the day-to-day practice, highlighting the importance of clinical judgement in the application of study results. The ethical aspect of experimental studies is also very important, as interventions can be both beneficial and harmful.[229] In PJI research most studies are observational, though the previously mentioned RCTs on PJI treatment constitute the rare exceptions.[105,121,122] These studies can be used to illustrate some of the problems encountered in PJI research. The study by Zimmerli et al. was based on experimental data from observational and animal studies indicating superiority of rifampicin+ciprofloxacin combination over ciprofloxacin only in the treatment of staphylococcal orthopaedic implant infections. The treatment effect was estimated to be very large (75% vs. 20% cure) and the power calculation concluded that inclusion of 30 subjects would be sufficient. Inclusion of 33 subjects was accomplished after 5 years, constituting mainly osteosynthesis infections (18/33) and methicillin susceptible *S. aureus* (26/33). Study results proved superiority of the intervention (100% vs. 58% cure, $p<0.02$) in the per-protocol analysis. However, in the intention to treat analysis cure rates were not significantly different (89% vs. 60%, $p=0.1$) due to a large number of dropouts (27%). The results of this study have been extrapolated to all kinds of orthopaedic implants, all species of staphylococci, and

other fluoroquinolones, though never replicated. The closest replication is a Norwegian RCT that failed to demonstrate superiority of rifampicin addition to treatment with cloxacillin or vancomycin.[230] This study differs in many important aspects from the study by Zimmerli et al. (6 weeks of treatment vs. 3-6 months, use of cell wall antibiotic, inclusion of arthroplasty infections only), suffers from serious issues (26% dropouts, lack of power, is the companion/comparison drug a relevant choice?), and has been heavily criticized.[231] Considering the broad acceptance of rifampicin as the drug of choice in PJI with implant retention, an adequately powered RCT on the subject is not to be expected and could very well be considered unethical. The RCT by Lora-Tamayo et al. concerns treatment duration, comparing 12 and 8 weeks of antibiotics in DAIR treated staphylococcal PJI.[121] To fulfil the requirements of the power calculations the authors set out to include 195 subjects, reviewed 175, and managed to include 63. In the final per-protocol analysis only 44 subjects remained. The results indicate non-inferiority of 8 weeks vs. 12 weeks, but generalizability of the results can be discussed due to the highly selected patients included and remaining for analysis. This problem with external validity is not unusual in RCTs, where voluntary participation and selection criteria puts the studied population at risk of being substantially different than the patients in general.[232]

Observational studies can be divided into descriptive and analytical studies, based on whether there is a control group to compare with or not.[229] Descriptive studies (case reports and case series) are at the bottom of the evidence hierarchy. The main use of descriptive studies is to (as the name implies) describe the condition in question regarding frequency, population, symptomatology, and other features of interest. The case definition needs to be stringent to maintain specificity. Descriptive studies can be used for hypothesis generation and as a probe for future research. The main limitation is not being able to draw causal conclusions. Other restrictions include availability of data and stringency in its collection. On the plus side are affordability and the lack of difficult ethical issues.[233] Analytical studies (e.g., cohort studies and case-control studies) have the benefit of a comparison group enabling causal inference. In cohort studies participants are assigned depending on exposure and followed forward in time (though data can be collected retrospectively) to evaluate the outcome. An example of a cohort is the SKAR, where knee arthroplasty patients are “assigned” to an exposure at inclusion (this can be a particular type of implant) and followed towards an outcome (in the SKAR this is often revision of the implant).[234] In case-control studies cases are identified through the outcome of interest while controls are people that have not experienced the outcome. The researcher looks back in time to assess the frequency of the (hypothesized) explicatory exposure in both groups to draw conclusions regarding its effect on the outcome. In case-control studies the groups should be as similar as

possible regarding all aspects except exposure, and matching is often used to control for known confounders, such as sex and age.[229]

Bias and confounding

Bias, or systematic error, is an inherent part of observational studies and should be managed through study design or in the interpretation of results. Many kinds of bias have been described, though a common approach is to group biases into three categories: selection bias, information bias and confounding.[232,235]

Selection bias occurs when the studied groups differ in important aspects other than exposure, due to selection criteria or procedures of recruitment. An example is non-respondents in a questionnaire study.

Information bias, also known as ascertainment-, misclassification-, and observation bias, occurs when acquisition of information is erroneous or inaccurate. Examples are classification of participants in the wrong category (non-infected vs. infected) or gathering information differently among exposed and unexposed. Double-blinding is an example of a measure to reduce information bias in an RCT.

Confounding is described as "a confusion of effects" and is an important issue in epidemiological research and study design.[235] A confounder is associated with the exposure and affects the outcome, leading to false conclusions regarding the effect of the exposure. Confounding can be prevented by study design, through randomization, restriction, or matching. In the statistical data analysis stratification or regression models can be used to adjust for available confounders.

Missing data

Missing data can be present in any study. Variables of interest can be missing in registers or lacking in medical records and questionnaires can be unreturned, to name a few examples. Missing data will reduce representativeness of the study population and can skew the results. Data can be missing randomly or non-randomly, where the latter is more problematic. Non-randomly missing variables are missing because of some aspect that influence the investigated outcome (e.g., men are generally less likely to return questionnaires), which has the possibility to invalidate made inferences. In the collection of register data, a minimal variable set is common to reduce the risk of missing variables, or non-registration of cases. This is a necessary trade-off between the wish to have as much data as possible and the risks of missing data. In analysis missing variables can be handled through omission or imputation.[236]

Ethics

Approvals were obtained from the regional ethics review board at Lund University for all the studies in this thesis. For **papers I** and **II** (Dnr 2016/343) there was no need for informed consent other than the option to opt out. For **papers III** and **IV** (Dnr 2016/28) the need for consent was waived by the ethics review board.

Ethical considerations

Being observational studies, none of the investigations in the thesis impacted diagnosis or treatment for the included patients. There was no risk of harm through sampling, treatment allocation or other issues prevalent in experimental studies. The main ethical problem involved infringement on personal integrity. In **papers I & II** the public was informed by advertisements in the local press, as advised by the ethics review board. The advertisements included information on how to opt out, which no study subjects used. In **papers III** and **IV** linkage of national registers was performed. These registers contain abundant information of a sensitive nature and must subsequently be handled with utmost care and rigour. To reduce the risk of integrity infringement, data was handled pseudonymized until identification was required (in the 2505 patients elected for medical chart review). Data analysis was performed anonymously as dictated by the ethical approvals.

Results

Populations of papers I-IV

	Study I	Study II	Study III & IV	
			PJI	non- PJI
Characteristics	Streptococcal PJI	Enterococcal PJI	PJI ≤ 2 years of primary TKA	Primary TKA
Patients, n	83	55	644	40,384
Male sex, %	61	56	59	41
Age, median, years	70	77	69	69
Affected joint				
Hip, %	54	64	0	0
Knee, %	43	36	100	100
Infection type				
Early, %	30	62	52	
Delayed, %	10	20	na	
Haematogenous, %	60	18	na	
1st surgical treatment				
Debridement, %	78	73	73	
Exchange, %	17	7	8	
No surgery, %	5	13	6	
Cure, %	89	67	na	

Paper I

Population and microbiology

102 streptococcal PJI episodes were initially reviewed for inclusion, of which 83 were finally included. Cases were excluded due to non-significant growth (n=12), treatment partially outside Skåne (n=2) and recurrent infection (n=5).

Patients were more frequently male (n=51, 61%) and median age was 70 years. Comorbidities were common, with 65% having 1 comorbidity and 25% more than 1 comorbidity. 45 episodes (54%) were hip infections and 36 (43%) PJIs of the knee. 50 (60%) episodes were classified as hematogenous, 25 (30%) as early and 8 (10%) as late infections. Blood cultures were positive in 18 (22%) episodes.

Group B streptococci (n=25, 30%) and other β-haemolytic streptococci of groups A, C and G (n=26, 31%) were the most frequently isolated pathogens. 18 polymicrobial infections, with *S. aureus* (n=6) and CoNS (n=5) being the most common additional findings. Clinical presentation was similar between species.

Treatment

Surgical treatment was performed in 78 out of 83 cases and DAIR was the most common surgical strategy, used in 64 (77%) episodes. Of these, 5 proceeded to later implant exchange. Implant exchange was performed in 19 (23%) cases and was used as first surgical intervention in 14 cases. In the 5 episodes without surgical treatment 4 were due to high age and comorbidities and 1 due to patient decision. Median time from symptom debut to first surgery was 8 days (IQR 3–16)

Intravenous antibiotic treatment was heterogenous. The most commonly used agents were penicillin G and cefotaxime. Oral treatment was given with penicillins (amoxicillin or penicillin V) in 45 (54%) episodes, clindamycin in 10 (12%) episodes, and other antibiotics in 15 (18%) episodes. Rifampicin combination treatment was given in 12 episodes (15%), with clindamycin (n=6) and ciprofloxacin (n=4) as most common accompanying drugs. In 9 of the 12 rifampicin treated episodes a polymicrobial infection with staphylococci was present.

Median duration of antimicrobial treatment was 110 days (IQR 88-167). Chronic suppressive antibiotic treatment was given in 4 episodes.

Outcome

81 episodes were included in the outcome analysis. 2 episodes were excluded due to non-PJI related death ≤1 year after episode end.

Overall success rate was 89% (72 out of 81 episodes). 63 DAIR treated episodes were included in the outcome analysis. 5 of these episodes included later implant exchange, of which 3 were cured. 53 of the remaining 58 DAIR treated episodes were cured (91%). All episodes initially treated with one-stage exchange were cured (n=5) and 8 out of 9 two stage exchanges were successful (Figure 7).

10 episodes successfully treated for streptococcal PJI later developed re-infections with other pathogens.

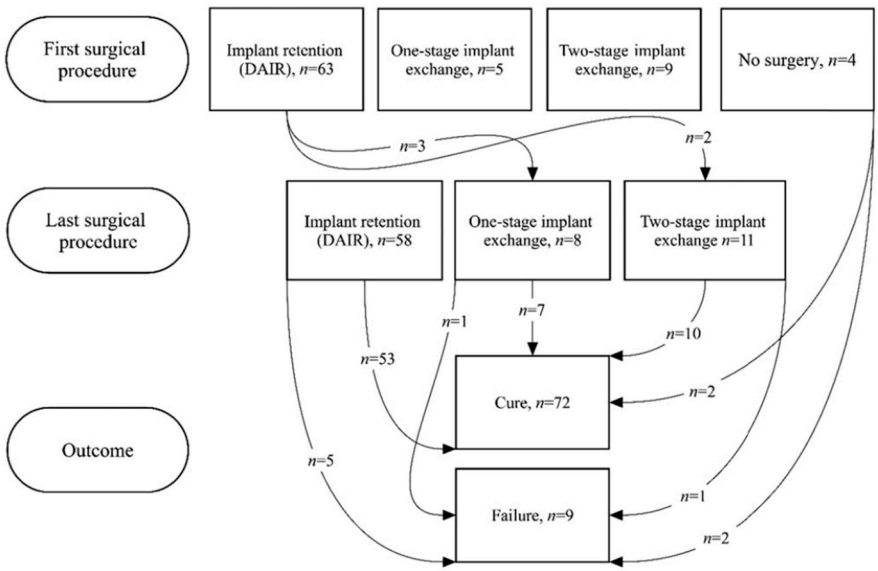

Figure 7. Details on surgical treatment and outcome of streptococcal PJI.

Paper II

Population, presentation, and microbiology

67 PJI episodes in 65 patients were reviewed for inclusion, and 12 episodes were subsequently excluded due to not fulfilling the inclusion criteria (non-significant growth, n=6, treatment outside of Skåne, n=2, non-PJI, n=2, episode start before study period, n=2). 55 PJI episodes in 54 patients were finally included.

At the time for PJI diagnosis median age was 77 (IQR 74-87) years, 56% were male and 51% (28) had one or more comorbidities.

In 46 episodes *Enterococcus faecalis* was isolated and *Enterococcus faecium* was isolated in 9 episodes. One episode grew both *E. faecalis* and *E. faecium* and in one episode *E. casseliflavus* was isolated. No vancomycin resistant enterococci (VRE) were isolated.

In 35 (64%) episodes the infection was polymicrobial, with predominantly staphylococci (*S. aureus*, n=14, and CoNS, n=17) as the co-infecting organisms.

Hip joints were affected in a majority of episodes, 35 out of 55 (64%), and knee joints in the remaining 20 (36%) episodes. Median CRP was 88 mg/L (IQR 29-126) and median leukocyte count was $10.1x10^9$/L (IQR 9.2-12.5). Clinical presentation was similar between enterococcal species. Polymicrobial infections presented more frequently with discharge (88% vs. 25%) and lack of fever (80% vs. 50%) than monomicrobial infections. Infections were classified as early in 34 (62%) delayed in 11 (20%) and haematogenous in 10 (18%) episodes. In 5 out of 10 episodes with haematogenous infections the primary focus was unknown and the remaining 5 had colon tumour (n=2), infective endocarditis (n=1), urinary tract infection (n=1) and cholecystitis (n=1). In 7 episodes enterococci were isolated during ongoing treatment for PJI with other aetiologies and in 48 episodes enterococci were isolated primarily.

Treatment

In 48 episodes surgical treatment was performed and in 7 cases no surgery was done. DAIR was the most frequent initial strategy, performed in 40 (73%) episodes. Of the DAIR treated episodes, 32 were debrided once, 4 had repeat debridements and 4 had later implant exchanges or removals. Implant exchange was performed in 6 episodes. In 12 episodes the initial treatment intention was not complete cure (as defined above), but intended to control the infection by prosthesis removal, amputation, or chronic suppression therapy.

Intravenous (i.v.) antibiotics with enterococcal activity were given for a median of 14 (IQR 8-21) days, and totally (i.v. + oral) for a median of 96 (IQR 48-140) days. Many different antibiotics were used, often with multiple changes during the treatment period. I.v. β-lactams with enterococcal activity (ampicillin, imipenem, piperacillin/tazobactam) were administered in 30 (55%) episodes and i.v. glycopeptides (vancomycin or teicloplanin) in 39 (71%) episodes. β-lactams were most commonly used for oral follow up treatment, used in 35 (64%) episodes. Linezolid was used in 14 (26%) episodes and a rifampicin containing combination was used for ≥ 2weeks in 10 (18%) episodes. 8 of these infections also involved staphylococci.

Outcome

Outcome analysis was performed on 49 episodes with follow-up ≥1 year or earlier failure. Excluded episodes were lost to follow up (n=4) or died from other causes within 1 year (n=2).

Overall cure was achieved in 33 (67%) episodes. Failure was due to chronic suppression (n=5), resection arthroplasty or amputation (n=6), relapse (n=3) and infection related death (n=2). In 40 episodes the treatment intention was to cure the infection (as defined above), and 32 (80%) of these episodes resulted in cure. Details of surgical treatment and outcome is presented in Figure 8.

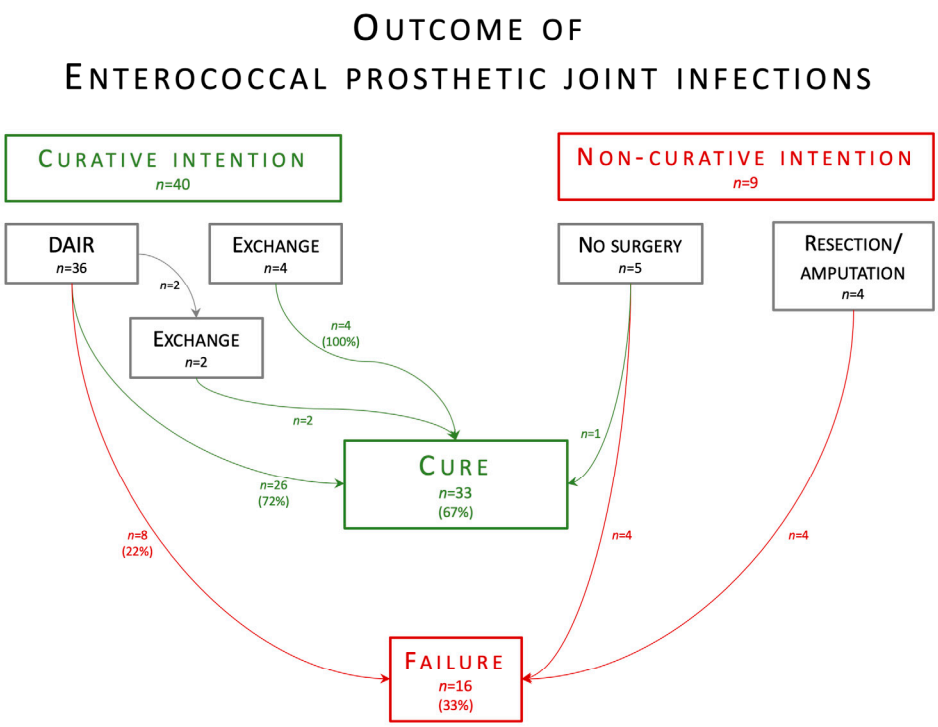

Figure 8. Details of surgical treatment and outcome of enterococcal PJIs.

The cumulative probability of cure was significantly worse for *E. faecium* when compared to *E. faecalis* (Figure 9). Clinical aspects associated with failure were ≥2 comorbidities and age. Cured episodes presented more frequently with discharge from the wound (27 out of 33) compared to failed episodes (7 out of 16). Cure was seen in all 8 episodes treated with a rifampicin combination.

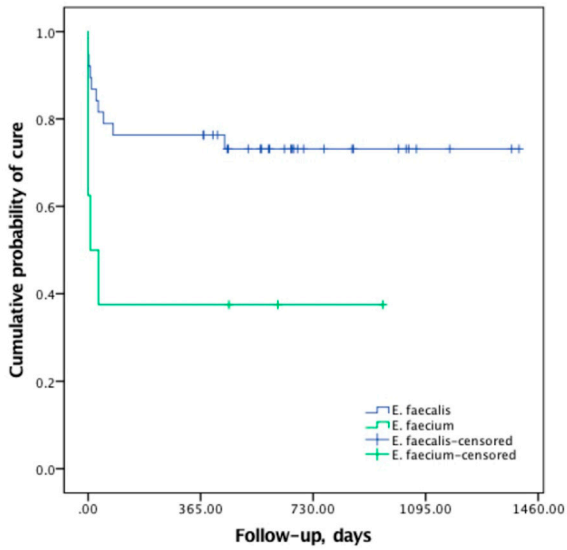

Figure 9. Kaplan-Meier curves comparing the cumulative probability of cure from PJI due to *E. faecalis* and *E. faecium*.

Paper III

Cumulative incidence

Overall, the cumulative 2-year incidence rate of PJI was 1.45% (CI 1.34-1.57); 1.44% (CI 1.27–1.61) for cases operated in 2007–2008 and 1.46% (CI 1.31–1.61) in 2012–2013. The HR for PJI in 2012-2013 was 1.01 (CI 0.86-1.17) when comparing with 2007-2008, and after adjusting for available confounders (age, sex, osteoarthritis, and fixation) the HR was 0.98 (CI 0.84-1.15).

Infection registration in the SKAR captured few of the reoperated cases, although improving the capture rate for both reoperated and revised cases during the latter time period (Table 5).

Table 5. Capture rate of the SKAR compared to verified cases in paper III

	2007-2008		2012-2013		Total	
	Verified	SKAR	Verified	SKAR	Verified	SKAR
Reoperations	136	35 (26%)	93	48 (52%)	229	83 (36%)
Revisions	114	74 (65%)	258	200 (78%)	372	274 (74%)
Total	250	109 (44%)	351	248 (71%)	601	357 (59%)

Time to diagnosis was similar during both time periods, with a median of 29 days (1-716) from primary surgery. 52% of cases were diagnosed within 30 days, and 73% within 90 days of primary TKA (Figure 10).

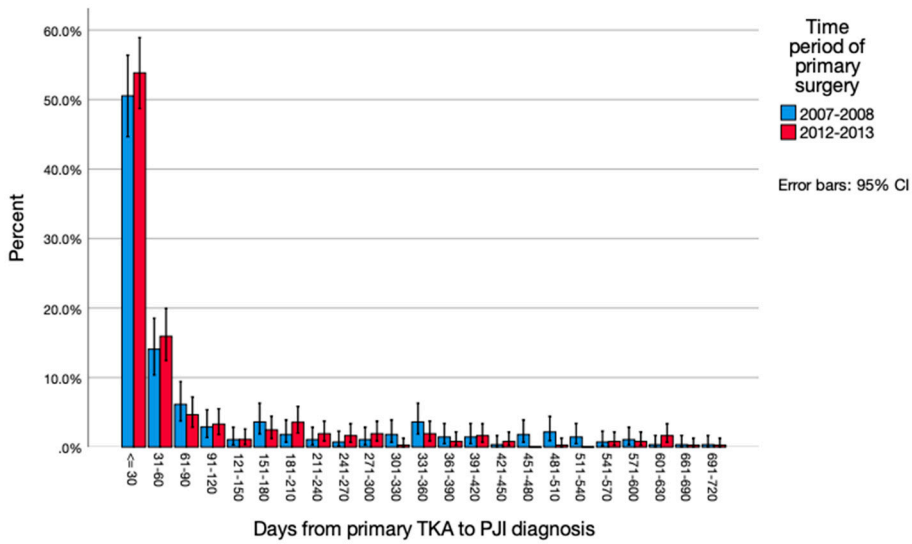

Figure 10. Time to PJI-diagnosis during 2007-2008 and 2012-2013

Surgical treatment

Data on surgical treatment was not obtained in 4 cases. 604 of the remaining 640 had surgery performed as part of the treatment for PJI. Changes in surgical strategy occurred between the 2 study periods, with an increase in the proportion of debridement with exchange of insert from 32% to 63% and a corresponding decrease in debridement without exchange of insert (from 33% to 18%) and arthroscopic procedures (from 16% to 7.7%). The proportion of cases treated without surgery also decreased (from 8.7% to 3.3%) between time periods (Table 6).

Table 6. First surgical intervention for PJI before and after the PRISS project. Data presented as numbers (%).

	2007-2008 n=280	2012-2013 n=364	Total n=644
Revisions			
Debridement with exchange of insert	88 (31)	227 (62)	315 (49)
1-stage exchange	1 (0.4)	7 (1.9)	8 (1.2)
2-stage exchange, removal	21 (7.5)	24 (6.6)	45 (7)
Arthrodesis	3 (1.1)	0 (0)	3 (0.5)
Resection arthroplasty	1 (0.4)	0 (0)	1 (0.2)
Amputation	1 (0.4)	0 (0)	1 (0.2)
Reoperations			
Arthroscopy	45 (16)	28 (7.7)	73 (11)
Debridement without exchange of insert	91 (33)	65 (18)	156 (24)
Other surgery	2 (0.7)	0 (0)	2 (0.3)
No surgery	24 (8.6)	12 (3.3)	36 (5.6)
Missing data	3 (1.1)	1 (0.3)	4 (0.6)

Paper IV

Patients were included only once and, subsequently, after exclusion of 4,333 TKAs in bilateral procedures, 41,104 patients remained. 40,362 patients had no PJI, and 466 patients were diagnosed with PJI within 90 days of primary TKA. We excluded patients with PJI diagnosis >90 days after TKA (n=177) and patients where no data was obtained (n=99).

In the PJI group the all-cause mortality rate was significantly higher when compared to the non-PJI group (Figure 11). After adjusting for sex, age, diagnosis (dichotomized on osteoarthritis or not), and time-period of primary surgery the difference in mortality remained, with HR 1.8 (CI 1.6-2.1). ASA-class was available in the 2012-2013 cohort, and after adding ASA-class to the Cox-regression model the mortality risk remained increased for the PJI cohort, with HR 1.93 (CI 1.51-2.45). ASA 3-4 was a strong predictor for mortality (HR 2.02 [CI 1.87-2.19]).

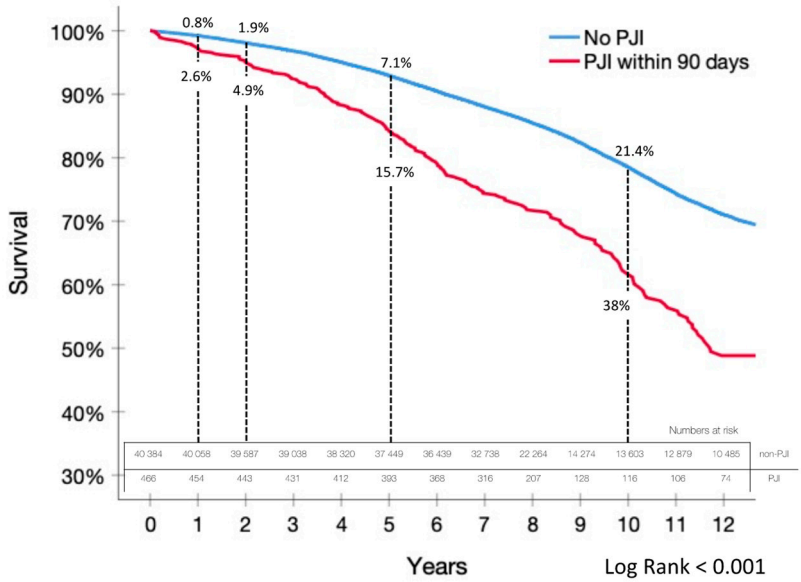

Figure 11. Kaplan-Meier curves comparing all-cause mortality of patients with PJI within 90 days of TKA to patients without PJI after TKA.

Mortality rates were similar for PJI patients during both time periods (Figure 12), although over-all mortality was higher during 2007–2008.

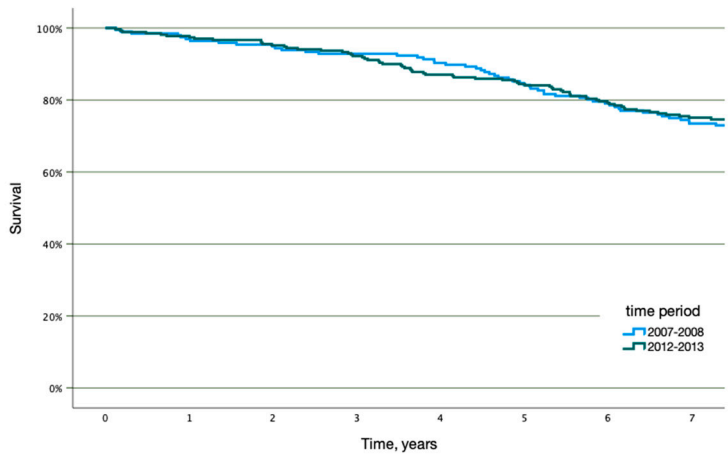

Figure 12. Kaplan-Meier curves comparing mortality rates for patients with PJI within 90 days of TKA during 2007-2008 and 2012-2013.

Discussion

Most of the literature on PJI has been centred around staphylococcal infections. This is natural, considering that more than half of all PJIs are caused by staphylococci. A lot of what we know about the principles of treatment are therefore based on or derived from studies on staphylococcal PJI. Knowledge has been extrapolated to infections caused by other microbes on the assumption that microbes cause PJI in the same way. Of course, this is not true. Microbes differ widely in virulence, biofilm formation capacity, antimicrobial susceptibility, and many other factors. Studies on PJI caused by bacteria other than staphylococci are therefore important to help us better understand the full spectrum of PJI, and how to best manage our patients.

On streptococcal PJI

In **paper I** we investigated PJI caused by streptococci. We found a demographic and aetiological spectrum similar to previous reports, identifying GBS as the most common streptococcal species in PJI.[96,237-240] Despite being more virulent, no major differences in clinical presentation were found when comparing β-haemolytic streptococci to α-haemolytic strains, which is concurrent with the largest multi-centre study on streptococcal PJI by Lora-Tamayo, et al.[96] GBS have been identified as a risk factor for treatment failure in some reports, [95,240] but this was not supported in our material.

Acute haematogenous infections have been reported to have a less favourable prognosis in *S. aureus* PJI.[25,128] Of the PJIs in **paper I** 60% were acute haematogenous and 30% acute postoperative. A high proportion of acute haematogenous infections has been reported in several previous studies (

), while the number of acute vs. chronic postoperative infections vary. We found a somewhat lower, non-significant, success rate among haematogenous cases compared to acute postoperative (85% vs. 100%). Lora-Tamayo et al.[96] found no such association, although success rates were substantially lower across all infection types.

Surgical treatment strategy of PJI is determined on the basis of clinical picture, with special focus on symptom duration. DAIR is generally recommended for acute postoperative and haematogenous PJIs within previously mentioned time limits. In **paper I** 77% of cases were treated with DAIR as initial strategy, with 87% adherence to recommended time limits. The importance of aetiology in this context has not been fully elucidated but some support for use of limits on symptom duration can be found. Sendi, et al.[241] found higher success rates in GBS PJI episodes with adherence to treatment algorithms, though not only focusing on time criteria. Fiaux, et al.[210] reported a low success rate of 58% after DAIR, with compliance to time limits being only 38% and Lora-Tamayo, et al.[96] reported a significantly worse success rate in cases not fulfilling time criteria (52% vs. 63%). Neither of these studies, however, reported worse outcome for cases treated with DAIR within 30 or 90 days after implantation, supporting symptom duration, rather than time from primary surgery, as the important determinant. Furthermore, the importance of thorough debridement was elucidated in the study by Lora-Tamayo et al., where modular exchange was associated with a better outcome, especially in cases *not* fulfilling time criteria.

Table 7. Overview of studies on streptococcal PJI.

Publication	Study type	Time period	n	% GBS	Age, median	Knee/ Hip	Haemato genous	% DAIR	DAIR success rate
Meehan 2003[238]	Retrospective, single centre	1969-1998	19	32%	70 (r.44-86)	13/6	N/A	100%	17/19 (89%)†
Everts 2004[239]	Retrospective, single centre	1984-1995	18	33%	72 (r. 30-91)	9/9	11/18 (61%)	89%^	15/16* (94%)
Zeller 2009[242]	Retrospective, single centre	1994-2006	24	100%	74 (IQR 59-76)	0/24	N/A	25%	4/6 (67%)
Sendi 2011[241]	Retrospective, multi cetre	1990-2008	36	100%	71 (IQR 65-79)	13/23	11/30 (31%)	56%	13/20 (65%)
Corvec 2011[243]	Retrospective, single centre	2002-2006	12	100%	59 (IQR 43-69)	5/7	N/A	58%	3/7 (43%)**
Betz 2015[244]	Retrospective, single centre	1996-2012	9	N/A	78	N/A	N/A	100%	9/9 (100%)
Fiaux 2016[237]	Retrospective, multi centre	2001-2009	95	39%	69 SD 13.7	45/50	18/95 (19%)	58%	32/55 (58%)
Lora-Tamayo 2017[96]	Retrospective, multi centre	2003-2012	462	34.4%	72 (IQR 65-78)	N/A	242/462 (52%)	100%	257/444 (58%)
Akgün 2017[240]	Retrospective, single centre	2009-2015	30	40%	71 (r.47-90)	18/12	16/30 (53%)	6/30 (20%)	4/6 (67%)
Andronic 2021[245]	Retrospective, single centre	2011-2019	22	4.5%	68 (r.50-90)	8/11	21/22 (96%)	12/22 (55%)	6/12 (50%)

†Including 8 patients on long term suppression. ^10 patients treated without surgery. *Including 4 patients on long term suppression. **4/7 patients lost to follow-up.

The role of rifampicin in treatment of streptococcal PJI remain to be clarified. In vitro studies on streptococcal biofilms are scarce. Albano et al.[246] demonstrated very low anti biofilm activity of rifampicin on streptococci associated with PJI, though planktonic MICs were low. In another study, by Gonzalez Moreno et al.[247],

synergistic effect of rifampicin in combination with gentamycin on streptococcal biofilm was demonstrated. No conclusive clinical data has yet been published. Fiaux et al.[237] reported a beneficial effect of rifampicin on DAIR treated cases, but this was not supported in the study be Lora-Tamayo et al.[96] In **paper I** rifampicin treatment was used in polymicrobial PJIs involving staphylococci and could, therefore, not be evaluated.

Reported outcomes after streptococcal PJI vary widely. The over-all success rate of 89% and 84% after DAIR in **paper I** is in line with some of the smaller previous reports, but more recent studies suggest a remarkably worse prognosis (see

). Outcomes are, however, generally difficult to compare due to the lack of a standardized definition of cure. Some studies, for example, include patients on long term suppression antibiotic treatment among successful cases. Reinfections are also regarded differently. We chose to disregard reinfections in the outcome analysis, not counting the 10 cases that had a recurrent infection with another species. From a patient perspective this is questionable since new treatment is necessary regardless of bacterial aetiology. But from a medical and microbiological perspective the distinction is important when trying to determine and evaluate treatment practices. The dismal prognosis in reports on streptococcal PJI have led some centres to recommend long term suppression for all streptococcal PJIs, as this seems to prevent relapse.[248] However, the results presented in **paper I** demonstrates that it is possible to achieve high cure rates without long term suppression. From available data two clues to successful treatment can be discerned: adherence to treatment protocols (especially regarding symptom duration) and thorough debridement with modular exchange (in DAIR).

On enterococcal PJI

Over the recent decades, invasive nosocomial enterococcal infections have increased, especially in settings with fragile patients, such as in intensive care units.[100] Enterococci have a lower degree of virulence compared to *S. aureus* and β-haemolytic streptococci and, therefore, often require a more susceptible host or a foreign material to cause clinical infection.[99] Moreover, enterococci have an inherent ability to resist antibiotics and a capacity to form biofilm, making them hard to eradicate.[249] These factors together contribute to making "a second-rate pathogen into a first-rate clinical problem", to use the words of Arias and Murray.[99] The population suffering from enterococcal PJI is no exception, being described with a high proportion of predisposing conditions, advanced age, and fragility.[250-252] This was also seen in

paper II, where median age was 77 years and half of the patients had one or more comorbid condition. *E. faecalis* is reported to be responsible for 80-90% of enterococcal PJIs, which was also the case in **paper II**, with *E. faecium* almost exclusively accounting for the remaining cases.[250,251,253,254] *E. faecium* are known to have a high degree of β-lactam resistance and oral treatment alternatives are usually very limited or lacking.[88,100] In the multi-centre study by Tornero et al.[251] *E. faecium* was associated with worse outcome than *E. faecalis*. We found the same association in **paper II**. There are multiple plausible reasons for this: antimicrobial resistance, biofilm formation and patient fragility to name a few. Also, among clinicians, it is a well-established "fact" that invasive infections with *E. faecium* come with a poor prognosis, which could influence the choice of treatment and make poor prognosis a self-fulfilling prophecy in the retrospective setting. A high proportion of enterococcal PJIs are polymicrobial, with frequent co-infecting pathogens being staphylococci and a variety of Gram-negatives.[251,254] Polymicrobial infections have been reported with a worse prognosis,[251,254] but this was not supported in **paper II.**

Table 8. Overview of studies on enterococcal PJI

Publication	Study type	time period	n	Age	Comorbidity ≥1	E. faecalis (%)	Polymicrobial (%)	% DAIR	Over all cure	DAIR cure
El Helou 2008[179]	Retrospective, single centre	1969-1999	50	70 (32-89)	N/A	N/A	0%	10%	76%*	80%
Rasouli 2012[250]	Retrospective, single centre	2000-2010	36	N/A	78%	75%	39%	28%	67%*	50%
Tornero 2014[251]	Retrospective, multi centre	1999-2012	203	70 (± 13)	N/A	89%	54%	53%	56%	47%
Duijf 2015[255]	Retrospective, single centre, early PJI (<90 days) & DAIR only	2009-2013	44	71 (52-87)	N/A	N/A	80%	100%	-	66%
Tornero 2015[256]	Retrospective, single centre, early PJI (<90 days) & DAIR only**	1999-2012	74	69 (25-93)	48%	91%	65%	100%	-	62%
Kheir 2017[252]	Retrospective, 3 centres	1999-2014	87	N/A	54%	N/A	58%	38%	52%^	39%
Ascione 2019[253]	Retrospective, single centre	2009-2015	31	73 (39-83)	55%	90%	35%	52%	58%	56%
Renz 2019[254]	Retrospective, 2 centres	2010-2017	75	76 (30-90)	N/A	85%	51%	16%	85%	100%
Rossman 2021[129]	Retrospective, single centre, 1-stage exchange	2002-2017	40	68 (35-82)	N/A		45%	-	63%†	-

*Including resection arthroplasty. A subset of cases from Tornero 2014, PJI ≤90 days and DAIR. ^27/40 failures due to non-enterococcal reinfections. †9/15 failures due to non-enterococcal reinfections.

Treatment guidelines have suggested use of 2-stage exchange procedures for enterococcal PJI, regarding enterococci as "difficult-to-treat" (DTT) pathogens.[31] Evidence supporting the superiority of 2-stage exchange over other procedures are, however, lacking. In the available literature a variety of surgical treatment strategies have been reported and DAIR treatment has often been used in early and haematogenous enterococcal PJI. El Helou, et al.[179] reported 94% success rate for 2-stage exchange and 100% for DAIR treatment. However, 23 out of 50 cases were treated with resection arthroplasty and it is unclear if these cases were initially planned for re-arthroplasty or given up from the start. Not progressing to stage 2 is an underestimated risk in 2-stage procedures and associated with significant morbidity and mortality.[146] The largest cases series on enterococcal PJI was published by Tornero, et al.[251] and reported a 57% success rate in 2-stage exchange and 77% in 1-stage exchange. Late infections (>2 years) treated with implant exchange had a 92% success rate, being the only positive prognostic variable. In the re-analysis of early PJIs (<90 days postoperatively) from the same material Tornero et al.[256] found a DAIR success rate of 62% concurrent with the 66% cure rate from Duijf et al.[255] on a similar DAIR treated population. In **paper II** we reported a 2-stage success rate of 100%, including 2 cases initially treated with debridement. Treatment with DAIR had a success rate of 72%, quite similar to reports on *S. aureus* PJI.[126] Early and haematogenous PJIs constituted 80% of the cases and while 83% of early PJIs were eventually cured only 1 out of 7 (14%) of the haematogenous cases.

Optimal antibiotic treatment of enterococcal PJI remains elusive. Traditionally ampicillin/amoxicillin has been the drug of choice in *E. faecalis* infections. β-lactams, however, have poor effect in biofilms. Biofilm formation capacity has been demonstrated in enterococcal foreign body infections and is believed to be an important virulence factor.[249] This has led to speculation on whether biofilm active antimicrobials (i.e., rifampicin) would be beneficial in PJI treatment. In vitro experiments have demonstrated diverging results with rifampicin treatment on enterococcal biofilms. Holmberg et al.[155,169] showed that rifampicin combinations with ciprofloxacin or linezolid reduced the minimal biofilm eradication concentration (MBEC) on isolates of *E. faecalis* and *E. faecium*, though still requiring higher concentrations than it is possible to achieve *in vivo*. Rifampicin monotherapy led to resistance development. Similarly, Albano et al.[246] demonstrated the need for very high minimum biofilm bactericidal concentrations (MBBC) in a recent experiment, substantially higher than MBBCs found for staphylococci [158]. Clinical data is scarce. In **paper II** we found a tendency towards better outcome in cases treated with a rifampicin combination, although most of these cases were polymicrobial infections involving staphylococci. Tornero et al.[251] also found an association with rifampicin

treatment and higher rates of remission in patients with early (<30 days) PJI. Addition of an aminoglycoside was evaluated by El Helou et al.[179] and found to be without benefit but with an increased risk of ototoxicity. Other antibiotics of interest such as high dose daptomycin, dalbavancin and ceftriaxone/ampicillin-combination have only been reported in small case series.[164,257,258] Antibiotic therapy is difficult (impossible, even?) to evaluate retrospectively since many different factors influence the choice of therapy, such as clinical response and tolerance. Also, many different antibiotics have been used in the studies, often consecutively or in combination in the same patients. These factors and the descriptive nature of data preclude the drawing of any general conclusions on the superiority of one antimicrobial strategy over another.

On incidence and prevention of PJI

In **paper III** we found an incidence rate of PJI within 2 years of primary TKA of 1.45%, with similar PJI incidence rates during both time periods of the study. Other studies of comparable size, using only administrative data, report cumulative incidence rates between 0.32% and 1.55% [9,10,259], placing our estimate in the upper region within this spectrum. Comparing with incidence rates in hip arthroplasty, studies on Nordic materials report incidence rates of 0.86% and 0.9% at 1 and 2 years respectively, though these studies are probably underestimations.[15,260] To put the figures in further perspective, a recent Swedish study on septic arthritis after anterior cruciate ligament reconstruction found an incidence of 1.1%.[261] This population was much younger than patients undergoing TKA and with a low prevalence of diabetes and obesity.

Incidence rates of PJI are difficult to measure and methods for surveillance are lacking. Lindgren et al.[15] suggested using the same method as in **paper III** for surveillance of PJI, but we found this method to be too cumbersome. Noteworthily, arthroplasty registers are prone to underestimation of PJI, which has been demonstrated in several studies.[10,11,260,262] In **paper III** 44% of identified PJIs were not captured by the SKAR. The SKAR, however, is primarily focused on revisions and captured 73% of infected revisions. Increasing capture rates were also seen between study periods, rising from 44% to 71% overall, reflecting efforts to improve registration. Diagnosis of PJI is sometimes elusive and no gold standard exists. This impedes reporting of the diagnosis to registers as well as stringent coding of the diagnosis.

The main aim of **paper III** was evaluation of the PRISS project. PRISS hoped to reduce infection rates by half, a goal that was not reached. The PRISS project included a bundle of multiple measures to reduce the risk of infection, and it is difficult to explain

the lack of measurable effect. Increasing rates of PJI have been reported, [17,18,259] possibly counteracting, or hiding, the effects of PRISS. Reasons for this increase are unclear, but demographic changes and increasing antibiotic resistance have been suggested, as well as confounders relating to improved diagnostics and lower thresholds for surgical intervention among clinicians. Multiple risk factors have been associated with PJI (see the section on prevention above), but in many cases it is unclear if optimization of risk factors leads to risk reduction.[193] Risk factors included in the SKAR were adjusted for: sex, age, fixation, and indication for TKA, and did not alter the results. Other risk factors, such as ASA-class, BMI, and prophylactic antibiotics were not included in the SKAR until 2009 and were, therefore, not available for comparison.

Antibiotic resistance is a constant threat to modern medicine and increasing rates of resistant pathogens have been reported in many countries.[87] In PJI, a Norwegian study has reported increasing rates of methicillin resistance among CoNS, [180] while a more recent Danish study found no increase of β-lactam resistance in PJI of THA.[16] The substantial geographic variability in resistance patterns, however, makes international comparisons difficult.[263,264] The standard prophylactic antibiotic in arthroplasty in Sweden is cloxacillin, which is still effective against a majority of the major pathogens. Our material was not analysed regarding microbiology, due to large amounts of missing data. We can, therefore, not answer if a shift in antibiotic resistance occurred between the time periods.

On surgical treatment

In **paper III** the surgical strategy of PJI before and after PRISS was investigated. 604 patients (94%) underwent surgery as part of PJI treatment. In the period before PRISS a substantial proportion of the patients were treated with debridement without exchange of insert or with arthroscopy. Thorough debridement is now considered key to successful treatment and debridement with exchange of insert has been demonstrated to improve success rates.[96] Arthroscopic management of PJI is discouraged due to the risk of only performing a partial debridement.[265] In the period after PRISS treatment strategies had changed considerably with a clear increase of debridements with insert exchange and a reduction in arthroscopy. We believe this to be the result of increased awareness among treating physicians, possibly due to the development of clear national and international guidelines on PJI management.

On mortality

There is increasing awareness that PJI is associated with increased risk of death. Lum et al.[266] performed a meta-analysis of knee-PJIs treated with 2-stage exchange and found a mortality rate of 4.33% per year after PJI. In **paper IV** we found mortality rates of 2.6% and 38% at 1 and 10 years for patients diagnosed with PJI within 90 days of primary surgery, significantly higher than for patients without PJI. The somewhat lower mortality rates in our study can possibly relate to differences in patient selection or demographics. Only patients with PJI within 90 days of an elective primary TKA were included to narrow the spectrum of patients. In contrast to Lum et al., who analysed 2-stage exchange patients, more than 80% in our material were treated according to a DAIR protocol. 2-stage procedures for PJI are mostly used for chronic infections and a sizable proportion of patients is not reimplanted within 1 year reflecting a high level of morbidity.[267] In hip arthroplasty similar results have been published by Wildeman et al.[268] reporting a 45% mortality rate at 10 years after PJI. Gundtoft et al. reported 1 year mortality of 8% after revision for hip-PJI, with enterococcal PJI having a three-fold relative mortality risk compared to other pathogens.[269] In these studies patients with hip fractures were included, which is a group of high fragility that could impact overall mortality.[270]

Mortality during the 2 time periods of our study did not differ. We also found no apparent difference in mortality between different surgical treatment methods. Thus, improvements in PJI management did not reflect on mortality. Most patients were treated with debridement during both periods, leaving only few patients in the other groups. This limits the possibility of finding a difference.

Mortality among patients selected for elective arthroplasty is lower than in the general population, possibly due to the selection of healthier patients for elective arthroplasty.[271] It is also possible that arthroplasty has health improving effects due to increased mobility, leading to reductions of mortality in arthroplasty patients. PJI leads to worse joint function, possibly counteracting the general health benefits of arthroplasty.[268] A more plausible explanation for the effect of PJI on mortality would be the presence of unknown confounders responsible for increasing the risk for PJI and mortality. There are several risk factors for PJI that are also associated with increased mortality, such as male sex, tobacco use, obesity, cardiovascular disease, and diabetes.[272] We used ASA-class, available in the 2012-2013 cohort, as a proxy for comorbidity since detailed data on risk factors were not available. ASA-class is internationally accepted as a measure of morbidity to identify patients with high surgical risk and is associated with mortality in hip arthroplasty patients.[273] We found that the increased risk of mortality in PJI patients remained after adjusting for

ASA-class in addition to other confounders (sex, age, indication for TKA and time period for surgery). Other variables of interest could possibly be investigated in the future through linkage of national diagnosis registers or the cause of death register.

Study design, bias, strengths, and limitations

In this thesis **paper I** and **paper II** are descriptive studies, designed as retrospective cases series based on review of medical charts. The methodology was chosen as a means to explore the less well described entities of streptococcal and enterococcal PJI, considering the rarity of these conditions and the availability of data. With both streptococcal and enterococcal PJI previously described as having poor prognoses, we wanted to see whether that held true also in our regional population. The main strength of both studies lies in the population-based study sample, reducing the risk of selection bias present in studies from tertiary centres or single institutions. Selection bias was minimized by inclusion of all patients with positive cultures in the region, though cases diagnosed outside Skåne would have been missed. The main bias is related to the retrospective collection of data with risks of information bias due to incompleteness or low precision. In outcome analysis missing data was handled through omission of cases lost to follow up.

Papers III & IV are cohort studies with retrospective data collection. Study design was chosen to enable incidence calculations as the entire TKA population during the years in question was included. Major strength are the national unselected sample and the size of the study. Inclusion of all patients from every arthroplasty unit give a true picture of PJI incidence during the selected years. Selection bias could possibly have been introduced by case-finding of possible PJI patients through long outpatient antibiotic therapies. Patients dying rapidly or receiving complete treatment in the hospital would have been missed, leading to underestimation of real PJI cases. Based on clinical experience, we believe these cases to be very few. We also have no reason to believe that this aspect changed significantly between time periods of the study. Some patients were not followed up at the primary operating unit, leading to information loss. In these cases, medical records from hospitals in the city of residence were also reviewed to attain for this issue. The presence of some missed infected cases cannot be completely ruled out. Misclassification bias is also possible since the presence of a PJI diagnosis was determined by the reviewing physician. Careful review of all reported cases was performed to minimize this risk. Some 113 questionnaires were not returned, most belonging to the same unit. These cases were omitted in the incidence calculations.

However, a sensitivity analysis was performed where missing cases were counted as a) infected and b) non-infected. This did not affect the overall results.

Bilaterality is often an issue in orthopaedic research. In **paper IV** bilaterality was managed by inclusion of patients only once, excluding the second primary TKA or (in PJI cases) the uninfected TKA. Since the "risk" of a second procedure is probably higher in healthy and uninfected cases we believe this approach to minimize the effects of bilaterality. The risk for misclassification bias regarding mortality was minimised (presumably null) with use of data from the national population register. In **paper IV** there is a potential för immortality bias in the PJI-group that was not attained for. The effect of immortality bias would, however, be to skew the results towards an even larger survival benefit in the uninfected group and is probably neglible.

Conclusions

- Streptococcal PJIs are predominantly acute, most often haematogenous infections. DAIR is the preferred treatment method and cure is achieved in >80% of patients. Of concern is the high proportion of patients suffering reinfections.
- Enterococci are often part of a polymicrobial infection in PJI. Patients are of advanced age and comorbidities are frequent. Overall, prognosis is poor but when cure is intended it can be achieved in >80% of patients. PJI caused by *E. faecium* carries a poor prognosis.
- Cumulative incidence of PJI within 2 years of primary TKA was 1.45% and incidence rates were similar before and after PRISS. The cause for lack of effect of the PRISS project remains unclear.
- Patients with PJI within 90 days of primary TKA have a higher mortality rate than TKA patients without infection. This difference remains for 10 years, indicating that mortality is not only related to PJI but to general frailty in the affected population.

Future perspectives

PJI is a devastating complication to prosthetic joint replacement surgery. In this thesis various aspects of clinical and epidemiological nature were investigated. In **papers I & II** properties of streptococcal and enterococcal PJI were elucidated with special attention to the poor prognoses previously reported. We report outcomes from these infections that are in line with reports of staphylococcal PJI. A comparative analysis of PJIs with different aetiology would be of interest.

The role of rifampicin in treatment of non-staphylococcal Gram-positive PJI remain unclear. To finally answer whether rifampicin addition is beneficial in the treatment of streptococcal and enterococcal PJI prospective studies are warranted. With cure rates such as the ones reported in this thesis (>80%) prospective studies would need inclusion of a very large number of patients to be able to prove a superior efficacy. Given the low incidence of these infections it is not reasonable to expect studies of that magnitude to be made.

In **paper III** we found similar incidence rates of PJI before and after an ambitious national infection control program. To understand why infection rates did not decrease, though massive efforts were made, requires further research. Many risk factors for infection have been identified in previous studies, but the preventive effect of optimization remains to be understood. With infection rates being very low already it is easy for minor improvements to go undetected, which complicates study.

Methods for accurate surveillance of PJI are lacking. Surveillance is hampered by lack of widely accepted diagnostic criteria and inconsistent registration. To be able to evaluate effects of preventive efforts surveillance methods need to be developed. We noted improvements in the surgical management of PJI, indicating increased consistency in PJI management among clinicians. Capture rates in the SKAR also improved, possibly as an effect of PRISS. These factors could make surveillance based on national arthroplasty registers "good enough", but truly accurate surveillance would probably require use of multiple data-sources, such as the National Patient Register and microbiology databases. Efficient use of resources would require automation.

Prophylactic antibiotics are important for infection prevention. The correct choice of spectrum and substance relies on knowledge of microbial aetiology and preventive

effect. Longitudinal follow up of aetiology of PJI would be beneficial for future decisions on optimum prophylactic regime.

PJI is associated with increased mortality. We conclude in **paper IV** that the long-term increase in mortality among PJI patients probably reflects the overall fragility in the patients suffering from PJI, rather than a direct effect of the infection. Morbidity of PJI patients could be further investigated by linking of existing data to the National Patient Register and the SDPR.

A more visionary take on the future of PJI would include the development of better diagnostic tools. The search for a simple diagnostic test for PJI is ongoing and has improved the diagnostic arsenal slightly, though much work remains. Increased ability to tailor treatments to the state of the bacterial biofilm would also be much appreciated. The use of time as a marker for biofilm maturation has its clear limitations and would greatly benefit from development of biochemical tests or other methods of improved determination. Further, standardized antimicrobial susceptibility testing of biofilm embedded bacteria need to be developed. Today no standard exists that accurately reflects the situation *in vivo*, leaving us with insufficient knowledge on what to expect from treatment.

Populärvetenskaplig sammanfattning

Möjligheten att kunna byta ut en skadad led mot en ledprotes är en verklig medicinsk landvinning som hjälpt miljontals patienter genom åren. I Sverige har antalet ledprotesingrepp ökat stadigt sedan 70-talet och under 2019 genomfördes mer än 40 000 ledprotesoperationer. Under 2020 och 2021 minskade visserligen antalet ingrepp betydligt pga. covidpandemin, men antalet operationer förväntas ånyo fortsätta öka under åtminstone det kommande årtiondet. All kirurgi medför dock risk för komplikationer. Djup infektion som engagerar ledprotesen, så kallad ledprotesinfektion, är en besvärlig men ovanlig komplikation. Årligen drabbas en mindre andel av alla ledprotesopererade, men eftersom antalet ledprotesingrepp ökar, förväntas också antalet ledprotesinfektioner att öka.

En ledprotesinfektion kan uppstå på olika sätt. Det vanligaste är att bakterier fastnar på protesen i samband med, eller i direkt anslutning till, själva protesoperationen. Oftast uppstår då infektionssymptom inom de första veckorna till månaderna efter operationen, men ibland kan det dröja upp till två år. Något mindre vanligt är att bakterier följer med blodbanan och slår sig ned i en befintlig ledprotes, ofta pga. en infektion någon annanstans i kroppen. Detta kallas hematogen infektion och kan uppstå även många år efter att protesen opererades in. Vanliga symptom vid en ledprotesinfektion är ökad smärta från leden, hudrodnad, svullnad/stelhet och att det vätskar från operationssåret. Symptomen kan komma snabbt under loppet av några dagar eller utveckla sig smygande under flera veckor till månader.

Vanligen medför en ledprotesinfektion att man måste opereras igen och få behandling med flera olika antibiotika under lång tid. Slutresultatet efter en ledprotesinfektion är dessutom ofta sämre än för den som inte drabbats av infektion. Sammantaget leder detta till stort lidande för de enskilda patienterna och höga kostnader för samhället. Stort forskningsintresse har därför ägnats åt ledprotesinfektioner under de senaste åren. Dock saknas fortfarande viktig kunskap om hur optimal behandling skall utformas, vilka resultat man kan förvänta sig och hur man bäst förebygger ledprotesinfektioner.

Denna avhandling innehåller fyra arbeten som på olika sätt belyser ledprotesinfektioner på regional och nationell nivå. I det första arbetet (I) undersöktes ledprotesinfektioner orsakade av streptokocker. Streptokocker är ett bakteriesläkte som orsakar några av våra

vanligaste infektioner, till exempel halsfluss och rosfeber. Ledprotesinfektioner orsakas dock endast i cirka 10% av fallen av streptokocker. I studien inkluderades skånska patienter där patientfaktorer, diagnostik, behandling (med såväl kirurgi som antibiotika) och behandlingsresultat kartlades. Resultaten visade att ledprotesinfektion med streptokocker oftast hade hematogent ursprung och vanligen behandlades med protesbevarande kirurgi (vilket innebär att leden rensas och spolas utan att protesen behöver bytas ut). Behandlingsresultaten var relativt goda och nästan 90% av patienterna botades.

Det andra arbetet (II) handlar om ledprotesinfektioner orsakade av enterokocker. Enterokocker är ett bakteriesläkte som är normalt hemmahörande i tjocktarmen. Enterokocker har låg sjukdomsalstrande förmåga, men har en tendens att vara svåra att behandla om de väl orsakar en infektion. Ledprotesinfektioner orsakas i runt 5% av fallen av enterokocker. I studien, där patienter från Skåne inkluderades, kartlades patientfaktorer, diagnostik, behandling och behandlingsresultat. Resultaten visade att enterokockinfektioner ofta drabbar äldre och sköra patienter. Vanligen uppstår infektionerna tidigt efter protesoperationen, inte sällan tillsammans med andra bakteriearter. Behandlingsresultaten är mindre goda och mindre än 70% av patienterna botades med bevarad ledfunktion. I många fall hade dock de patienter som inte botades hög ålder och/eller betydande samsjuklighet. Botande behandling (dvs omoperation och avancerad antibiotikabehandling) var därför aldrig aktuell. I de fall man bedömde att förutsättningar fanns för botande behandling lyckades denna hos 80%.

I det tredje arbetet (III) utvärderades effekten av ett nationellt infektionsförebyggande projekt på förekomsten av ledprotesinfektion efter knäprotesoperation. Mellan 2009 och 2012 genomfördes PRISS-projektet (ProtesRelaterade Infektioner Skall Stoppas), med målet att halvera antalet ledprotesinfektioner. Projektet genomfördes på samtliga enheter med planerad ledproteskirurgi och innehöll skräddarsydda förbättringar av många aspekter av vården före, under och efter en ledprotesoperation. I studien identifierades samtliga patienter med ledprotesinfektion i knä under två år före respektive efter PRISS. Resultaten påvisade en infektionsfrekvens på 1.44% före PRISS och 1.46% efter PRISS, vilket innebär att målet med projektet inte uppfylldes.

I det fjärde arbetet (IV) undersöktes i vilken utsträckning en ledprotesinfektion efter knäprotesoperation också medför ökad dödlighet. I studien jämfördes dödligheten hos de patienter som drabbats av en ledprotesinfektion med dödligheten hos icke-infekterade patienter som opererats under samma tid. Resultaten visade att det fanns en tydligt ökad risk för död hos ledprotesinfekterade både 1, 5 och 10 år efter operationen. Resultatet kvarstod efter statistisk justering för ålder och kön.

Sammanfattningsvis visar denna avhandling:

I. Att ledprotesinfektion orsakad av streptokocker har god prognos.

II. Att ledprotesinfektion orsakad av enterokocker är utmanande att bota, men när botande behandling är ett alternativ lyckas denna relativt ofta.

III. Att infektionsfrekvensen inom 2 år efter knäprotesoperation är 1.45%, med liknande siffror före och efter PRISS-projektet. Det är oklart varför projektet inte lyckades med sin målsättning.

IV. Att ledprotesinfektion medför ökad dödlighet både på kort och lång sikt. Det faktum att ökningen i dödlighet kvarstår under lång tid antyder att dödligheten inte kan skyllas enbart på ledprotesinfektionen. Sannolikt speglar det en allmän skörhet i patientgruppen som drabbas av ledprotesinfektion.

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