Tampere University

RASMUS LIUKKONEN

Prosthetic Joint Infection After Hip or Knee Arthroplasty

Treatment trends and outcomes

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ACADEMIC DISSERTATION
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ACADEMIC DISSERTATION
Tampere University, Faculty of Medicine and Health Technology
Coxa Hospital for Joint Replacement
Finland

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You miss 100 percent of the shots you don't take.
Wayne Gretzky

ABSTRACT

Prosthetic joint infection (PJI) is a feared complication after joint replacement surgery. The incidence of PJI has been reported to range between 1% and 2%. Prosthetic joint infections are treated with revision surgery, where the infectious tissues are debrided, and prosthetic components are removed or exchanged either partly or totally. In general, PJIs are associated with multiple surgeries, inferior patient-reported outcomes, as well as increased comorbidity and mortality.

The aims of this dissertation were to examine the epidemiology of PJI and trends in the treatment of patients who have the infection, to compare different treatment strategies, and to examine how outcomes after revision surgery due to early PJI can be better predicted.

The data of this study were collected retrospectively from electronic patient records at the Coxa Hospital for Joint Replacement for the period January 1, 2008, to September 12, 2021. Patients were identified by searching the ICD-10 (International Classification of Diseases 10th revision) code T84.5 (Infection and inflammatory reaction due to internal joint prosthesis). Thereafter, the 2013 International Consensus Meeting diagnostic criteria were applied to confirm the diagnosis of PJI. Infections were further classified as early, acute hematogenous, and chronic.

In studies I and III, descriptive statistics were used to examine the temporal trends and epidemiology of PJI. In studies II and IV, the Kaplan-Meier method and cumulative incidence functions were used for the survival analyses. In addition, Cox proportional hazards regression and Fine-Gray regression were used for regression analyses in studies II and IV. To examine the prediction of failure after early PJI, logistic regression and decision-curve analysis were used for the statistical analyses in study V. In studies I to IV, STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) guidelines were followed for the reporting of the results. In study V, the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) guidelines were followed in the reporting of the results.

The incidence of early PJIs of the hip increased from 0.11 per 100 primary THAs in 2008 to 1.09 in 2021. Among PJIs of the knee, no clear trends were observed, but the yearly changes in incidences were large. Among patients with PJI of the hip, the comorbidity burden increased during the study period. However, among patients with PJI of the knee, no change in the comorbidity burden was found.

The use of one-stage revisions increased remarkably during the study period. The incidence of one-stage revisions increased from 0.10 per 100 primary total hip arthroplasties (THAs) in 2010 to 0.91 per 100 primary THAs in 2021. A similar trend of increased use of one-stage revision was also observed among knee PJIs, as 12.1% of the revisions in 2008–2009 were one-stage, whereas the proportion had risen to 43.8% in 2020–2021. In contrast, the use of two-stage revisions for knee PJIs decreased remarkably from 57.6% in 2008–2009 to 6.3% in in 2020–2021.

At 1-year follow-up, 26.6% (confidence interval [CI], 22.2%–31.2%) of hip PJI patients had undergone a reoperation and 7.9% (CI, 5.2%–10.9%) had died. The lowest risk for reoperation was after one-stage revision (20.2%, CI, 13.4%–28%), and highest if debridement, antibiotics, and implant retention (DAIR) was performed (36.6%, CI, 28.5%–44.7%). Among early hip infections, one-stage revision was associated with a lower risk for reoperation (hazard ratio [HR] 0.51, CI, 0.31–0.84) with no added mortality risk (HR 1.05, CI, 0.5–2.2) when compared to DAIR. The results after knee PJI were better. After 1-year follow-up, 22.8% (CI, 18.6%–27.3%) of patients had to be reoperated and 3.6% (CI, 2.0%–5.9%) died. Furthermore, after 1-year follow-up the failure rates favored one-stage revision over two-stage revision for all knee infection types. In addition, the results after DAIR were good; for early infections, the risk of failure within the 1-year follow-up was the lowest when DAIR was performed (26.1%, CI 15%–35.8%).

In study V, DAIRs and one-stage revisions were analyzed, and a preoperative prediction score, the KLIC-score, was externally validated. After DAIR, the KLIC-score had a moderate predictive ability (odds ratio [OR] 1.45 per one-unit increase, CI, 1.13–1.90) for early failure, but after one-stage revision the predictive ability was inferior (OR 1.20, CI, 0.93–1.56). After 60 days, the discriminative ability of the KLIC-score was poor both after DAIR (area under curve [AUC] 0.63, CI, 0.55–0.72) and one-stage revision (AUC 0.56, CI, 0.46–0.66). Results from the decision-curve analyses were similar, and the KLIC-score offered no remarkable net benefit to clinical decision-making.

In conclusion, the findings of this dissertation reveal that the incidence of early PJIs has not decreased, but rather it has even increased during the previous decade. In addition, this study has also shown that one-stage revision is a viable treatment option for both early hip PJIs and chronic knee PJIs. As the number of PJIs will likely increase in future, the findings of this dissertation should be used during discussions on future treatment strategies. The results of this dissertation also show that the prediction of failure after PJI treatment is difficult, and that current prediction models are not valid for clinical use.

Finally, as the number of PJIs will increase in future, but the literature on PJIs remains divergent and limited, further high-quality studies on this important topic are warranted. Therefore, future research should focus on large, high-quality, prospective trials that compare different treatment approaches for PJIs, especially for cases of early PJIs.

TIIVISTELMÄ

Tekonivelinfektio on pelätty komplikaatio tekonivelleikkauksen jälkeen. Tekonivelinfektioita hoidetaan uusintaleikkauksella, jossa infektoitunut kudos poistetaan sekä proteesiosat poistetaan tai vaihdetaan joko osittain tai kokonaan. Tekonivelinfektiot johtavat usein toistuviin uusintaleikkauksiin, heikkoon toiminnalliseen lopputulokseen ja alentuneeseen elämänlaatuun, sekä lisääntyneeseen sairastavuuteen ja kuolleisuuteen.

Tämän tutkimuksen päätarkoituksena oli tarkastella tekonivelinfektioiden epidemiologiaa ja hoidon ajallisia trendejä, verrata erilaisia hoitomenetelmiä sekä selvittää, kuinka tekonivelinfektioiden uusintaleikkauksien jälkeisiä tuloksia voidaan ennustaa. Tutkimuksen materiaali kerättiin retrospektiivisesti Tekonivelsairaala Coxassa 1. tammikuuta 2008 ja 12. syyskuuta 2021 välisenä aikana potilaskertomuksista. Potilaat tunnistettiin ICD-10 (kansainvälisen tautiluokituksen 10. versio) koodilla T84.5 (sisäisestä nivelproteesista [endoproteesista] aiheutunut infektio tai tulehdusreaktio). Diagnoosit vahvistettiin vuoden 2013 kansainvälisen konsensuskokouksen diagnostisilla kriteereillä. Infektiot kategorisoitiin varhaisiin, akuutteihin hematogeenisiin sekä kroonisiin infektioihin.

Tutkimuksissa I ja III käytettiin kuvailevia tilastollisia menetelmiä tekonivelinfektioiden epidemiologian sekä hoidossa esiintyneiden trendien tutkimiseen. Tutkimuksissa II ja IV käytettiin Kaplan-Meier-menetelmää ja kumulatiivisia ilmaantuvuusfunktioita elinaika-analyyseihin. Lisäksi Coxin regressiota sekä Fine-Gray-regressiota hyödynnettiin tutkimuksien II ja IV regressioanalyyseissä. Tutkimuksen V tilastollisissa analyyseissä käytettiin logistista regressiota sekä päätöskäyräanalyysiä. Tutkimuksissa I–IV noudatettiin STROBE-ohjeistusta (STrengthening the Reporting of OBservational studies in Epidemiology) raportoinnissa, ja tutkimuksessa V noudatettiin tulosten raportoinnissa TRIPOD (Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis) ohjeistusta.

Varhaisten lonkkatekonivelinfektioiden ilmaantuvuus kasvoi 0,11 infektiosta 100 lonkkatekonivelen ensileikkausta kohden vuonna 2008 1,09 infektioon vuonna 2021. Polven tekonivelinfektioiden ilmaantuvuuksissa ei havaittu selkeitä trendejä, mutta sen sijaan, vuosittainen vaihtelu ilmaantuvuudessa oli suurta. Lonkkatekonivelinfektiopotilailla havaittiin sairaustaakan lisääntymistä, mutta polven tekonivelinfektion saaneilla potilailla samanlaista ilmiötä ei ollut nähtävissä.

Yksivaiheisten proteesinvaihtoleikkausten ilmaantuvuus kasvoi eniten, nousten 0,10:stä vuonna 2010 0,91:een vuonna 2021. Sama ilmiö yksivaiheisen proteesinvaihtoleikkausten lisääntyneessä käytössä havaittiin myös polven tekonivelinfektioiden hoidossa, sillä vuosina 2008–2009 12,1 % proteesinvaihtoleikkauksista oli yksivaiheisia, mutta vuosina 2020–2021 osuus oli 43,8 %. Lisäksi kaksivaiheisten proteesinvaihtoleikkausten osuus polven tekonivelinfektioiden hoidossa väheni merkittävästi: vuosina 2008–2009 57,6 % leikkauksista oli kaksivaiheisia, kun taas vuosina 2020–2021 osuus oli 6,3 %.

Vuoden seurannan jälkeen, 26,6 % (luottamusväli [LV] 22,2–31,2 %) lonkkatekonivelinfektion saaneista potilaista oli joutunut toiseen uusintaleikkaukseen ja 7,9 % (LV 5,2–10,9 %) oli kuollut. Toisen uusintaleikkauksen riski oli suurin puhdistusleikkauksen jälkeen (36,6 %, LV 28,5–44,7 %) ja pienin yksivaiheisen proteesinvaihtoleikkauksen jälkeen (20,2%, LV 13,4–28 %) yhden vuoden seurannassa. Varhaisten lonkkatekonivelinfektioiden hoidossa yksivaiheisen proteesinvaihtoleikkauksen jälkeen uuden uusintaleikkauksen riski oli pienempi (vaarasuhde 0,51, LV 0,31–0,84) ilman lisättyä kuolemanriskiä (vaarasuhde 1,05, LV 0,5–2,2) verrattuna puhdistusleikkaukseen. Tulokset polven tekonivelinfektion jälkeen olivat paremmat kuin lonkan: vuoden seurannan jälkeen 22,8% (LV 18,6–27,3%) potilaista oli joutunut toiseen uusintaleikkaukseen ja 3,6% (LV 2,0–5,9%) oli menehtynyt. Jokaisen polvi-infektiotyypin kohdalla yksivaiheisen proteesinvaihtoleikkauksen tulokset vuoden seurannan jälkeen olivat parempia kuin kaksivaiheisen proteesinvaihtoleikkauksen. Polvi-infektioiden kohdalla puhdistusleikkauksien tulokset olivat erinomaisia ja etenkin varhaisten infektioiden hoidossa epäonnistumisen riski oli pienin vuoden seurannassa (26,1%, LV 15%–35,8 %).

Tutkimuksessa V analysoitiin ja validointiin KLIC-ennustepisteytys varhaisten tekonivelinfektioiden vuoksi suoritetuille puhdistusleikkauksille sekä yksivaiheisille proteesinvaihtoleikkauksille. KLIC-pistemäärän lisääntymisellä oli kohtalainen ennustearvo varhaisen epäonnistumisen suhteen puhdistusleikkauksen jälkeen (vetosuhde 1,45, LV 1,13–1,90), mutta yksivaiheisen proteesinvaihtoleikkauksen suhteen pisteytys oli vain heikosti ennustava epäonnistumisen suhteen (vetosuhde 1,20, LV 0,93–1,56). Puhdistusleikkauksen AUC 60 päivän jälkeen oli 0,63 (LV 0,55–0,72) ja yksivaiheen proteesinvaihtoleikkauksen 0,56 (LV 0,46–0,66), osoittaen heikkoa erottelukykyä varhaisen epäonnistumisen ennustamisessa. Lisäksi myös päätöskäyräanalyysi osoitti, ettei KLIC-ennustepisteytys tarjoa huomattavaa hyötyä kliinisen työn päätöksentekoon.

Yhteenvetona voidaan todeta tämän tutkimuksen osoittaneen, että varhaisten tekonivelinfektioiden ilmaantuvuus ei ole vähentynyt, vaan päinvastoin, ilmaantuvuus on jopa kasvanut edellisen vuosikymmenen aikana. Lisäksi tutkimus osoitti, että yksivaiheinen proteesinvaihtoleikkaus on varteenotettava vaihtoehto sekä varhaisten lonkkatekonivelinfektioiden että kroonisten polvitekonivelinfektioiden hoidossa. Koska tekonivelinfektioiden absoluuttisen määrän odotetaan kasvavan entisestään tulevaisuudessa, tuloksiamme tulisi käyttää tulevien hoitomenetelmien suunnittelussa. Lisäksi tutkimus osoitti, että tekonivelinfektion hoidon onnistumisen ennustaminen on vaikeaa, eivätkä nykyiset ennustemallit ole päteviä kliiniseen käyttöön.

Lopuksi, koska tekonivelinfektioiden määrä tulee kasvamaan tulevaisuudessa, mutta kirjallisuus on ristiriitaista sekä rajallista, tarvitsemme tulevaisuudessa lisää korkealaatuisia tutkimuksia tästä aiheesta. Tulevaisuudessa tulisi keskittyä korkealaatuisiin prospektiivisiin tutkimuksiin, joissa vertaillaan isossa aineistossa ja satunnaistetussa tutkimusasetelmassa eri hoitotapoja tekonivelinfektioiden hoidossa. Erityisesti varhaisten tekonivelinfektioiden hoitolinjoista tarvitaan lisää laadukasta tutkimusta.

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ABBREVIATIONS

aHR	Adjusted Hazard Ratio
ARMD	Adverse Reactions to Metal Debris
ASA	American Society of Anesthesiologists
AUC	Area Under Curve
BMI	Body Mass Index
CCI	Charlson Comorbidity Index
CDC	Centers for Disease Control and Prevention
CRP	C-Reactive Protein
CT	Computed Tomography
CI	Confidence Interval
CNS	Coagulase-Negative Staphylococci
DAIR	Debridement, Antibiotics, and Implant Retention
DCA	Decision Curve Analysis
DM	Diabetes Mellitus
EBJIS	European Bone and Joint Infection Society
HR	Hazard Ratio
ICD-10	International Classification of Diseases 10th revision
ICM	International Conference of Musculoskeletal Infection
IDSA	Infectious Diseases Society of America
IQR	Interquartile Range
MARS	Metal Artifact Reduction Sequence
MRI	Magnetic Resonance Imaging
MSIS	Musculoskeletal Infection Society
OR	Odds Ratio
PCR	Polymerase Chain Reaction
PJI	Prosthetic joint infection
ROC	Receiver Operating Characteristics
SD	Standard Deviation
sdHR	Subdistribution Hazard Ratio
SSI	Surgical Site Infection
THA	Total Hip Arthroplasty
TJA	Total Joint Arthroplasty
TKA	Total Knee Arthroplasty

ORIGINAL PUBLICATIONS

This dissertation is based on the following original publications referred to in the text by their Roman numerals I to V.

Publication I **Liukkonen Rasmus,** Honkanen Meeri, Reito Aleksi, Skyttä Eerik, Karppelin Matti, Eskelinen Antti. Trends in Revision Hip Arthroplasty for Prosthetic Joint Infection: A Single-Center Study of 423 Hips at a High-Volume Center Between 2008 and 2021. *J Arthroplasty*. 2023 Jun;38(6):1151–1159.

Publication II **Liukkonen Rasmus,** Honkanen Meeri, Skyttä Eerik, Eskelinen Antti, Karppelin Matti, Reito Aleksi. Clinical Outcomes After Revision Hip Arthroplasty due to Prosthetic Joint Infection - A Single-Center Study of 369 Hips at a High-Volume Center with a Minimum of One Year Follow-Up. *J Arthroplasty*. 2024 Mar;39(3):806–812.

Publication III **Liukkonen Rasmus,** Honkanen Meeri, Skyttä Eerik, Eskelinen Antti, Karppelin Matti, Reito Aleksi. Trends in Revision Knee Arthroplasty for Prosthetic Joint Infection: A Single-Center Study of 384 Knees at a High-Volume Center between 2008 and 2021. *J Arthroplasty*. 2023 Nov;38(11):2447–2454.

Publication IV **Liukkonen Rasmus,** Honkanen Meeri, Skyttä Eerik, Eskelinen Antti, Karppelin Matti, Reito Aleksi. Clinical Outcomes After Revision Knee Arthroplasty due to Prosthetic Joint Infection - A Single-Center Study of 359 Knees at a High-Volume Center with a Minimum of One Year Follow-Up. *In review*.

Publication V **Liukkonen Rasmus,** Honkanen Meeri, Eskelinen Antti, Reito Aleksi. KLIC Score Does Not Predict Failure After Early Prosthetic Joint Infection: An External Validation with 153 Knees and 130 Hips. *J Arthroplasty*. 2023 Dec 11:S0883-5403(23)01205-6.

AUTHOR'S CONTRIBUTIONS

Study I	Liukkonen collected the patient data, performed appropriate statistical analyses, wrote the initial manuscript, and interpreted the results. Liukkonen was the corresponding author for this manuscript.
Study II	Liukkonen collected the patient data, designed, and performed appropriate statistical analyses, wrote the initial manuscript, and interpreted the results. Liukkonen was the corresponding author for this manuscript.
Study III	Liukkonen collected the patient data, performed appropriate statistical analyses, wrote the initial manuscript, and interpreted the results. Liukkonen was the corresponding author for this manuscript.
Study IV	Liukkonen collected the patient data, designed, and performed appropriate statistical analyses, wrote the initial manuscript, and interpreted the results. Liukkonen was the corresponding author for this manuscript.
Study V	Liukkonen collected the patient data, designed, and performed appropriate statistical analyses, wrote the initial manuscript, and interpreted the results. Liukkonen was the corresponding author for this manuscript.

1 INTRODUCTION

Prosthetic joint infection (PJI) is one of the most devastating complications after total joint arthroplasty (TJA) that is associated with multiple surgeries, inferior patient-reported outcomes, and increased mortality. Consequently, PJI represents a major burden for the patient (Natsuhara et al., 2019; Wildeman et al., 2021). In addition to the burden for individual patients, PJI is also a tremendous economic burden for the global health care system, as it increases the need for hospitalization, leading to increased treatment costs (Premkumar et al., 2021).

Due to advances in surgical techniques and aseptic standards, the incidence of PJI has decreased since the early stages of TJA. There have, however, been conflicting reports regarding incidence rates during the past decades. For example, the incidence of PJI after total hip arthroplasty (THA) has been reported to have increased during recent decades (Dale et al., 2009, 2023; S. M. Kurtz et al., 2018; Lenguerrand et al., 2017), but at the same time, decreasing incidences of PJI after total knee arthroplasty (TKA) have been reported (Bozzo et al., 2022; F.-D. Wang et al., 2018). In contrast, increases in the incidence of PJI after TKA have also been reported (Rupp et al., 2021), and some reports have even suggested that this increase will continue in future (Chang et al., 2020). The comorbidity burden among primary TJA patients has increased during previous decades, and this increase is expected to grow (Carender et al., 2022). Comorbidities also increase the risk for surgical complications such as PJIs. Therefore, increased comorbidities may very well lead to a further increase in the incidence of PJIs (Lenguerrand et al., 2019).

Staphylococcus aureus is traditionally considered the most common pathogen in early or acute hematogenous PJIs, whereas coagulase-negative staphylococci (CNS) usually causes chronic infections (Benito et al., 2019; Triffault-Fillit et al., 2019). High rates of CNSs, however, have also been observed in early infections (Tai et al., 2022), and it has been estimated that around 5% to 15% of PJIs are culture-negative (Palan et al., 2019; Tai et al., 2022). Previously, microbiological findings have usually been reported without stratifying them by joint (Benito et al., 2019; Tai et al., 2022; Triffault-Fillit et al., 2019). However, as the microbiological profiles have been reported to differ between joints, joint-specific examination is needed (Preobrazhensky et al., 2021).

Treatment algorithms have traditionally been used in patient selection processes. Early infections, for example, are preferably treated with debridement, antibiotics, and implant retention (DAIR), and delayed infections with two-stage revision surgery (Izakovicova et al., 2019; Zimmerli et al., 2004). However, the scientific background of such algorithms lacks definitive evidence, and hence no definitive algorithm for patient selection exists (Bialecki et al., 2019; Karachalios & Komnos, 2021; Li et al., 2018). Previous clinical research has predominantly relied on small, diverse groups of cases, often in multi-center settings, with limited comparison between different surgical approaches (Bourgonjen et al., 2021; Grammatopoulos, Bolduc, et al., 2017; Grammatopoulos, Kendrick, et al., 2017; Ilchmann et al., 2016; Kandel et al., 2019; Kang et al., 2018; Kuiper et al., 2018; Nurmohamed et al., 2021; Tirumala et al., 2021). Furthermore, despite extensive research, the outcomes of PJI revisions have not improved during the previous decades (Xu et al., 2020).

In recent years, the usefulness of the traditional gold standard revision strategy, i.e., two-stage revision, has been a topic of discussion, especially as knowledge of a one-stage revision strategy has increased. In addition, for knee PJIs, a so-called "1.5-stage exchange arthroplasty", where the second stage of the originally intended two-stage operation is canceled and the articulating spacer from the first stage is retained in the joint, has become a viable treatment option. Moreover, it has been reported that the reinfection rates after this technique are acceptable when compared to two-stage revisions (Hernandez et al., 2021; Nabet et al., 2022; Srivastava et al., 2019). However, as the 1.5-stage revision is a rather new concept, the evidence on the long-term results is still lacking.

In addition to the implementation of 1.5-stage revision in the modern treatment of PJIs, other contemporary treatment strategies have been reported. For example, results from one-stage cement-in-cement revisions among hip PJIs have been reported to be rather good when compared to traditional strategies (Fishley et al., 2022). As there is still a lack of large comparative clinical studies, especially randomized controlled trials, of the differences between revision strategies among certain infection types, treatment algorithms might change further in future. For example, when knowledge of the indications for one-stage revisions increases, it may lead to an even greater decrease in the use of two-stage revision and even a decrease in the use of DAIR.

Even though PJI has been an important topic throughout the implementation of modern TJAs and has been extensively researched, the prediction of failure after PJI treatment is difficult. Previously, several prediction scores have been reported, but the clinical applicability of these scores has proven to be inadequate. As the number

of early PJIs and the absolute number of chronic PJIs is anticipated to increase in future, well-designed and well-calibrated prediction models would assist clinicians in making treatment decisions.

The purpose of this dissertation was to examine the epidemiology of PJI and recent trends in the treatment of PJI, to compare different treatment strategies, and finally to examine how outcomes after revision due to early PJI can be better predicted.

2 REVIEW OF THE LITERATURE

2.1 Concept of Total Joint Arthroplasty

2.1.1 Historical aspect

In 1923, American surgeon Marius Smith-Petersen described a surgical technique in which the femoral head was coated with glass to stimulate tissue regeneration on the glass surface, which would later be removed in a revision surgery (Hernigou, 2014). In 1938, Philip Wiles performed the first THA surgery, during which both the acetabulum and femoral head were replaced with stainless steel components (Wiles, 1958).

The first total knee arthroplasty (TKA) surgery was performed by the German surgeon, Theophilus Gluck, who replaced the knee joint with a solidly articulated endoprosthesis made of ivory in the late 19th century (Amendola et al., 2012; Ranawat & Ranawat, 2012). Gluck's concept of replacing knee joints with artificial materials was groundbreaking, but the results of these implants were at best mediocre, often failing due to inadequate fixation or infection (Ranawat & Ranawat, 2012). In 1971, English surgeon, John Insall, implanted the first TKA in which all the knee joint surfaces were replaced (Insall, Hood, et al., 1983; Insall & Kelly, 1986).

Sir John Charnley developed his version of total hip arthroplasty (THA) in the 1950s, replacing the hip socket with a polyethylene cup and using a cemented steel femoral stem component (Charnley, 1960). However, a high risk for postoperative infections was observed with Charnley's joint replacement technique with follow-up periods of less than 5 years (Charnley, 1972).

Between 1960 and 1970, Charnley focused heavily on improving aseptic techniques, which significantly reduced the rate of infections during the 1960s. Charnley paid particular attention to minimizing microbes in the operating room, which he demonstrated increased the risk for infection. Other innovations by Charnley included the use of double gloves and layered closure of surgical wounds. Indeed, Charnley's insights in the field of aseptic techniques set the standards for future operating rooms (Charnley, 1972).

2.1.2 Modern use of total hip and knee arthroplasty

In 2021, a total of 10 062 primary THAs and 14 200 primary TKAs were performed in Finland (Figure 1). The most common indication for primary TJA was osteoarthritis, both for THA (87%) and for TKA (94%). (Finnish Institute of Health and Welfare, 2021)

Sir John Charnley originally described THA as a procedure primarily intended for older, less active individuals (Charnley, 1961). Nowadays, however, TJAs can also be successfully performed on younger, more active patients (Aujla & Esler, 2017; Halvorsen et al., 2019; Walker et al., 2016). Thanks to recent advancements in surgical techniques and prosthetic technology (such as fixation techniques and long-lasting materials), the number of TJAs has steadily increased year on year, and this increase is expected to continue in future too (S. Kurtz et al., 2005; Niemeläinen et al., 2017).

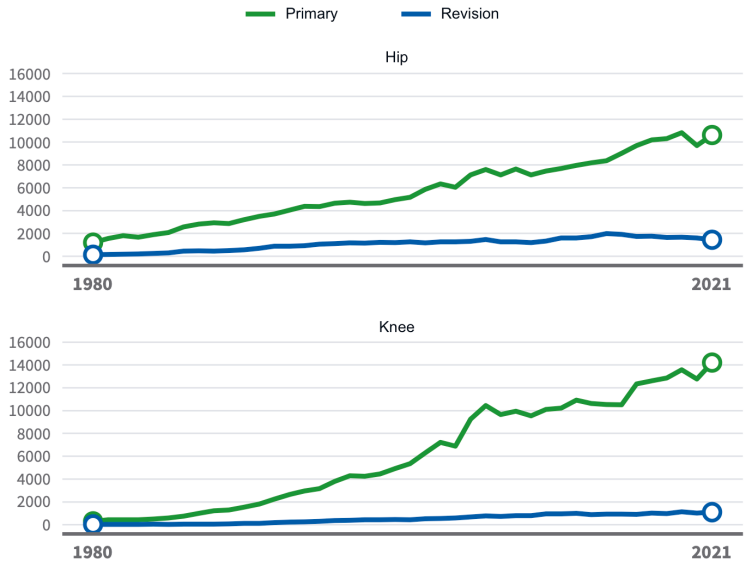

Figure 1. The number of primary and revision arthroplasties of the hip and knee in Finland from 1980 to 2021. (Finnish Institute of Health and Welfare)

Total joint arthroplasty is a cost-effective solution that has a significant effect on the quality of life of the patient (Agarwal et al., 2021; Lavernia & Alcerro, 2011; Räsänen et al., 2007). Prosthetic joints can last for decades, making TJAs suitable for younger patients as well. The positive outcomes in younger patients, coupled with an aging population, will likely further increase the demand for TJA in future (Carr et al., 2012).

2.1.3 Results of primary total hip or knee arthroplasty

Currently, the expected lifespan of a knee replacement is generally longer than that of a hip replacement. The risk for revision surgery after THA over a 15-year period has been reported to be in the range of 9% to 14% (Bayliss et al., 2017; Evans, Evans, et al., 2019). In contrast, , the 15-year revision risk for TKAs is in the range of 4% to 7% (Bayliss et al., 2017; Evans, Walker, et al., 2019). Based on a meta-analysis by Evans et al., approximately 58% of THAs due to osteoarthritis should last for 25 years without the need for revision surgery (Evans, Evans, et al., 2019). Evans et al. also estimated that in the treatment of osteoarthritic knees, 82% of TKAs should last for 25 years without requiring revision surgery (Evans, Walker, et al., 2019).

In Finland, a total of 1 452 revision THAs and 1 100 revision TKAs were performed in 2021 (Finnish Institute of Health and Welfare, 2021). As the annual number of primary TJAs performed has steadily increased, the absolute number of revision surgeries has followed the upward trend. Furthermore, as the annual number of TJAs performed increases year on year, the durability of the prosthetic joint has become an increasingly important factor, both from the patient's perspective and from a societal standpoint, considering the health care costs and indirect costs such as sick leave and disability.

2.1.4 The most common complications

Despite advances in surgical techniques and components, certain complications still cause problems that can lead to revision surgeries. In Finland, infection (29%), dislocation (22%), and periprosthetic fracture of the femur (16%) are the most common complications that lead to revision surgeries after primary THA. For TKAs, the most common complications are infection (36%) and instability (17%). (Finnish Institute of Health and Welfare, 2021)

Regardless of the reasons leading to revision surgery, the outcomes of such surgeries are not as favorable as primary procedures. Indeed, it has been reported that approximately 20% of hips that undergo revision surgery end up requiring a second revision surgery within a 5.5-year follow-up period, with infection (30.2%) being the most common cause (Jafari et al., 2010). Over a 10-year follow-up period, as many as 28% of patients may require a second revision surgery, with infection (45%) still being the most common reason for revision (Kuijpers et al., 2020).

2.2 Definition and diagnostics of prosthetic joint infection

2.2.1 Diagnostic methods

The diagnosis of PJI is preferably confirmed or excluded before revision surgery. As PJI cannot be confirmed by a single diagnostic test, many different methods, and tests, alone or in combination, are used in clinical practice to confirm PJI. In a clinical setting, a stepwise approach to diagnosis is the preferred method. Thorough clinical examinations and evaluation of serologic markers should be the first-line approach before moving on to more invasive measures, such as joint aspiration (Abdel Karim et al., 2019).

Furthermore, the suspicion of the presence of PJI in clinical practice usually begins when the patient with a prosthetic joint has common symptoms of infection. For early PJIs, these symptoms can include wound drainage and effusion. For infections that occur after a longer follow-up, the symptoms might start rapidly with swelling of the joint, and systemic infectious symptoms, such as fever, might be present. In contrast, symptoms might be of a rather chronic nature, including long-lasting pain in the joint, reduced range of motion, and effusion. The patient might also have no clear signs of infection but states: "*the joint has never been good after the surgery"* (Izakovicova et al., 2019).

After suspicion has been raised, a diagnosis can be confirmed with a variety of tests. Usually, a combination of tests are used, as the clinical manifestation can vary a lot among PJI patients.

The diagnosis of PJI does not always need confirmatory laboratory tests, microbial cultures, or imaging studies. Indeed, the presence of a fistula has traditionally been considered to be a definitive, stand-alone indication for PJI (McNally et al., 2021). Joint purulence was also considered to be a definitive indication for PJI in the PJI diagnostic criteria issued by the Infectious Diseases Society of America (IDSA) in 2012. However, this was later removed from further definition because it is inarguably a more subjective factor than others and can lead to observational bias (Osmon et al., 2013). Purulence has also been found in hips with adverse reactions due to metal debris (ARMD) caused by metal-on-metal surfaces, which makes it an even less diagnostic factor for PJI.

2.2.1.1 Synovial fluid, tissue specimens, serum biomarkers

Performed under sterile conditions before the start of antimicrobial treatment, the joint aspiration, has become firmly embedded as the best preoperative diagnostic method (Qu, Zhai, Wu, et al., 2013). Hence, it has been suggested that joint aspiration should be performed for painful prosthetic joints before surgical revision (Izakovicova et al., 2019). From the synovial fluid, the leukocyte count and the percentage of granulocytes are commonly used biomarkers in the diagnosis of PJI (Schinsky et al., 2008; Trampuz et al., 2004). Previously, the sensitivity of elevated leucocyte count ($>1.7 \times 10^3/\mu L$) has been reported to be 94% and specificity 88% for diagnosing PJI; a differential of >65% neutrophils had a sensitivity of 97% and specificity of 98%. However, these are not valid diagnostic cut-offs for early postoperative situations or patients with inflammatory joint diseases, as both the leukocyte count and percentage of granulocytes are usually elevated within these patients (Trampuz et al., 2004).

In addition to leucocyte count and percentage of granulocytes, microbial cultures have been used as the traditional method to identify the presence of a causative pathogen in the affected joint, whether cultured preoperatively from joint aspiration or cultured from intraoperative tissue specimens. The microbial cultures from intraoperative tissue specimens are crucial, especially for patients who have received antimicrobial treatment before the joint aspiration, as the antimicrobial treatment significantly increases the risk for false negatives (Barrack et al., 1997). At least three tissue samples, up to a maximum of five, should be collected to achieve the greatest diagnostic sensitivity and specificity (Peel et al., 2017).

In addition to traditional biomarkers, new synovial biomarkers have been investigated during recent decades. Moreover, promising results for the use of leucocyte esterase and α-defensin in the diagnostic process have been reported (Deirmengian et al., 2014; Parvizi, Jacovides, et al., 2011). Since the early 1980s, a colorimetric strip test has been employed to identify urinary tract infections by relying on a color shift resulting from a chemical reaction with active leukocyte esterase Leukocyte esterase was included in the 2014 PJI diagnostic criteria generated at an international consensus meeting. It was not, however, included in the most recent PJI diagnostic guideline issued by the European Bone and Joint Infection Society (EBJIS) in 2021 (McNally et al., 2021; Parvizi et al., 2014). As part of the immune response to PJI, neutrophils release various antimicrobial peptides, including α-defensin (Ganz et al., 1985). Although α-defensin was recently included

in the PJI diagnostic criteria issued by the EBJIS (McNally et al., 2021), it is not yet routinely used in a clinical setting in Finland.

As preoperative joint aspirations and other diagnostic methods, such as blood cultures or other serum biomarkers, are not always available prior to the initial decision being taken to perform revision surgery due to suspected PJI, the confirmatory diagnosis of PJI could also be made after revision surgery, based solely on the microbiological findings from intraoperative tissue specimens. Furthermore, preoperative microbial confirmation is not a prerequisite before revision surgery (Karczewski et al., 2018).

Histopathology of the periprosthetic tissue could be indicative of PJI, since neutrophil granulocytes can be detected through histopathological techniques performed by a pathologist (Gontarewicz et al., 2012; Tsaras, Maduka-Ezeh, et al., 2012).

No routine blood test alone, however, has sufficient diagnostic capability to confirm or exclude a diagnosis of PJI when compared to joint aspiration or microbial cultures (Carli et al., 2019). If PJI is caused by a low-virulent pathogen, the systemic inflammatory markers can be almost normal (Akgün et al., 2018; Pérez-Prieto et al., 2017; Piper et al., 2010). In addition, as c-reactive protein (CRP) levels might be elevated for up to 3 weeks after the initial TJA, single measurements should not be interpreted as being diagnostic for PJI (Shih et al., 1987). Hence, they should not be used alone for the diagnosis of PJI. When the patient has a suspected septic infection, the blood tests are crucial, whereas for the diagnostic process, blood tests alone are less so.

2.2.1.2 Imaging techniques

Plain radiographs might be useful for detecting infection when analyzed serially over time following the implantation of the initial TJA (Tigges et al., 1994). However, as plain radiographs of PJI patients might be normal, the use of such a technique is neither sensitive nor specific enough. Therefore, plain radiographs do not have any additional value in the diagnostic process and are not routinely used to diagnose PJI.

Computed tomography (CT) provides excellent contrast between bone and soft tissue, making it a valuable tool for assessing significant bone defects that might have caused by the infection before surgery. In contrast, magnetic resonance imaging (MRI) offers superior resolution when it comes to detecting abnormalities in soft tissue compared to CT. Specifically, metal artifact reduction sequence (MARS) MRI is particularly beneficial for distinguishing cases involving metallosis during the

diagnostic process. However, neither of these techniques is routinely used to diagnose PJI. Instead, they are used to differentiate PJI from other abnormal causes of failure, such as ARMD (Peel et al., 2023).

In addition to plain radiographs, CT, and MRI, other proposed imaging possibilities include bone scintigraphy and positron emission tomography (PET) (Corstens & van der Meer, 1999; Kwee et al., 2008), but they have no fixed role in the routine diagnostic process. In their recent diagnostic guideline, the EBJIS introduced nuclear imaging as an emerging possibility (McNally et al., 2021). However, the role of this technique is still as a rule-out test, although some reports have also supported its use in confirming the diagnosis (Glaudemans et al., 2013; Sconfienza et al., 2019).

2.2.1.3 Other diagnostic methods

Other diagnostic methods include sonication and the use of polymerase chain reaction (PCR). Sonication is a technique where explanted prostheses are sonicated to dislodge adherent bacteria from the biofilm. Thereafter, the sonication fluid is cultured to identify the causative pathogen (Trampuz et al., 2007). The diagnostic accuracy of the cultured sonication fluid has been reported to be good, and it might be aidful in the diagnostic process (Peng et al., 2023).

Molecular techniques capable of identifying bacterial DNA have been proposed as a solution to overcome the challenges in diagnosing PJI, particularly in patients, who have previously received antimicrobial treatment or patients with culture-negative PJIs (Esteban & Gómez-Barrena, 2021; Indelli et al., 2021; Wouthuyzen-Bakker, 2023). The most commonly used molecular techniques involve various PCR techniques applied to tissue specimens, such as those obtained from synovial fluid or intraoperative samples (Esteban & Gómez-Barrena, 2021; Jacovides et al., 2012; Lee et al., 2013). It has been reported that when PCR is used in pathogen identification from synovial fluid, 84% sensitivity and 89% specificity can be achieved. Likewise, from sonication fluid, 81% sensitivity and 96% specificity can be achieved (Qu, Zhai, Li, et al., 2013). For patients who have undergone previous antimicrobial treatment, the combination of sonication and PCR has been proven to be valuable (Portillo et al., 2012). However, the use of PCR for PJI diagnostics is restricted, as it has not been proven to be cost-effective and is more prone to contamination, leading to a greater risk for false-positive findings (Achermann et al., 2010).

2.2.2 Diagnostic criteria

Before 2011, PJIs were diagnosed according to the Centers for Disease Control and Prevention (CDC) criteria for the definition of surgical site infections (SSIs) (Horan et al., 1992), but there was no accurate agreed definition specified for the diagnosis of PJI. In 2011, the MSIS developed a diagnostic algorithm that was based on major criteria (sinus tract or microbiology) or four out of six minor criteria (Parvizi, Zmistowski, et al., 2011). In 2012, the IDSA proposed simpler criteria based on the presence of one out of five criteria (Osmon et al., 2013). The 2011 definition by the MSIS was later modified at the first International Conference of Musculoskeletal Infection in 2013 (Parvizi et al., 2014). Since then, it has remained the most used definition of PJI. These definitions are presented in Table 1.

Table 1. Definitions for PJI from 2011 to 2013 (Parvizi et al. 2011, Osmon et al. 2013, Parvizi et al. 2014)

2011 MSIS	**2012 IDSA**	**2013 ICM**
One out of two major criteria	*One out of five criteria*	*One out of two major criteria*
Sinus tract Two positive microbiological cultures	Sinus tract Joint purulence Histology Two positive microbiological cultures Virulent pathogen	Sinus tract Two positive microbiological cultures
OR *Four out of six minor criteria*		OR *Three out of five minor criteria*
Elevated CRP&ESR Elevated synovial WCC Elevated synovial PMN% Joint purulence One culture Histology		Elevated CRP&ESR Elevated synovial WCC or leukocyte esterase Elevated synovial PMN% One culture Histology

Cut-off values: CRP >100 for early (<6 weeks from previous operation) and >10 for delayed/late infections (>6 weeks from previous operation); ESR >30 within delayed/late, does not apply for early infections; WBC count >10 000 for early and >3 000 for delayed/late infections; PMN% >90% for early and >80% for delayed/late infections. PJI = prosthetic joint infection, MSIS = Musculoskeletal Infection Society, IDSA = Infectious Diseases Society of America, ICM = International Consensus of Musculoskeletal Infection, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, WCC = white cell count, PMN = polymorphonuclear neutrophils.

These definitions set the standards for research. Prior to 2011, the definitions of PJI varied and caused apparent bias to the results of separate studies, making the comparability of different studies difficult.

At the second International Conference of Musculoskeletal Infection in 2018, a new definition was developed that was based on major criteria or weighted score from the minor criteria (Parvizi et al., 2018). This definition was not universally accepted nor recognized by the EBJIS or the MSIS. A major limitation was that this definition, as well as the earlier definitions, presented a bimodal strategy for the diagnosis (infected or not infected) based on a test that was neither 100% specific nor 100% sensitive. Nevertheless, as the 2018 definition also included the "inconclusive" group, consisting of possible infections that presented with some of the minor criteria but did not reach the required score for the definitive diagnosis of PJI, it was more sensitive than previous definitions. (Table 2)

Table 2. The diagnostic criteria proposed in 2018 (Parvizi et al. 2018)

Major Criteria (at least one of the following)	**Decision**
Two positive cultures of the same organism Sinus tract with evidence of communication to the joint or visualization of the prosthesis	Infected

Minor criteria	**Threshold**		**Score**	**Combined score**
	Acute*	**Chronic**		≥6 infected
Elevated serum CRP (mg/ml) *or*	100	10	2	4-5 inconclusive
elevated D-dimer (μg/l)	Unknown	860		≤3 not infected
Elevated ESR (mm/hour)	No role	30	1	
Elevated synovial WCC (1/μl) *or*	10 000	3 000	3	
leukocyte esterase *or*	++	++		
positive α-defensin (signal/cutoff)	1.0	1.0		
Elevated synovial PMN%	90	70	2	
Single positive culture			2	
Positive histology			3	
Positive purulence			3	

* Acute infection was defined as a PJI occurring within the first 90 days after the initial TJA. CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, WCC = white cell count, PMN = Polymorphonuclear Neutrophils.

In 2021, the EBJIS developed the most recent definition of PJI (McNally et al., 2021). The major difference to previous definitions was that this definition recognized three different groups according to the likelihood of the presence of PJI: infection unlikely, infection likely, and infection confirmed. It also included some of the more subjective measures that were not included in the previous definitions, such as early loosening of the prosthesis, poor wound healing, or fever. These minor criteria help in the identification of "low-grade" infections, which may have been missed using the previous definitions. However, as this new definition used more subjective measures than, for example, the 2013 definition, it may be prone to observer bias in the research setting. (Table 3)

Table 3. The 2021 EBJIS definition criteria for PJI (McNally et al. 2021)

	Infection Unlikely	Infection Likely	Infection Confirmed
	(all findings negative)	(two positive findings) *	(any positive finding)
Clinical and Blood Workup			
Clinical features	Clear alternative reason for implant dysfunction (e.g., fracture, implant breakage, malposition, tumor)	1) Radiological signs of loosening within the first 5 years after the implantation 2) Previous wound healing problems 3) History of recent fever or bacteremia 4) Purulence around the prosthesis	Sinus tract with evidence of communication to the joint or visualization of the prosthesis
CRP		> 10 mg/L	
Synovial Fluid Cytological Analysis			
WCC (cells/μL)	≤ 1 500	> 1 500	> 3 000
PMN (%)	≤ 65%	> 65%	> 80%
Synovial fluid Biomarkers			
Alpha-defensin			Positive immunoassay or lateral-flow assay
Microbiology			
Aspiration fluid		Positive culture	
Intraoperative (fluid and tissue)	All cultures negative	Single positive culture	≥2 positive samples with the same microorganism
Sonication (CFU/mL)	No growth	>1 CFU/mL of any organism	>50 CFU/mL of any organism
Histology			
High-power field (400x magnification)	Negative	Presence of ≥ 5 neutrophils in a single HPF	Presence of ≥ 5 neutrophils in ≥ 5 HPF *or* Presence of visible microorganisms
Others			
Nuclear imaging	Negative 3-phase Isotope Body Scan	Positive WBC scintigraphy	

If antibiotic treatment has been given or other possible causes of inflammation are present, such as active inflammatory joint disease or the early postoperative period, the results from diagnostic tests should be interpreted with caution, and molecular techniques may have a place. *Infection is only likely if there is a positive clinical feature or raised serum CRP together with another positive test. PJI = prosthetic joint infection, CRP = C-reactive protein, WCC = white cell count, PMN = Polymorphonuclear Neutrophils, WBC = white blood cell.

2.3 Classification

2.3.1 Timing of the infection

Prosthetic joint infections have traditionally been classified based on the time from the previous aseptic operation. Early infections occur within the first three postoperative months from the previous operation, delayed infections between 3 and 24 months, and late infections at least two years after the previous operation (Zimmerli et al., 2004). However, this classification system alone is not so relevant in clinical decision-making.

2.3.2 Type of infection

In addition to the classification based on the time from the previous operation, several classification protocols have been used to reflect the pathogenesis of the infection. PJIs can be classified as acute or chronic, based on the duration of the symptoms. PJIs with symptoms for 21 to 28 days are usually considered acute PJIs, whereas infections with symptoms lasting for longer are considered chronic PJIs. This classification system is based on the maturation process of the biofilm, as the maturation of the potential biofilm usually takes about this time (Almasri & Dahman, 2023; Izakovicova et al., 2019). This classification system might not be definitive because the accurate cut-off between the mature and immature biofilm is almost impossible to define for individual patients.

In many PJI studies, all the infection types are grouped in one single cohort, but preferably, some classification should be used to make the interpretation and generalization of the results easier. In addition, as these classification systems rely mostly on the period since the previous operation or from the onset of symptoms, but other clinically relevant information, such as type of previous operation (primary TJA, revision TJA) or other comorbidities, are not considered, they might include somewhat heterogenic patients. Furthermore, as the clinical manifestations and pathogenesis may differ between different pathogens and types of infection, pathogen-specific studies are warranted.

2.3.3 Other classification systems

Three classification methods have been described that aim to help in clinical decision-making and provide more patient-specific guidelines. McPherson et al. classified PJIs using the duration of the infection, the medical status of the patient, and the condition of the local infection site (McPherson et al., 2002). This classification was based on the Cierny-Mader classification of long bone osteomyelitis (Cierny & Mader, 1984), and has since been demonstrated to be useful in clinical decision making (Bryan et al., 2017; Wolf et al., 2014).

Alt et al. adopted the tumor, node, and metastasis (TNM) classification of malignancy for PJI, the PJI-TNM classification, and presented it in 2020 (Alt et al., 2020). The classification was developed based on the permutation of three variables: T: Tissue and implant conditions, N: Non-human cells (bacteria and fungi), and M: Morbidity of the patient. Since the presentation of the original PJI-TNM system, it has been simplified to a more simpler version, PJI-pTNM (Lunz et al., 2023). The clinical utility of this classification is that it helps decision making between different revision types, as it guides the management of PJI into four possible treatment categories: DAIR (T0N0), implant removal (T1, T2, N1, N2), a 'less aggressive' operation (M3b), or non-operative management (M3a, M3c) (Alt et al., 2020).

The BACH classification was originally developed for the classification of long bone osteomyelitis (Hotchen et al., 2019), but a joint-specific version (JS-BACH) of the classification was adapted for PJI in 2021 (Hotchen et al., 2021). This classification included information on implant type, loosening, bone loss, and history of periprosthetic fractures. Based on these four variables, PJIs are categorized into three groups: uncomplicated PJI, complex PJI, or PJI with limited treatment options. The clinical utility of the JS-BACH classification has been reported to be good, as it might help predict the likelihood of recurrence and quality of life following surgery for PJI.

2.4 Pathogenesis

2.4.1 Microbiology

The microbiology has been previously reported to be associated with the time since the previous operation and the duration of symptoms. Traditionally, *S. aureus* and

gram-negative bacteria are considered the most likely causative pathogens among early and acute infections, whereas chronic infections are believed to be caused by less virulent pathogens, such as CNS (Zimmerli et al., 2004). These less virulent pathogens take time to proliferate sufficiently to cause symptoms, and hence are often called "low-grade" infections. Recent studies, however, have also shown, that CNS might also cause a remarkable proportion of early infections (Tai et al., 2022). Furthermore, although the microbiological profile of PJIs is usually reported for both the knee and hip joint together, recent studies have reported that the microbiological profile between the knee and hip joints can differ, indicating that joint-specific examination would be beneficial (Preobrazhensky et al., 2021).

The detection of the causative microbe is the basis of antimicrobial treatment. However, despite efforts to detect the pathogen, the causative pathogen remains unclear in up to 15% of PJIs, and the microbiological cultures are negative (Goh & Parvizi, 2022; Palan et al., 2019).

Although most PJIs are believed to be caused either by contamination from the initial surgery or soon thereafter, it has been estimated that up to two-thirds of PJIs are caused by intra-operative contamination (Zimmerli et al., 2004). In addition to direct contamination, the causative pathogen might also spread hematogenously to the prosthesis. High vascularity around the periprosthetic tissue exposes the prosthesis to hematogenous spread, especially during the first year of implantation. The source of the hematogenous PJIs can, for example, be from the skin and soft tissues (Wouthuyzen-Bakker et al., 2018) or from dental sources (Danilkowicz et al., 2021; Friedlander, 2009). These hematogenous infections are usually caused by virulent pathogens, such as *S. aureus,* and usually have a rather acute course.

2.4.2 Biofilm

The early phases of PJI have been theoretically explained by the possible formation of microbial biofilm. A microbial biofilm on a prosthetic joint is a complex community of microorganisms, primarily bacteria, that adhere to the surface of an prosthetic joint, such as a hip or knee replacement. These microorganisms create a protective layer or matrix of extracellular substances, making them resistant to antimicrobial treatment and the body's immune response (Costerton et al., 1999). The development of biofilm is shown in Figure 2.

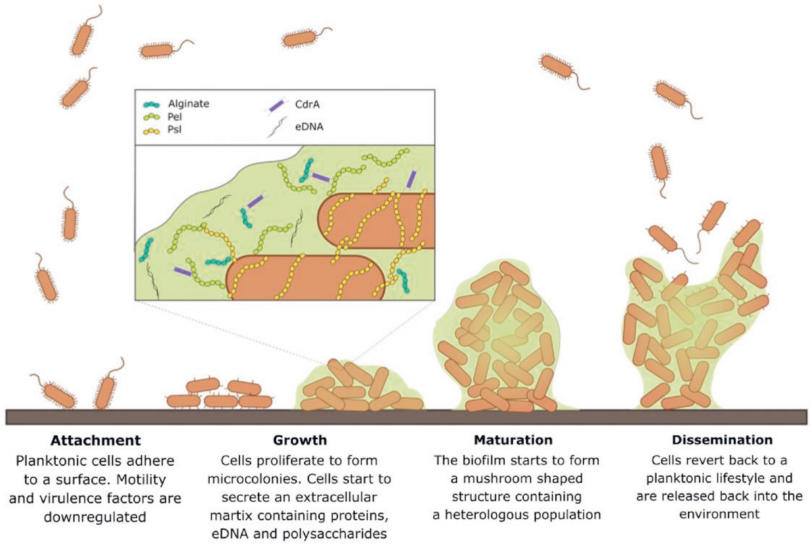

Figure 2. Development of microbial biofilm on a prosthetic surface (Maunders et al. 2017). Image reproduced by the terms of Creative Commons Attribution License (https://creativecommons.org/licenses/by/4.0/).

The development of biofilm is based on the cycles of attachment, growth, maturation, and dispersal (Maunders & Welch, 2017). First, the bacteria attach to the surface of the prosthesis. Then, the bacteria start the growth period. The maturation stage is when the biofilm grows a matrix to protect the bacteria inside. This maturation process might take up to four weeks after initial attachment to the implant surface (Zimmerli et al., 1982).

Mature biofilms are extremely resistant to commonly used antibiotics, ranging up to 1 000 times more resistant when compared to infections without biofilm formation (Liu et al., 2021; McConoughey et al., 2014). In addition to the possible formation of biofilms, the implanted prostheses reduce the minimal infecting doses of common pathogens. For example, it has been estimated, that the minimal infecting dose of *S. aureus* is reduced by over 100 000-fold when a prosthetic surface is presented (Gbejuade et al., 2015).

2.4.3 Clinical manifestation

Early PJIs typically exhibit pronounced local and systemic inflammation symptoms (Zimmerli et al., 2004), and wound drainage is also often present. In contrast, delayed

infections, which usually occur between three months and three years after implantation, present with milder symptoms. Among these infections, early implant loosening, and joint pain may be present. These infections are mainly caused by less virulent organisms and can be very difficult to differentiate from aseptic failures.

Acute, hematogenously spread PJIs can manifest suddenly after a long, pain-free period. Typically, intense pain and acute onset of symptoms is present after a long painless period lasting for tens of years after implantation (Rakow et al., 2019). Other clinical signs may include fever and effusion.

2.5 Epidemiology

The incidence of PJI after THA ranges between 0.5% and 0.7% during the first postoperative year (Gundtoft et al., 2017; Huotari et al., 2015; S. M. Kurtz et al., 2018). The cumulative incidence of late hip infections ranges between 0.04% and 0.06% per prosthesis year (Huotari et al., 2015). Following TKA, the risk for PJI has been reported to be around 2% within the 2-year follow-up (S. M. Kurtz et al., 2010, 2018). For late knee infections, the cumulative incidence ranges between 0.06% and 0.08% per prosthesis-year (Huotari et al., 2015). Previously, it has been reported that the incidence of PJI was higher after TKA. However, within recent years, the incidence of PJI after THA has been reported to be nearly similar or even higher than after TKA (Dale et al., 2023).

In the early stages, the risk for infection after TJA has been reported to be as high as 7% to 9% (Charnley, 1972). Even though the incidence of PJI has decreased a lot since the implementation of the concept of TJA, there have been conflicting reports regarding the incidences during the past decades. For example, it has been reported that the incidence of PJI after THA has increased during recent decades (Dale et al., 2009, 2023; S. M. Kurtz et al., 2018; Lenguerrand et al., 2017), whereas after TKA, decreasing incidences of PJI have been reported (Bozzo et al., 2022; F.-D. Wang et al., 2018). However, increases in the incidence of PJI have also been reported after TKA (Rupp et al., 2021), and some reports have even suggested this increase will continue (Chang et al., 2020). Recent trends in the incidence of PJI after primary THA in the Nordic countries, examined by the Nordic Arthroplasty Register Association, are shown in Figure 3.

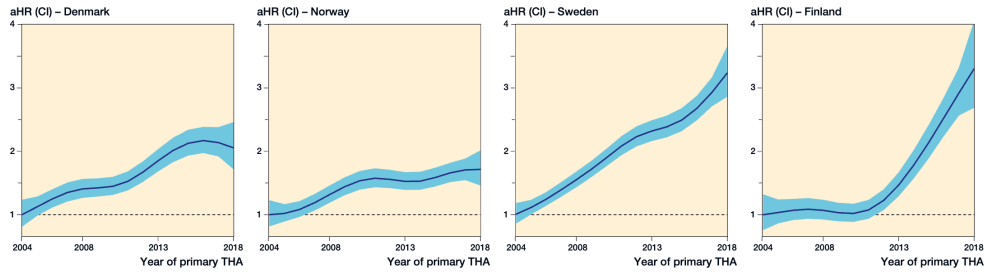

Figure 3. The relationship between year of primary surgery and risk of revision due to PJI (with 95% CI) for all THAs, adjusted for sex, age, indication for primary THA, and fixation. (Dale et al. 2023). Image reproduced by the terms of Creative Commons Attribution License (https://creativecommons.org/licenses/by/4.0/).

The variation between reported incidences may be due to differences in the infection definitions, as the number of detected infections varies between the most commonly used PJI definitions (Sigmund et al., 2022). However, as the number of primary TJAs increases steadily (Finnish Institute of Health and Welfare, 2021; Niemeläinen et al., 2017; Sloan et al., 2018), and the expected lifespan of primary components increases due to advances in surgical techniques, the absolute number of late PJIs is also expected to increase in future (Huotari et al., 2015).

In addition to the differences between the standardized definitions, the reporting of infections in the registers might be inaccurate. It has previously been reported that these nationwide registers might underestimate the true incidence of PJIs (Jämsen, Huotari, et al., 2009). For example, any revision procedure due to infection, such as closure of a draining wound, could be reported as a revision due to PJI, increasing the number of PJIs in such a register. In addition, when examining the incidence of PJI in an epidemiological setting between multiple centers or at the national or even global level, the definitions might vary greatly. This is because infection diagnostics in some centers might not be as capable or available as in others. Nuclear imaging or other modern techniques, for example, are not available everywhere, leading to differences in the resources available for infection diagnostics. In other words, as the diagnostic process is not standardized and the definition of PJI is not binomial, such as in the definition of the presence of fracture, it might lead to reporting bias between different centers and registers. Thus, large clinical studies, with accurate information on the infections, are also needed to examine the epidemiological trends in PJI incidence.

The variations in the reported incidences might also be partly explained by the different indications for revision surgery. Surgeons may perform DAIR due to prolonged wound drainage to "save" the implant and thereafter report this to the

register as revision due to infection. The threshold to perform these minor procedures may be lower than for full operations involving the removal of the definitive prosthesis. In addition, the threshold to perform these procedures might also differ between institutions. When the different indications and thresholds for procedures are combined with differences in the definitions of PJI, the true incidence of PJIs might be different than the reported incidence.

As the incidence of PJI is predicted to continue increasing (Chang et al., 2020; O'Toole et al., 2016; Premkumar et al., 2021), it will automatically increase the economic burden as well (Sabah et al., 2021; Vanhegan et al., 2012). Because PJI is associated with multiple surgeries, increased morbidity, and mortality (Natsuhara et al., 2019), as well as longer periods in hospital, the projected increase also poses a major burden to the global health care system.

2.6 Risk factors and prevention

Since the early development of TJA, the risk factors for the PJI have been a widely studied topic. The risk factors for PJI can be divided into preoperative risk factors, intraoperative risk factors, and postoperative risk factors. The preoperative risk factors are mostly patient-related, whereas the intra- and postoperative risk factors can be further categorized into patient-related risk factors and operation-related risk factors. Risk factors can also be categorized into modifiable (body mass index (BMI)) and unmodifiable (age) risk factors. The risk factors for PJI might differ between the knee and hip joints, mostly due to anatomical differences (Peel et al., 2011).

The measures to prevent PJI can be categorized in the same way as risk factors. Generally, preoperative measures aim to improve the patient's condition, intraoperative measures aim to prevent contamination, and postoperative measures aim to optimize the immediate healing process by preventing wound infections and, in the long-term, to prevent the hematogenous spread of pathogens from other remote infections. In 2017, the CDC published its most recent guideline regarding the prevention of SSIs, which also included a dedicated section for PJIs (Berríos-Torres et al., 2017).

2.6.1 Preoperative factors

The risk for PJI increases when certain chronic comorbidities are present. Especially among those patients with multiple comorbidities as measured by Charlson's Comorbidity Index (CCI), the risk for PJI is high (S. M. Kurtz et al., 2010). In addition to multiple comorbidities, the increased comorbidity burden, measured with the American Society of Anesthesiologists (ASA) score, has also been associated with an increased risk for PJI (Mäkelä et al., 2021). Single comorbidities, especially the presence of diabetes mellitus (DM), rheumatoid arthritis, or obesity, have been associated with increased risk for PJI (Bozzo et al., 2022; Jämsen, Huhtala, et al., 2009; Jämsen et al., 2012; Kerkhoffs et al., 2012; Kunutsor, Whitehouse, Blom, et al., 2016; Mäkelä et al., 2021).

Furthermore, diabetes mellitus has been strongly associated with increased risk for PJI after TJA by both large meta-analyses (Kunutsor, Whitehouse, Blom, et al., 2016) and large nationwide registry studies (Bozzo et al., 2022; Jämsen, Huhtala, et al., 2009). Controversially, Kremers et al. have reported contradictory findings (Maradit Kremers et al., 2015). In their study, they proposed that the increased rate of PJIs was mostly due to other factors that co-exist with DM, such as obesity and higher ASA scores. However, as the presence of DM does not indicate how the comorbidity is treated, the differences between the previously published results might be due to differences in diabetes control among the included patients. In 2010, Jämsen et al. revealed that preoperative hyperglycemia increases the risk for PJI (Jämsen, Nevalainen, et al., 2010), as does higher blood glucose levels on the day of the surgery (Wier et al., 2023). Therefore, one might argue that if only poorly-controlled DM increases the risk for PJI, well-controlled DM might not be a significant risk factor for PJ, Moreover, because the prevalence of DM has been shown to be increasing, it has been predicted that the incidence of PJI will also increase (O'Toole et al., 2016).

Rheumatoid arthritis has also been identified as a risk factor for PJI, both in a recent meta-analysis (Kunutsor, Whitehouse, Blom, et al., 2016) and a large nationwide registry study (Jämsen, Huhtala, et al., 2009). The association between rheumatoid arthritis and increased risk for PJI might be explained by the immunosuppressive medication commonly used for treating rheumatoid arthritis. However, the increased risk for PJI has not been associated with the type of medications used for rheumatoid arthritis (Cordtz et al., 2018).

Obesity has been associated with an increased risk for PJI by multiple meta-analyses (Kerkhoffs et al., 2012; Yuan & Chen, 2013). Different cut-off values for

obesity have been proposed, but as a continuous variable, from the statistical viewpoint, it should not be dichotomized. Moreover, it would be wrong to assume that a BMI 31 shares the same risk as a BMI 45 when the cut-off value is set to 30. However, as an increase in the continuously analyzed BMI has also been associated with increased risk for PJI (Jämsen, Varonen, et al., 2010), it should be considered as a valuable predictor of the risk for developing the PJI. In addition to the obesity, malnutrition has been reported as a significant risk factor for the development of PJI (C. Wang & Lv, 2023).

Acute comorbidities, especially infections, increase the risk for PJI (Cizmic et al., 2019) and usually result in a planned surgery being postponed. Hence, different screening methods have been applied to detect other possible sources of infection before TJA. The most commonly screened regions are infections of the feet (Kimyai-Asadi et al., 1999) and asymptotic urinary tract infections (Martínez-Vélez et al., 2016). In addition to these infections, dental health and possible infections of the teeth have been associated with a possible increase in the risk for PJI. Furthermore, skin conditions, such as atopic dermatitis, have been associated to the increased risk of infections (Lim et al., 2007).

Along with comorbidities, other patient-specific factors, such as age, sex, smoking, previous operations to the same joint, and indication for TJA, have also been reported to influence the risk for PJI (Bozzo et al., 2022; Jämsen, Huhtala, et al., 2009; S. M. Kurtz et al., 2010). Even though most patients are female, the male sex is associated with an increased risk for PJI (Bozzo et al., 2022; Jämsen, Huhtala, et al., 2009). Interestingly, younger age has also been associated with an increased risk for PJI (Bozzo et al., 2022), but contradictory results have also been reported (S. M. Kurtz et al., 2010), indicating that the effect of age on the risk for PJI might not be that strong. Moreover, as both sex and age are potential unmodifiable risk factors, they have a very limited effect on the risk for PJI and are not routinely considered in the decision-making process on whether to operate. However, smoking is a factor that significantly increases the risk for PJI (Alamanda & Springer, 2018; Kunutsor, Whitehouse, Blom, et al., 2016), and is easily modifiable, which is why it is taken into account when making the initial decision to operate. Other factors that might increase the risk for PJI preoperatively are previous surgeries to the same joint and indication for the primary TJA, as it has been reported that previous trauma to the hip increases the risk for PJI later (Bozzo et al., 2022; Jämsen, Huhtala, et al., 2009). The association between previous operations and increased risk might be due to the increased scar tissue caused by the previous surgery. In addition to previous operations, intra-articular injections to the hip might increase the risk of PJI,

especially if performed less than 3 months before the THA (Albanese et al., 2023; Saracco et al., 2023).

2.6.1.1 Preoperative preventative measures

Preoperative measures focus mainly on the optimal treatment of chronic diseases, primarily the treatment of DM. As hyperglycemic patients are at higher risk for PJI, the optimal treatment of diabetes mellitus significantly reduces the risk for PJI (Jämsen, Nevalainen, et al., 2010). The screening for other infections, such as asymptomatic urinary tract infections and dental infections, has also been proposed. However, the current consensus neither supports screening for asymptomatic bacteriuria (Honkanen et al., 2018; Rodríguez-Pardo et al., 2021) or a standardized protocol to perform dental clearance for each TJA patient (Kwan et al., 2023; Lampley et al., 2014), and these are no longer required. In cases of acute infections, such as skin infections or acute urinary tract infections, the surgeries are postponed, and the infections are properly treated before TJA is performed. In addition, smoking cessation is always advised, as the impact of smoking on the results is significant (Kunutsor, Whitehouse, Blom, et al., 2016).

The duration of preoperative stay in the hospital should be minimized to reduce the risk of colonization of the patient's skin with possibly resistant hospital-acquired bacterial strains (Jämsen, Furnes, et al., 2010). Arrival at the hospital on the day of operation is a routine.

2.6.2 Intraoperative factors

The intraoperative risk factors for PJI are mostly based on an increased risk for contamination. Duration of the operation has been associated with the risk for PJI (S. M. Kurtz et al., 2010; Ong et al., 2008). The reason for this might be as simple as the longer the initial surgical incision is exposed to the air, the longer it is also exposed to airborne bacteria. The reason might also be more complicated, as more complex surgeries might need more time and, due to their complexity, other factors might also contribute to the increased risk for PJI. Additionally, it has been reported that performing TJA on obese patients requires longer surgeries, which may also contribute to an increased risk for PJI (Liabaud et al., 2013).

Different surgical techniques have also been associated with increased risk for PJI. For example, the requirements of a tibial bone graft has been associated with

increased risk for PJI (Lenguerrand et al., 2017). The reason for this is unclear, and it might be that those factors that guide the selection of the surgical technique contribute to the increased risk for PJI. In addition to surgical techniques, other treatment-related factors, such as the use of allogenic blood transfusions, have been associated with increased risk for PJI (Pulido et al., 2008).

2.6.2.1 Intraoperative preventative measures

Probably the most effective commonly used intraoperative practice to prevent PJI is the use of antibiotic prophylaxis. It has been proven to be an effective (Inabathula et al., 2018; Kheir et al., 2021; Siddiqi et al., 2019) and cost-effective solution for reducing the risk for PJI (Lipson et al., 2022). Therefore, preoperatively administered antibiotic prophylaxis is advised to be used routinely among TJA patients (Garvin & Hanssen, 1995; Ratto et al., 2016).

The prevention of contamination starts before the patient arrives in the operation room. Before surgery, the surgeons and their assistants should perform a thorough alcohol-based hand rub, and patients should shower or bathe with soap or an antiseptic agent to reduce the possible bioburden of the skin (Berríos-Torres et al., 2017). The risk of contamination is also routinely reduced by the preoperative preparation of the skin. This is also included in the guidelines regarding the routinely performed preventative measures for SSIs (Dumville et al., 2015; Ratto et al., 2016). In addition to the commonly performed chlorhexidine preparations (Darouiche et al., 2010), iodine-impregnated incision drapes are commonly used to protect the surgical sites, especially in THAs.

After the beginning of the operation, the commonly used preventative measures include the use of antibiotic-impregnated cement and limiting the duration of the operation as much as possible (Parvizi et al., 2013; Tarabichi & Parvizi, 2023). Other proposed measures include, for example, routine glove changes, reducing traffic to the operation room, and the laminar airflow of the operation room.

The effect of laminar airflow on PJI rates was first described in the early stages of modern TJA by John Charnley who reported that it would significantly decrease the risk for PJI (Charnley, 1972). In 1982, Lidwell et al. also reported in their RCT, that laminar airflow significantly decreases the risk of PJI (Lidwell et al., 1982). However, as other preventative measures were invented that are still in use today, such as the use of antibiotic prophylaxis, space suits and double gloves,, the effect of these inventions alone on the risk for infection has been questioned (Gastmeier et al., 2012; Hooper et al., 2011). Furthermore, the prevention of intraoperative

contamination is a multifactorial process that is based on well-managed hygiene and sterile working. Nowadays, the operational techniques, preparations, and other intraoperative preventative measures are widely standardized and supervised with checklists. It might be, therefore, that the rate of PJIs cannot be reduced significantly with new intraoperative inventions, as the current level of aseptic procedures have reached such high standards.

2.6.3 Postoperative factors

During the immediate postoperative period, SSIs are associated with the greatest risk for PJI development (Peel et al., 2011). Other immediate postoperative risk factors that may increase the risk for PJI include TJA related complications such as atrial fibrillation and myocardial infection (Pulido et al., 2008). This association might also be due to the aggressive anticoagulation medicines used for other comorbidities, as aggressive anticoagulation has been associated with an increased risk for bleeding, and the subsequent increased risk for hematoma formation (Kapadia et al., 2016). Hematoma might, in turn, increase the risk for SSI because it has been reported that the formation of a hematoma can lead to an increased risk for PJI (Jong et al., 2017).

After implantation of the TJA, the patient is at lifetime risk for PJI. This is due to the possible hematogenous spread from remote infections, such as dental infections (Coll et al., 2020), urinary tract infections (C. Wang et al., 2021), or skin infections (Wouthuyzen-Bakker et al., 2018). Hence, the appropriate management of other infections is necessary because the possible bacteremia caused by such infections can reach the surface of the prosthesis and cause PJI.

2.6.3.1 Postoperative preventative measures

The aim of immediate postoperative measures is to reduce the risk for wound infections. After the initial surgery, the main aim is to improve wound healing and prevent contamination. These steps include keeping the wound as dry and sterile as possible with appropriate dressings. A minimum of 48-hour wound coverage is advised if the dressings remain dry (Al-Houraibi et al., 2019). This practice is to improve the immediate healing of the surgical incision, thereby decreasing the risk for wound contamination (Cosker et al., 2005).

In the long term, the preventative measures aim to prevent bacteremia that may cause the hematogenous spread of pathogens. The use of antibiotic prophylaxis for

dental procedures after TJA is no longer advised for every patient, as there is no supporting evidence for this practice (Colterjohn et al., 2014; Slullitel et al., 2020).

2.7 Treatment

2.7.1 Surgical treatment

Thorough debridement with the removal of all infected tissue and the eradication of any possible biofilm is the basis of the surgical treatment of PJI (Izakovicova et al., 2019). Treatment algorithms have traditionally guided the treatment decisions (Izakovicova et al., 2019; Karachalios & Komnos, 2021; Zimmerli et al., 2004). However, the evidence behind these algorithms is vague, and no definitive algorithm for the treatment of PJIs exists (Bialecki et al., 2019; Karachalios & Komnos, 2021; Li et al., 2018).

The least invasive surgical option for PJI is the debridement, antibiotics, and implant retention (DAIR) procedure, where only the modular components are replaced (Izakovicova et al., 2019; Zimmerli et al., 2004). The components can be removed and replaced either in a one-stage operation or in two separate operations, if the DAIR procedure is not considered to be enough (Izakovicova et al., 2019; Zimmerli et al., 2004). In recent years, a so-called "1.5-stage exchange arthroplasty", where the second stage of the originally intended two-stage operation is canceled and the articulating spacer from the first stage is retained in the joint, has also become a viable treatment option (Hernandez et al., 2021; Nabet et al., 2022).

2.7.1.1 Debridement, antibiotics, and implant retention

DAIR is the least invasive technique among the common treatment strategies for PJI. It starts with an open arthrotomy, which includes the thorough removal of devitalized and suspected infectious tissue. The exposed tissues are then rinsed with pulsed lavages and modular components are exchanged if possible.

DAIR is the preferred treatment choice in early postoperative infections (less than 30 days from the previous surgery) and late hematogenous PJIs with short duration of symptoms (less than three weeks). Furthermore, DAIR should be performed as early as possible, as the timing of debridement after the onset of symptoms is strongly associated with success rates (Tsang et al., 2017). In addition,

there should be good soft tissue condition and the implant should be stable. The optimal cut-off for the time since the previous operation among early PJIs or the time since the start of symptoms among acute hematogenous PJIs is not definitive. However, for infections with clear acute manifestation, the DAIR is the primary treatment option. In addition, if other approaches are contraindicated, the DAIR procedure might also be considered, even when the above-mentioned criteria are not fulfilled. (Karachalios & Komnos, 2021; Osmon et al., 2013; Zimmerli et al., 2004)

In addition to the timing of debridement, the exchange of modular components and the use of rifampin have been strongly associated with the treatment success of DAIR (Tsang et al., 2017; Wouthuyzen-Bakker et al., 2019). Other factors that influence the decision to perform DAIR instead of more thorough revision include the fixation and stability of the prosthesis, as for DAIR, the implant should always be stable (Zimmerli et al., 2004). Furthermore, the decision between performing the DAIR procedure and one-stage operation is not always a simple one. However, as a less invasive procedure with lower morbidity, the DAIR is considered in many ways a preferable solution to the one-stage revision.

Despite efforts to improve patient selection algorithms, a definitive answer to the question who the most suitable patients for DAIR are has not yet been found. DAIR would offer significant benefits to individual patients, as well as to the health care system via the lower economic burden. However, there is still a lack of studies, especially randomized controlled trials (RCTs), that compare DAIR and one-stage revision for overlapping indications, reflecting the necessity for further studies on this topic.

2.7.1.2 One-stage surgery

A one-stage revision is usually considered a surgical technique where the previous components and all fixation material, such as bone cement or screws, are explanted, and thorough irrigation and removal of necrotic tissue is performed. After that, the operation is continued in the same way as aseptic revision before new definitive implants are implanted.

One-stage revision is a viable strategy for the treatment of PJI, if certain criteria are fulfilled. In 2013, the IDSA declared in their guideline that one-stage revision would only be suitable for those THA patients who have a good soft tissue envelope and whose causative pathogen is known preoperatively and are susceptible to oral antimicrobial treatment (Osmon et al., 2013). However, the prerequisite of the preoperative pathogen has since been reported to be unnecessary (Karczewski et al.,

2018, 2023), and hence the absence of preoperative pathogen detection is not considered a contraindication nowadays.

At present, one-stage revision is not limited to PJIs occurring after THAs. In Germany, for example, almost 50% of all septic revision TKAs are performed in a one-stage manner, whereas the proportion of DAIRs has decreased to about 11% (Rupp et al., 2021). In addition to traditional one-stage revision, the results from the so-called "1.5-stage exchange arthroplasty", where the spacer is retained in the joint and the second stage is canceled, have also been reported to be acceptable, and the use of such an approach has subsequently increased (Hernandez et al., 2021; Srivastava et al., 2019).

While one-stage revision may serve as an alternative to the conventional two-stage approach, accurate preoperative planning and patient selection are prerequisites to optimize the likelihood of achieving successful infection control and favorable outcomes. Furthermore, it is essential to bear in mind that traditional two-stage revision leads to prolonged hospitalization and increased financial burden. The determination of whether, when, and for whom to employ a specific revision strategy in the management of PJI remains one of the greatest unresolved questions in the field of PJI research.

2.7.1.3 Two-stage surgery

Two-stage revision has historically been the most used option. This surgical technique was first introduced by Insall et al. (Insall, Thompson, et al., 1983), and the basic principle has since remained almost the same.

In two-stage revision, the first stage is similar to the first stage in one-stage revision, but a new definitive prosthesis is not implanted. Instead, a so-called spacer might be installed temporarily, or in some cases the joint may be left without any foreign material. The type of spacer varies but includes both articulating options and options where the spacer is molded from antibiotic cement (Fehring et al., 2000; Hofmann et al., 1995; Masri et al., 1994). A further option is a static option, where temporarily arthrodesis is used. For PJIs of the knee, articulating spacers are the preferred option, as they offer a more functional joint between the first and the second stage, as weight bearing and greater range of motion can be maintained (Hofmann et al., 1995), which may later affect the outcome. In addition, the spacers can be used for local antibiotics, providing a high concentration of antibiotics without systemic administration.

After the first stage, the treatment continues with the use of antimicrobics before the planned second stage. The second stage is usually performed within 8 weeks from the first stage, especially if a spacer is left in situ. However, sometimes longer intervals between the stages are needed (Izakovicova et al., 2019; Zimmerli et al., 2004). During the second operation, the spacer is removed and, if the soft tissue condition and bone stock are viable and there is no suspicion of the recurrent infection, the definitive prosthesis can be implanted. The type of definitive prostheses after the two-stage exchange depends strongly on the condition of the bones, and hence different revision prostheses are almost always used.

Two-stage revision has the largest burden for both the individual patient and for the health care system, as longer hospitalization periods and additional surgery are needed compared to the one-stage approach with or without prosthesis exchange. Hence, the indications for two-stage exchange include those patients who are not suitable for any other revision strategies.

The two-stage revision might easily be considered overtreatment if the patient's prognosis is not significantly greater than, for example, after one-stage revision. During recent years, the superiority of two-stage revision over one-stage revision has been questioned among chronic infections (Blom et al., 2022; Leta et al., 2019). When the added costs and the stress for the patient associated with the second operation of two-stage revision are considered, the decision to perform a two-stage revision instead of one one-stage revision should be considered thoroughly. However, as one-stage revision might not be suitable for everyone, more research on patient selection is warranted.

2.7.1.4 Other approaches

If none of the traditional revision strategies can be applied, other approaches may be used. However, usually one of the traditional three approaches is the first-line treatment, and other approaches are limited to patients with multiple revisions due to PJI.

The resection arthroplasty or amputation as a definitive solution can be considered for patients with very limited options. For example, patients with very poor soft tissue condition, or PJIs caused by micro-organisms for which no effective antimicrobial treatment available. Permanent resection arthroplasty might also be considered if the patient has previously failed two-stage revisions and the prognosis for survival after another multi-stage exchange is deemed poor. (Goldman et al., 2020; Osmon et al., 2013)

Unfortunately, resection arthroplasty might still not be enough for some patients, and those patients, amputation might be the only curative option available. Indications for amputation may include necrotizing fasciitis or a prior failed attempt of resection arthroplasty. In addition, for patients with very limited physical activity, amputation may also have functional benefit over definitive resection arthroplasty. However, as amputation as part of PJI treatment is relatively rare, it is advised that the infection is evaluated by a specialist with experience in the management of PJI before amputation is performed. In addition to resection arthroplasty and amputation, the infected joint may be fused. The functional outcome of the arthrodesis is, however, limited and should also be restricted to complicated patients treated by specialists. (Osmon et al., 2013; Rodriguez-Merchan, 2015)

Different combinations and approaches to traditional revision strategies have also been proposed. In 2021, McQuivey et al. published the "double DAIR" technique, where the first DAIR procedure is followed by a second similar operation 5 to 6 days later (McQuivey et al., 2021). In the first DAIR procedure, antibiotic beads are left in the joint and removed in the second operation. However, the surgical treatment of PJIs is almost completely based on the three traditional strategies, and other approaches are not in standard use.

2.7.2 Antimicrobial treatment

After surgical revision, an antimicrobial treatment is always continued postoperatively. The aim is to target the antimicrobial treatment to the exact pathogen if pathogen detection has been possible.

Administering a wide-spectrum antimicrobial treatment after surgical debridement and initial intravenous therapy can improve treatment effectiveness and reduce the risk for antimicrobial resistance. Once the causative pathogen responsible is identified, transitioning to a more focused therapy is recommended. Provided an appropriate oral medication with effective bone penetration is accessible, and favorable local conditions prevail at the surgical site along with decreased systemic inflammatory markers, such as CRP from the treatment's onset, oral treatment initiation can be considered at around 14 days after surgery. If DAIR is performed and implants are retained in the joint, the use of antibiofilm therapy, such as rifampin, is strongly associated with treatment success (Yusuf et al., 2024). Additionally, the duration of rifampin therapy has been reported as a strong

predictor of treatment success when DAIR is performed for early infections caused by *S. aureus* (Becker et al., 2020).

The duration of orally administered antimicrobials is usually around 4 to 10 weeks, depending on the revision type and type of the pathogen (Izakovicova et al., 2019). In the early stages of PJI treatment, the durations of antimicrobial treatments are advised to be up to 6 months for knee PJI and up to 3 months for hip PJI (Zimmerli, 2000; Zimmerli et al., 2004). However, nowadays, shorter durations of antimicrobial treatment are preferred because the results are as good as or even superior to longer treatment periods (Puhto et al., 2012). In 2021, Bernard et al. reported in their RCT that 12 weeks of antibiotic therapy was superior to 6 weeks of antibiotic therapy, with a persistent infection rate of 9.4% when administering 12 weeks of antibiotics compared to 18.1% with 6 weeks (Bernard et al., 2021). Furthermore, in their study, the benefit of 12 weeks of antibiotic therapy over 6 weeks was particularly pronounced among patients treated with DAIR, as the corresponding failure rates were 14.5% with 12 weeks of antibiotic therapy compared to 30.7% with 6 weeks (Bernard et al., 2021). Usually, intravenous antimicrobial therapy is administered for two to four weeks, but for certain pathogens, such as Streptococci, longer treatment durations are especially advised (Lora-Tamayo et al., 2017).

If the patient is unsuitable for revision surgery, long-duration suppressive antibiotic treatment might be prescribed (Osmon et al., 2013). As the aim of potential lifelong suppression therapy is not curative, this practice should be restricted to elderly patients who have multiple morbidities, contraindications for further surgeries, and limitations for limb-preserving surgery. Before beginning suppressive antimicrobial therapy, the causative pathogen should have been identified and no signs of radiological loosening of the implant should be present.

2.8 Prognosis of the PJI treatment

2.8.1 Clinical outcomes

Because both the definitions and surgical indications for PJI vary, a comparison of the reported results of different studies can be challenging. Moreover, research on PJI often lacks sufficient sample size due to the relatively rare incidence of this complication.

In a clinical setting, the success of PJI treatment is usually defined when the patient does not need any additional procedures or medications for infection control. However, the treatment of a PJI often fails to provide a dichotomous outcome; instead, the result may be a gradient of outcomes, with each step representing relative success. In the 2018 International Consensus Meeting on Periprosthetic Joint Infection, the MSIS proposed a categorization scheme for the different outcomes after PJI (Fillingham et al., 2019). This outcome-reporting scheme organizes different outcomes into four tiers that are further stratified into different subcategories. This system aimed to standardize and provide flexibility in defining success after the treatment of a PJI. (Table 4)

Table 4. PJI Treatment Outcomes, according to Musculoskeletal Infection Society categorization scheme (Fillingham et al. 2019)

Outcome
Tier 1: Infection control with no continued antibiotic therapy
Tier 2: Infection control with the patient on suppressive antibiotic therapy
Tier 3: Need for reoperation and/or revision and/or spacer retention
3A: Aseptic revision at >1 year from initiation of PJI treatment
3B: Septic revision (including DAIR) at >1 year from initiation of PJI treatment
3C: Aseptic revision at ≤1 year from initiation of PJI treatment
3D: Septic revision (including DAIR) at ≤1 year from initiation of PJI treatment
3E: Amputation, resection arthroplasty, or arthrodesis
3F: Retained spacer
Tier 4: Death
4A: ≤1 year from initiation of PJI treatment
4B: >1 year from initiation of PJI treatment

Within the system, each patient can only be assigned to a single tier, which provides a means to improve the transparency in the reporting of results of the treatment of a PJI. PJI = prosthetic joint infection, DAIR = debridement, antibiotic, and implant retention.

Another proposed systematic categorization system was proposed already in 2013 by Diaz-Ledezma et al. (Diaz-Ledezma et al., 2013). However, neither system has been widely adopted in PJI research. Of course, as the MSIS categorization scheme was only developed recently, this might be the reason why it has not yet been widely adopted within PJI research.

The outcomes in PJI research are usually defined dichotomously as success and failure. The limitation of these categories is that they may include different

definitions, such as continuation of suppressive antimicrobial therapy. This is of particular concern among multi-center retrospective studies, as the diagnostic definitions of PJI or the surgical decisions taken between different revision approaches in those studies are often not standardized. However, as the advantage of large, multi-center studies is their adequate sample size, which is often one of the greatest limitations in PJI research, they are also needed to evaluate the outcomes of PJI treatment.

In addition, previous clinical research has predominantly relied on small, diverse groups of patients, often in multi-center settings, with limited comparison between different surgical approaches. This makes the comparability of different studies harder. Further, the small study samples increase the risk of bias and confounding among the observed results, making generalizability even more difficult. However, since different types of PJI are managed differently, there is still a need for focused, pathogen-specific studies. Despite potential limitations in statistical power and the risk of confounding bias, such studies are warranted.

The optimal outcomes of the DAIR procedure have varied widely, depending on the type of infection, causative pathogen, and characteristics of the patient cohorts. This variation is due to the large heterogeneity across the published studies (Rahardja et al., 2023; Van Engen et al., 2023; van der Ende et al., 2021; Veerman et al., 2022). Although promising rates of successful outcomes after DAIR have been reported by several authors, the pooled outcomes after DAIR have been reported to be poor. A recent meta-analysis by Gerritsen et al. demonstrated an overall success rate of 67% for all DAIRs, with a success rate of 70% for PJIs after THA and 63% for PJIs after TKAs (Gerritsen et al., 2021). Their analysis reflected a common problem within PJI research, i.e., they reported very high (I^2 statistics 95%) heterogeneity amongst the analyzed studies. The outcomes after DAIR have been associated with the exchange of modular components. Similar results were demonstrated in a meta-analysis by Gerritsen et al. DAIR is usually considered to be a procedure for early PJIs within a period of 30 days of the previous surgery. However, this cut-off has been questioned, because similar success rates have been reported for DAIRs performed 4 to 12 weeks after the previous surgery (van der Ende et al., 2021). In addition to early PJIs, promising success rates have also been reported after DAIR for late acute infections (Barros et al., 2019; Löwik et al., 2020). Indeed, the DAIR procedure is today considered a first-line treatment for those hematogenous infections that manifest acutely after a long symptom-free period (Izakovicova et al., 2019; Osmon et al., 2013). The current literature on the outcomes after DAIR is very heterogeneous, and often direct comparisons between other surgical approaches have not been

performed. As the success rates in some studies have been very good, we might assume that DAIR is an efficient and safe procedure for some patients.

For certain infection types and pathogens, the results of DAIRs have been reported to be excellent. Huotari et al. reported a success rate of 89.3% for late acute infections caused by *S. aureus* if managed with DAIR, with a corresponding rate of 75.4% for early acute infections (Huotari et al., 2023). Additionally, the success rates after acute PJIs caused by Streptococci have been reported to be excellent with DAIR treatment (Huotari et al., 2018). The exchange of the modular components is the strongest predictor of success after DAIR (Wouthuyzen-Bakker et al., 2019), and hence, it is always suggested if possible. Furthermore, rifampin usage has been strongly associated with treatment success due to its antibiofilm capabilities (Puhto et al., 2015; Yusuf et al., 2024).

In their retrospective cohort study, Okafor et al. compared one-stage revisions and DAIRs procedures for acute infections after TKA and demonstrated superior results after one-stage revision (Okafor et al., 2023b). Their results concluded that the traditional algorithms that suggest performing DAIR for acute infections might not be optimal, and further research on patient selection is warranted**.** In 2023, Bosco et al. published their meta-analysis, including the pooled data from 18 studies, with 881 one-stage revision for PJI of the knee (Bosco et al., 2023). In their analysis, the overall pooled success rate was 92.1%. Among the analyzed studies, re-infection varied between 0% and 37.5% (Haddad et al., 2015; Rossmann et al., 2021). In addition to the superiority of one-stage revision over DAIR among acute infections, similar results were reported in several meta-analyses when compared with the two-stage revision (Goud et al., 2023; Kunutsor et al., 2015, 2018; Kunutsor, Whitehouse, Lenguerrand, et al., 2016). Each of these studies shares a common potential limitation in that the number of available studies on this topic is limited. In addition, as one-stage revision demonstrated superior results over two-stage revision in a recent randomized controlled trial (Blom et al., 2022), it might be a viable option not only for DAIRs but also for two-stage revision in certain patient groups.

The treatment of PJI is dependent on a variety of factors and two-stage revision might still be beneficial, or even the only possible option, for some patients. High success rates after two-stage revision have also been reported (Bongers et al., 2020), indicating that some patients will still benefit from the procedure. However, modern spacer prostheses offer good functional results (Hernandez et al., 2021), with the opportunity to either explant the prostheses and implant a definitive prosthesis in a second surgery, or leave the spacer as a definitive solution when the patient is pleased with the outcome from the spacer prosthesis. This so-called 1.5-stage revision might

be the future of two-stage revision for those patients with "borderline indications" between one- and two-stage surgeries. The literature is, however, still scarce on this topic.

2.8.2 The most common complications of the treatment

The most common complication associated with PJI treatment is infection relapse and re-infection (Bongers et al., 2020; Borsinger et al., 2021). Infection relapse is defined as an infection where the original causative pathogen is not completely eradicated, and thus causes a relapse of the infection. In contrast, re-infection is defined as an infection caused by a new microorganism. As revision for PJI is a very invasive procedure, especially when performed in a multi-stage manner, the risk for re-infection is always present. Furthermore, the risk for contamination increases if multiple procedures must be performed.

PJI revision shares the same risk factors for infections as primary TJAs, with the additional risk that comes with PJI treatment. The risk of intraoperative fractures in primary THA and TKA has been reported to range between 1.5% and 27.8%, and they can occur in any of the bones involved (Berend & Lombardi, 2010; Siddiqi et al., 2023). When different PJI revision strategies are compared, the risk of intraoperative complications, such as intraoperative fractures, is increased if the definitive components are replaced. The one- and two-stage revisions are remarkably more aggressive techniques compared to DAIR. Consequently, the usage of those techniques might be associated with an increased risk of intraoperative fractures.

A prosthetic joint infection increases the mortality risk significantly (S. M. Kurtz et al., 2018; Natsuhara et al., 2019). This is due, in part, to the increased stress that the initial infection causes, but also to the increased comorbidity the treatments cause. To potentially decrease the mortality risk after PJI treatment, the treatment should be as minimal as possible. For example, less aggressive procedures should be advocated when possible. However, recurrent surgeries increase the morbidity burden, which increases the mortality risk the most. Therefore, the decision between different surgical approaches might be the most important decision taken in the treatment of PJI.

3 AIMS OF THE STUDY

The primary aim of this dissertation was to examine both patient-related trends and trends in the surgical strategies employed in the treatment of PJI and to investigate how these strategies affect the prognosis of the treatment.

The specific aims of the studies were as follows:

Study I	To assess the trends in the demographics of patients with hip PJI, the surgical treatment strategies used, and the prevalence of causative pathogens.
Study II	To compare outcomes after hip PJI between the surgical strategies.
Study III	To assess the trends in the demographics of patients with knee PJI, the surgical treatment strategies used, and the prevalence of causative pathogens.
Study IV	To compare outcomes after knee PJI between the surgical strategies.
Study V	To validate a preoperative risk factor-based prediction model for failure after revision due to early PJI.

4 MATERIALS AND METHODS

4.1 Study design

This retrospective cohort study was performed at the Coxa Hospital for Joint Replacement, Tampere, Finland. Founded in 2002, the hospital is an academic tertiary referral center fully focused on joint replacement surgery. Nowadays, the annual volume of the hospital is more than 2 800 primary THAs and more than 4 000 primary TKAs. In addition, more than 250 revision THAs and 150 revision TKAs are performed annually.

The study period started on January 1, 2008, and ended on September 12, 2021. The study cohort was formed from patients whose first revision due to PJI was performed at Coxa Hospital during the study period. The patients were identified from our institution's database. Details of each treatment period and surgery (e.g., duration of surgery, implant fixation, blood loss) are recorded in the database. To validate that the data from the database was accurate, the electronic health records from the identified patients were used to manually collect precise information related to the received treatment such as comprehensive surgical details. In addition to electronic health records, microbiological results from tissue specimens were verified and collected manually from the laboratory database. All the microbiology analyses were performed in the accredited microbiology laboratory of Tampere University Hospital.

4.2 Patients

All the revision surgeries due to PJI within our study period were identified by searching the ICD-10 (International Classification of Diseases 10th revision) code T84.5 (Infection and inflammatory reaction due to internal joint prosthesis). Superficial wound infections and two-stage operations, where information on the first surgery was not available, were excluded. PJI diagnoses were confirmed with the 2013 International Consensus Meeting diagnostic criteria (Parvizi et al., 2014). If the criteria were not fulfilled, the joint was excluded. Only the first revisions due to

PJI were included, and those patients who underwent revision due to PJI in multiple joints were analyzed as separate operations.

The surgeries were categorized into one of the following three categories: DAIR; one-stage revision; or two-stage revision. DAIR included all surgeries where arthrotomy was performed and modular components possibly replaced, but the definitive prosthesis was not removed. In one-stage revision, at least one of the definitive components (tibial component, femoral component, acetabular component) was replaced in a single operation. In contrast, in two-stage revision, the components were sequentially removed and replaced in two operations with a period of resection arthroplasty or spacer prosthesis in between. If the planned second stage was not performed due to a satisfactory outcome from the first-stage operation, the surgery was categorized as a one-stage revision, as suggested by the MSIS (Fillingham et al., 2019).

The infections were classified as early (≤90 days from the previous surgery), acute hematogenous (>90 days from the previous surgery AND <28 days of symptoms), and chronic infections (>90 days from the previous surgery AND ≥28 days of symptoms) (Kapadia et al., 2016; Triffault-Fillit et al., 2019; Zimmerli et al., 2004).

4.2.1 Trends in PJI treatment (I, III)

In total, 807 PJI revisions were analyzed in studies I and III. Of those, 436 (54%) were early infections, 222 (27.5%) were acute hematogenous infections, and 149 (18.5%) were chronic infections. A total of 423 (52.4%) PJIs occurred after THA and a total of 384 (47.6%) after TKA. More than half of the patients were women (52%, n = 420). Further details on the patient characteristics in studies I and III are presented in Tables 5 and 6.

A total of 302 (37.4%) DAIRs, 245 (30.4%) one-stage, and 260 (32.2%) two-stage revisions were analyzed. After THA, a total of 150 (35.5%) DAIRs, 141 (33.3%) one-stage, and 132 (31.2%) two-stage revisions were analyzed. After TKA, a total of 152 (39.6%) DAIRs, 104 (27.1%) one-stage, and 128 (33.3%) two-stage revisions were analyzed. A flowchart of the patients in studies I and III is presented in Figures 4 and 5.

Table 5. Characteristics of the patients with hip PJI included in study I, stratified by the type of surgery

	DAIR (n=150)	One-stage (n=141)	Two-stage (n=132)
Patient characteristics			
Women, n (%)	93/150 *(62)*	70/141 *(49.6)*	63/132 *(47.7)*
Age, median (IQR), y	73 *(66–80)*	71 *(59–79)*	72 *(64–78)*
BMI, mean (sd)	28.9 *(6.1)*	29.9 *(6.6)*	27.5 *(4.9)*
CCI, median (range)	3 *(0–7)*	3 *(0–7)*	3 *(0–7)*
ASA-class, n (%)			
1	4 *(2.7)*	6 *(4.3)*	2 *(1.5)*
2	35 *(23.3)*	33 *(23.4)*	28 *(21.2)*
3	78 *(52)*	77 *(54.6)*	88 *(66.7)*
4	32 *(21.3)*	23 *(16.3)*	12 *(9.1)*
5	1 *(0.7)*	1 *(0.7)*	0
NA	0	1 *(0.7)*	2 *(1.5)*
Infection type, n (%)			
Early	117 *(78)*	119 *(84.4)*	52 *(39.4)*
Acute hematogenous	27 *(18)*	16 *(11.3)*	32 *(24.2)*
Chronic	6 *(4)*	6 *(4.3)*	48 *(36.4)*
Surgical characteristic			
Time since previous operation, median (IQR), d	18 *(13–47)*	21 *(15–37)*	248 *(34–1733)*
Symptom duration, median (IQR), d	12 *(6–17)*	15 *(8–22)*	19 *(7–80)*
Sinus tract, n (%)	92/148 *(62.2)*	91/138 *(65.9)*	50/132 *(37.9)*
Spacer usage, n (%)	-	-	24/132 *(18.2)*

Infections are classified as early (≤3 months from the previous surgery), acute hematogenous (>3 months from the previous surgery with <28 days of symptoms), and chronic (>3 months from the previous surgery with ≥28 days of symptoms). DAIR = debridement, antibiotics, and implant retention, IQR = interquartile range, d = days, y = years, sd = standard deviation, BMI = body mass index, CCI = Charlson's comorbidity index.

Table 6. Characteristics of the patients with knee PJI included in study III, stratified by the type of surgery

	DAIR (n = 152)	One-stage (n = 104)	Two-stage (n = 128)
Patient characteristics			
Female, n (%)	70 *(46.1%)*	51 *(49%)*	57%)
Age, median (IQR), y	70 *(63–77)*	74 *(66–81)*	70 *(62–78)*
BMI, mean (sd)	31.1 *(6.2)*	29.2 *(5.5)*	31.3 *(6.3)*
CCI, median (range)	3 *(0–7)*	3 *(0–8)*	3 *(0–6)*
ASA-class, n (%)			
1	3 *(2%)*	3 *(2.9%)*	2 *(1.6%)*
2	33 *(21.7%)*	13 *(12.5%)*	27 *(21.1%)*
3	101 *(66.4%)*	68 *(65.4%)*	83 *(64.8%)*
4	11 *(7.2%)*	17 *(16.3%)*	12 *(9.4%)*
5	1 *(0.7%)*	1 *(1%)*	0
NA	3 *(2%)*	2 *(1.9%)*	4 *(3.1%)*
Infection type, n (%)			
Early	73 *(48%)*	35 *(33.7%)*	40 *(31.3%)*
Acute hematogenous	78 *(51.3%)*	38 *(36.5%)*	31 *(24.2%)*
Chronic	1 *(0.7%)*	31 *(29.8%)*	57 *(44.5%)*
Surgical characteristic			
Time since previous operation, median (IQR), d	127 *(19–1272)*	312 *(34–1304)*	296 *(42–1420)*
Symptom duration, median (IQR), d	5 *(3–13)*	13 *(5–29)*	21 *(6–78)*
Sinus tract, n (%)	51 *(33.6%)*	28 *(26.9%)*	43 *(33.6%)*
Static spacer, n (%)	-	-	9 *(20.9%)*

Infections are classified as early (≤3 months from the previous surgery), acute hematogenous (>3 months from the previous surgery with <28 days of symptoms) and chronic (>3 months from the previous surgery with ≥28 days of symptoms). DAIR = debridement, antibiotics, and implant retention, IQR = interquartile range, d = days, y = years, sd = standard deviation, BMI = body mass index, CCI = Charlson's comorbidity index.

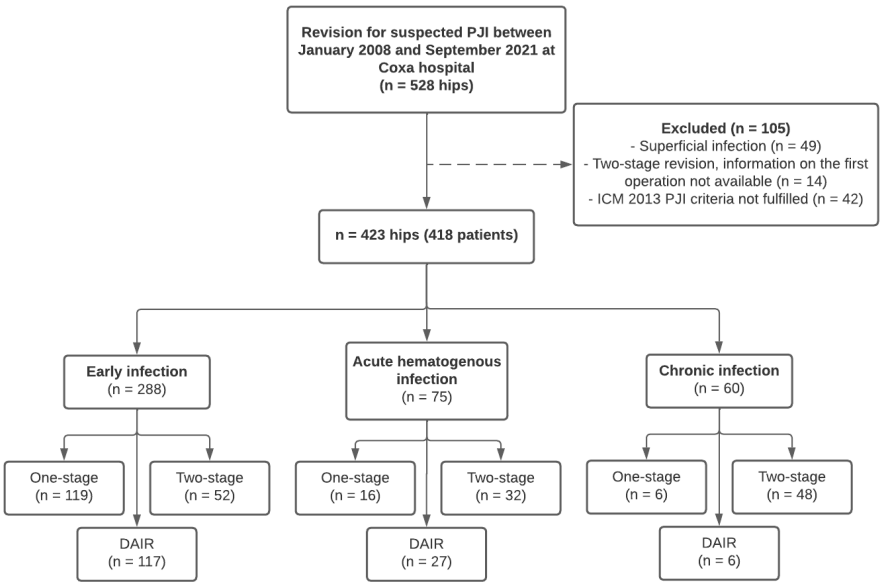

Figure 4. Flowchart of the patients in study I

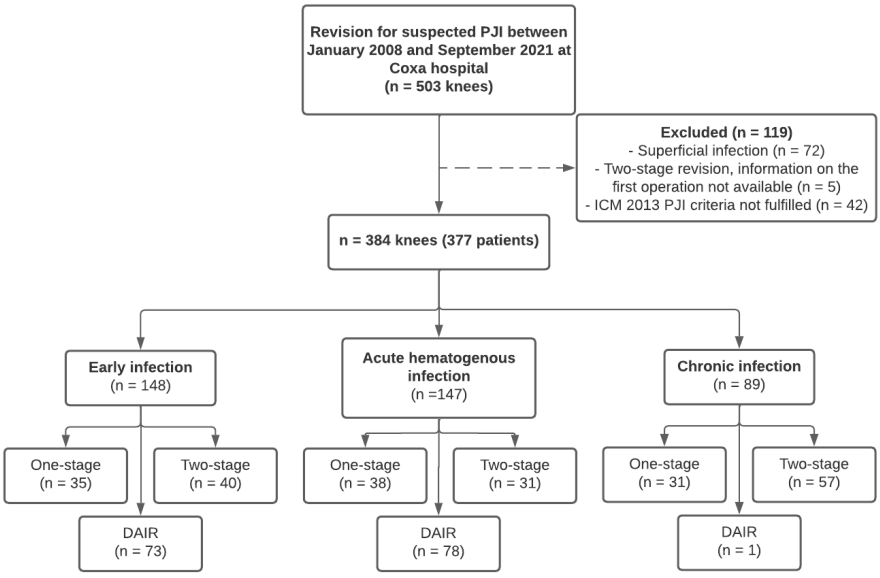

Figure 5. Flowchart of the patients in study III

4.2.2 Treatment outcomes (II, IV)

In studies II and IV, only patients with at least 1e-year follow-up were included. In total, 728 PJI revisions were analyzed. Of those, 384 (52.7%) were early infections, 204 (28%) were acute hematogenous infections, and 140 (19.2%) were chronic infections. A flowchart of the patients in studies II and IV is presented in Figure 6. A total of 369 (50.7%) PJIs occurred after THA and a total of 359 (49.3%) after TKA. More than half of the patients were women (52.1%, n = 379). Further details on the patient characteristics in studies II and IV are presented in Tables 7 and 8.

A total of 275 (37.8%) DAIRs, 212 (29.1%) one-stage, and 241 (33.1%) two-stage revisions were analyzed. After THA, a total of 134 (36.3%) DAIRs, 114 (30.9%) one-stage, and 121 (32.8%) two-stage revisions were analyzed. After TKA, a total of 141 (39.3%) DAIRs, 98 (27.3%) one-stage, and 120 (33.4%) two-stage revisions were analyzed.

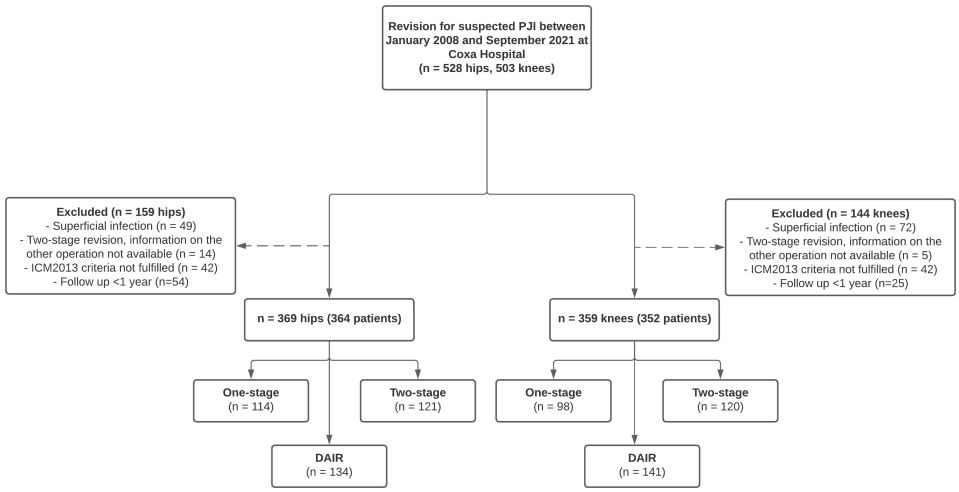

Figure 6. Flowchart of the patients in studies II and IV

Table 7. Characteristics of the patients with hip PJI included in study II

	DAIR (n=134)	One-stage (n=114)	Two-stage (n=121)
Patient characteristics			
Women, n (%)	83/134 *(61.9)*	54/114 *(47.4)*	60/121 *(49.6)*
Age, median (range), y	73 *(36–94)*	70 *(37–93)*	72 *(34–88)*
BMI, mean (range)	29.1 *(18–46)*	30.0 *(15–50)*	27.5 *(18–41)*
CCI, median (range)	3 *(0–7)*	3 *(0–7)*	3 *(0–7)*
ASA-class, n (%)			
1	4 *(3)*	6 *(5.3)*	2 *(1.7)*
2	35 *(26.1)*	29 *(35.4)*	27 *(22.3)*
3	67 *(50)*	63 *(55.3)*	78 *(64.5)*
4	27 *(20.1)*	14 *(12.3)*	12 *(9.9)*
5	1 *(0.7)*	1 *(0.9)*	0
NA	0	1 *(0.9)*	2 *(1.7)*
Infection type, n (%)			
Early	103 *(76.9)*	94 *(82.5)*	48 *(39.7)*
Acute hematogenous	25 *(18.7)*	15 *(13.2)*	28 *(23.1)*
Chronic	6 *(4.5)*	5 *(4.4)*	45 *(37.2)*
Surgical characteristic			
Time since previous operation, median (IQR), d	18 *(12–50)*	21 *(15–37)*	230 *(34–1620)*
Symptom duration, median (IQR), d	11 *(6–16)*	15 *(8–22)*	20 *(7–77)*
Sinus tract, n	83 *(61.9)*	72 *(63.2)*	45 *(37.1)*
Spacer usage, n	-	-	24 *(19.8)*
Previous indication, n (%)			
Osteoarthritis	60 *(44.8)*	85 *(74.5)*	76 *(62.8)*
Aseptic revision	41 *(30.6)*	12 *(10.5)*	27 *(22.3)*
Fracture	30 *(22.4)*	16 *(14)*	14 *(11.6)*
Other	3 *(2.2)*	1 *(0.9)*	4 *(3.3)*
Cemented prosthesis	91 *(67.9)*	60 *(52.6)*	55 *(45.4)*
Unstable prosthesis	0	17 *(12.3)*	20 *(16.5)*

Infections were classified as early (≤90 days from the previous surgery), acute hematogenous (>90 days from the previous surgery AND <28 days of symptoms), and chronic infections (>90 days from the previous surgery AND ≥28 days of symptoms). DAIR = debridement, antibiotics, and implant retention, IQR = interquartile range, d = days, y = years, BMI = body mass index, CCI = Charlson's comorbidity index.

Table 8. Characteristics of the patients with knee PJI included in study IV

	DAIR (n = 141)	One-stage (n = 98)	Two-stage (n = 120)
Patient characteristics			
Women, n (%)	66 *(46.8)*	49 *(50)*	67 *(55.8)*
Age, median (range), y	70 *(42–94)*	74 *(37–94)*	71 *(45–93)*
BMI, mean (range)	30.7 *(20–47)*	29.1 *(18–52)*	31.2 *(20–56)*
CCI, median (range)	3 *(0–7)*	3 *(0–8)*	3 *(0–6)*
ASA-class, n (%)			
1	3 *(2.1)*	3 *(3.1)*	2 *(1.7)*
2	31 *(22)*	12 *(12.2)*	25 *(20.8)*
3	93 *(66)*	64 *(65.3)*	77 *(64.2)*
4	10 *(7.1)*	16 *(16.3)*	12 *(10)*
5	1 *(0.7)*	1 *(1)*	0
NA	3 *(2.1)*	2 *(2)*	4 *(3.3)*
Infection type, n (%)			
Early	69 *(48.9)*	35 *(35.7)*	35 *(29.2)*
Acute hematogenous	71 *(50.4)*	35 *(35.7)*	30 *(25)*
Chronic	1 *(0.7)*	28 *(28.6)*	55 *(45.8)*
Surgical characteristic			
Time since previous operation, median (IQR), d	112 *(19–1336)*	332 *(30–1387)*	332 *(63–1498)*
Symptom duration, median (IQR), d	5 *(3–13)*	13 *(5–29)*	21 *(5–81)*
Sinus tract, n (%)	49 *(34.8)*	28 *(28.6)*	38 *(31.7)*
Previous indication, n (%)			
Osteoarthritis	109 *(77.3)*	84 *(85.7)*	99 *(82.5)*
Aseptic revision	24 *(17)*	10 *(10.2)*	18 *(15)*
Other	8 *(5.7)*	4 *(4.1)*	3 *(2.5)*

Infections were classified as early (≤90 days from the previous surgery), acute hematogenous (>90 days from the previous surgery AND <28 days of symptoms), and chronic infections (>90 days from the previous surgery AND ≥28 days of symptoms). DAIR = debridement, antibiotics, and implant retention, IQR = interquartile range, d = days, y = years, BMI = body mass index, CCI = Charlson's comorbidity index.

4.2.3 Validation of the preoperative prediction model (V)

For study V, early PJIs treated with DAIR or one-stage revision, with at least 1-year of follow-up, were included. A total of 283 patients were analyzed. More than half of these (56.2%, n=159) were treated with DAIR, and more than half of the revisions were performed due to PJI of the knee (n=153, 54.1%). The mean age of the patients was 69.3 years (standard deviation 11.6 years), and more than half of the patients (n=149, 52.7%) were female. *S. aureus* was the most common pathogen, causing 121 (42.8%) infections. Further details on patient characteristics are presented in Table 9.

Table 9. Characteristics of the included patients in study V

	DAIR (n=159)	**One-stage (n=123)**
Patient characteristics		
Age, mean (sd)	69.7 *(10.4)*	68.8 *(13.1)*
BMI, mean (sd)	30.2 *(5.7)*	29.9 *(6.0)*
Female, n (%)	89 *(60.0)*	60 *(48.8)*
Knee, n (%)	64 *(40.3)*	89 *(72.4)*
Comorbidities, n (%)		
ASA-score, mean (sd)	2.8 *(0.7)*	2.8 *(0.7)*
ASA-score ≥4	16 *(10.1)*	12 *(9.8)*
Renal failure	5 *(3.1)*	3 *(2.4)*
Liver cirrhosis	<3	0
CRP, mg/l		
≥115 mg/l, n (%)	144 *(90.6)*	112 *(91.1)*
Previous surgery type, n (%)		
Primary	94 *(59.1)*	99 *(80.5)*
Revision	36 *(22.6)*	12 *(9.8)*
Fracture	29 *(18.2)*	12 *(9.8)*
Cemented prosthesis, n (%)	132 *(83.0)*	79 *(64.2)*
KLIC-score, n (%)		
Mean (sd)	4.6 *(1.4)*	3.9 *(1.4)*
≤2	10 *(6.3)*	8 *(6.5)*
2.5–3.5	15 *(9.4)*	40 *(32.5)*
4–4.5	85 *(53.5)*	56 *(45.5)*
5–6	44 *(27.7)*	16 *(13.0)*
>6	5 *(3.1)*	3 *(2.4)*

DAIR = debridement, antibiotics, and implant retention, IQR = interquartile range, d = days, y = years, sd = standard deviation, BMI = body mass index, CCI = Charlson's comorbidity index.

4.3 Treatment strategies

The early and hematogenous infections were preferably treated with either DAIR or one-stage revision (Izakovicova et al., 2019; Osmon et al., 2013; Zimmerli et al., 2004). For early and hematogenous PJIs after THA, the one-stage revision was used if the time from the previous operation was on the edge of the optimal timeframe for DAIR (within the first 3 to 4 postoperative weeks from the index procedure). In addition, one-stage revision was preferred over DAIR when no cement had been used in the initial operation. The two-stage revision was the preferred strategy for chronic infections after THA. For chronic PJIs after TKA, two-stage or one-stage revisions were the preferred treatment methods. For all infection types, one-stage revision or DAIR were used when two-stage revision was contraindicated.

Preoperative synovial fluid samples were collected from each patient, if possible. In addition, a median of six intraoperative tissue specimens were also collected. Based on the microbiological findings from the pre- and intraoperative synovial fluid samples and tissue specimens, postoperative antimicrobial treatments were designed by the infectious-diseases specialists. The standard practice involved administering postoperative intravenous antibiotic therapy lasting between two to four weeks (typically four weeks), succeeded by oral therapy, irrespective of the surgical approach. Between 2008 and 2014, the overall treatment duration could have been longer (up to three months). However, if highly absorbable oral treatment was feasible, the use of intravenous treatment rarely surpassed four weeks. In our study, the median duration of antimicrobial treatment after DAIR was 8 weeks for both after hip and knee PJI.

The duration without antibiotics before the second-stage operation varied but commonly spanned at least two weeks. Furthermore, the use of antibiotics ceased after the second-stage operation if intraoperative cultures were negative and there were no specific patient-related indications for prolonged suppressive antibiotic therapy. In cases of staphylococcal infections, a rifampin-based combination was employed unless contraindicated (due to drug interactions or a high risk for adverse reactions), except in two-stage revisions, where no foreign material remained in place.

4.4 Definition of outcomes

4.4.1 Trends in PJI treatment (I, III)

For studies I and III, the primary outcome was the incidence of PJI per 100 primary TJAs, which was further stratified by infection and revision type. As our institution is a tertiary referral center, incidences were calculated based on the number of primary TJAs performed at our institution and the number of PJIs of which the primary arthroplasty was performed at our institution. Referrals and PJIs that manifested after revision TJA were not included in the analyses. Another primary outcome was the comorbidity burden, which was measured by analyzing the distribution of ASA classes.

Secondary outcomes were the prevalence of causative pathogens, measured as the proportion of performed revision surgeries. In addition, the distribution of the surgical strategies was examined by examining the relative proportions.

4.4.2 Treatment outcomes (II, IV)

In studies II and IV, the MSIS categorization scheme was used to categorize the treatment outcomes (Fillingham et al., 2019). Follow-up started from the day of the revision surgery, or in cases of two-stage revision, the day of the first-stage surgery. Follow-up ended when the patient was lost to our institution's regular follow-up program (e.g. death, reoperation, or patient moved to another area) or on the date of data collection, whichever came first. In our institution's regular follow-up program, all PJI patients are seen at the clinic three months after the revision surgery and followed up with a call after the first postoperative year. If the infection is under control, no additional follow-up visits due to PJI are required, and the normal protocol for TJA follow-up visits is applied.

In our survival analyses, reoperation due to any reason was the primary outcome. It has been suggested that aseptic revision performed within one year from the initial surgery for the treatment of PJI represents a failure secondary due to PJI. Therefore, these revisions were also included as failures in the survival analyses (Fillingham et al., 2019). Death from any cause was considered a competing risk because, due to a lack of information regarding the specific causes of death, it was not possible to

classify whether death was PJI-related or not (Boddapati et al., 2018; Zmistowski et al., 2013).

4.4.3 Validation of the preoperative prediction model (V)

The follow-up period began on the day of the revision surgery. The primary outcome was early failure which was considered when: 1) the patient needed an unscheduled surgery within 60 days of the revision; 2) the patient died within 60 days of the revision, or 3) the patient was prescribed long-term suppressive antibiotics within 60 days of the revision because further surgeries were contraindicated. Failure within the first postoperative year was the secondary outcome.

4.5 Statistical methods

4.5.1 Statistics overall

All analyses were performed using R (version 4.1.2; R Foundation for Statistical Computing, Vienna, Austria). Based on the distribution of the data, the means with standard deviations or medians with interquartile ranges (IQR) were reported for continuous variables. Categorized variables were presented as absolute numbers and percentages.

4.5.2 Trends in PJI treatment (I, III)

In studies I and III, patient demographics and the microbiology of the PJIs were compared in a longitudinal setting to examine the changes during our study period. To prevent selection bias, patient demographics, and the microbiology of the PJIs were compared in 2-year admission groups, rather than in yearly groups. The results were reported according to the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines (von Elm et al., 2007).

4.5.3 Treatment outcomes (II, IV)

In studies II and IV, cumulative incidences of reoperations and deaths were calculated (Scrucca et al., 2007), and the Kaplan-Meier estimator was used to calculate the risk of any-cause failure. Results were presented with 95% confidence intervals (CIs).

As the Fine-Gray regression has been reported to be the most accurate statistical model to evaluate a single patient's prognosis, it was used to identify potential predictors of failure. (Austin et al., 2016). In addition, the cause-specific Cox regression models were calculated for reoperations and deaths (Latouche et al., 2013). Schoenfeld's residuals were used to test the proportional hazard assumptions, and these assumptions were not violated in any of the reported models.

To comprehensively evaluate the impact of confounding factors and enhance outcome predictions, we conducted multivariable analyses. Given the numerous potential predictors, we engaged in variable selection processes, illustrated in Figures 7 and 8. Initially, global models were constructed, incorporating known risk factors and clinically relevant variables. These global models were then finalized to the Fine-Gray regression models through backward elimination, employing a significance level of 0.157 (Akaike Information Criteria selection). For the cause-specific Cox regression models, backward elimination with $P<0.10$ as a level of significance was used for the variable selection. Thereafter, model stabilities were assessed by bootstrap stability investigation with 200 repetitions. Based on these two investigations, the final variables for the regression analyses were selected. The outcomes of the multivariable analyses were reported with either adjusted sub-distributed hazard ratios (sdHR) or adjusted hazard ratios (aHR) with 95% CIs. The results were reported according to the STROBE guidelines (von Elm et al., 2007).

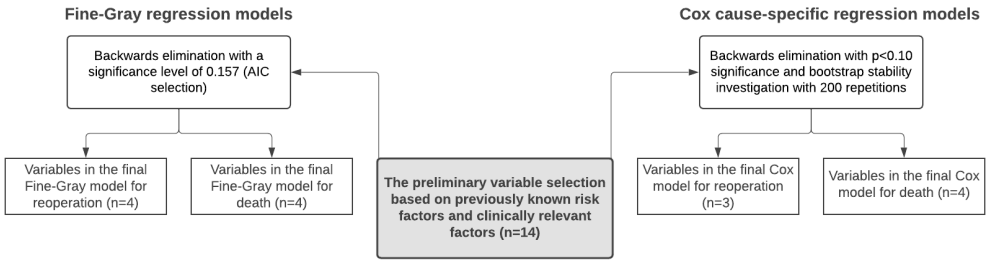

Figure 7. Variable selection process for multivariable analyses in study II

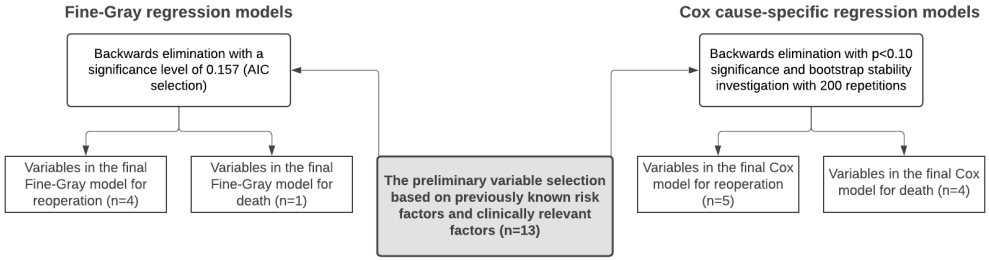

Figure 8. Variable selection process for multivariable analyses in study IV

4.5.4 Validation of the preoperative prediction model (V)

A KLIC-score was calculated individually for each patient (Tornero et al., 2015) (Table 10). The patient was excluded from the analyses when not all the required variables were available. Patients were then categorized into groups, according to their KLIC-score (≤2, 2.5–3.5, 4–4.5, ≥5).

Table 10. KLIC-score as described by Tornero et al. (2015)

Variable	Explanation	Score
K	Chronic Renal Failure (**K**idney)	2
L	**L**iver Failure	1.5
I	**I**ndex surgery = Revision surgery or prosthesis to treat femoral neck fracture	1.5
C	**C**emented prosthesis	2
C	**C**-reactive protein (CRP > 115 mg/L)	2.5
	Total	max 9.5

The analyses were conducted separately for both DAIRs and one-stage revisions. Kaplan-Meier estimator was used to calculate the risk for failure. Univariable logistic regression was used to assess the association of the KLIC-score with the risk for failure by analyzing the KLIC-score as both a continuous variable and a categorized variable. To evaluate the discriminatory ability, areas under the curves (AUC) were computed for each logistic regression analysis and the results were illustrated using the receiver operating characteristics (ROC) curves. Categorized KLIC-scores underwent binary logistic regression, followed by the calculation of sensitivity (SEN), specificity (SPE), positive predictive values (PPV), and negative predictive values (NPV). The outcomes were presented through odds ratios (OR) accompanied by corresponding 95% confidence intervals (CIs).

In addition, calibration plots were used to assess the model calibrations, and decision-curve analyses (DCA) were used to evaluate the clinical utility of the KLIC-score (Collins et al., 2014; On behalf of Topic Group 'Evaluating diagnostic tests and prediction models' of the STRATOS initiative et al., 2019). The Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis

(TRIPOD) guidelines were followed in the reporting of the results (Collins et al., 2015).

4.6 Ethical considerations

Permission to use our hospital's database was obtained from the Institutional Review Board at our hospital. Following the instructions from the local ethics committee, and Finnish legislation (the Act on the Secondary Use of Health and Social data (552/2019)), no ethical committee approval or informed written consent was required due to the retrospective register-based study design and because patients were not contacted. Thus, no approval from the local ethics committee was sought. Nevertheless, this study was planned and carried out in accordance with the standards for good scientific practice set by the World Medical Association's Declaration of Helsinki.

5 SUMMARY OF THE RESULTS

5.1 Epidemiology of the PJI (Studies I and III)

5.1.1 Incidence of PJI

A total of 41 109 primary THAs and TKAs was performed during our study period. Of these, 18 784 were primary THAs and 23 325 primary TKAs. In total, 447 revisions due to PJI were performed, making a total incidence of 1.06 PJIs per 100 primary TJAs. After primary THA, 209 PJIs were treated, making the incidence 1.11 PJIs per 10 primary THA. After primary TKAs, a total of 238 PJIs were treated, making the incidence 1.02 PJIs per 100 primary TKAs.

The incidence of early infections increased almost three-fold from 0.27 in 2008 to 0.74 in 2021. The largest incidence was observed in 2020, as 1.15 PJIs per 100 primary TJAs were operated at our institution. The increase in the incidence of early infections was also seen after stratifying the analyses by joint. Yearly incidences, stratified by the type of PJI, are shown in Figures 9, 10, and 11.

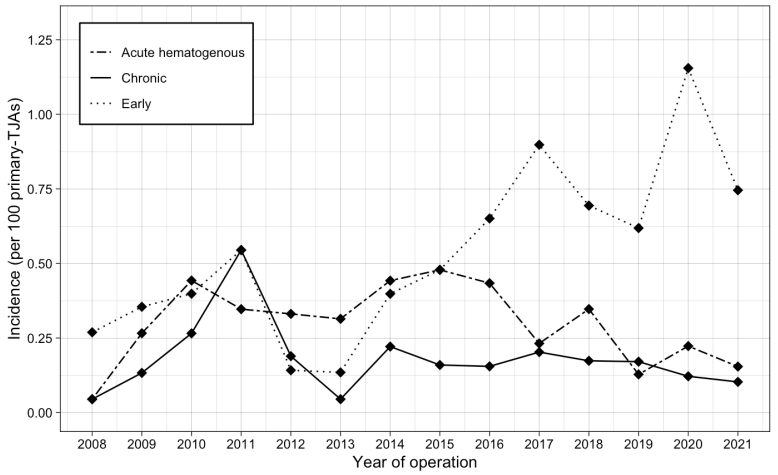

Figure 9. Incidence of PJI after primary THA or TKA at the Coxa Hospital for Joint Replacement between 2008 and 2021, stratified by the infection type

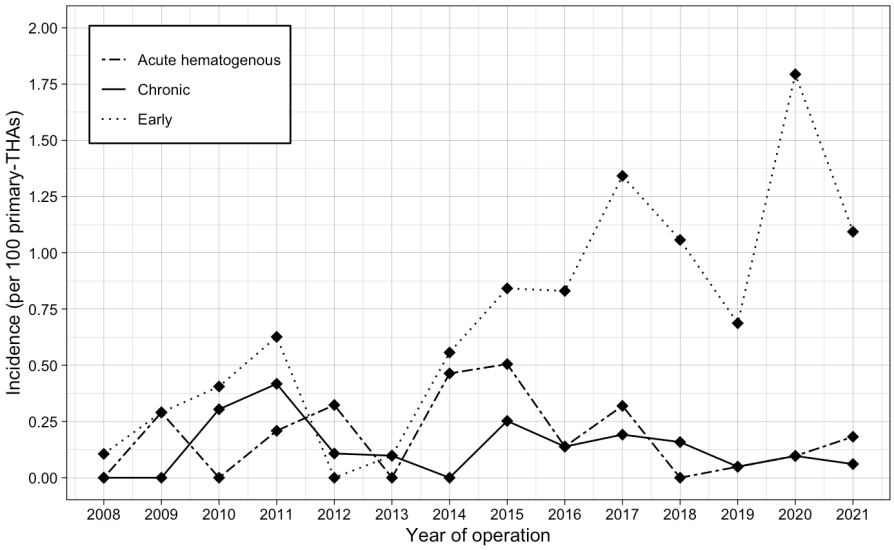

Figure 10. Incidence of PJI after primary THA at the Coxa Hospital for Joint Replacement between 2008 and 2021, stratified by the infection type

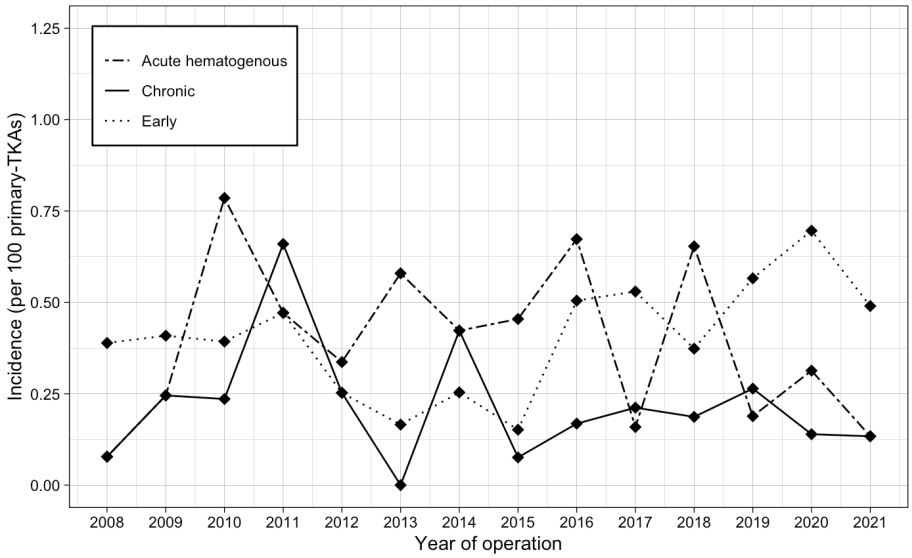

Figure 11. Incidence of PJI after primary TKA at the Coxa Hospital for Joint Replacement between 2008 and 2021, stratified by the infection type

The proportion of revisions due to chronic PJIs at the beginning of our study period was remarkably higher than at the end of the period. For example, in 2008-2009, 11 (21.2%) of 52 revisions were performed due to chronic PJI; however, the corresponding proportion in 2020-2021 was 8.9% (15 of 169). A similar trend was also observed with acute infections, as the proportion decreased from 32.7% (17 of 52) in 2008-2009 to 18.9% (32 of 169) in 2020-2021.

5.1.2 Comorbidity burden

The comorbidity burden was nearly the same among hip and knee patients, with the proportion of ASA 3 or greater patients being around 75% for both. The distribution of the ASA-classes is presented in Table 11.

Table 11. Comorbidity burden among PJI patients, as measured with the American Society of Anaesthesiologists classification system

ASA classification	Total, n (%)	Hip, n (%)	Knee, n (%)
1	20 (2.5)	12 (2.8)	8 *(2.1)*
2	169 *(20.9)*	96 *(22.7)*	73 *(19)*
3	495 *(61.3)*	243 *(57.4)*	252 *(65.6)*
4-5	111 *(13.3)*	69 *(16.3)*	42 *(10.9)*
NA	12 *(1.5)*	3 *(0.7)*	9 *(2.3)*

However, the comorbidity burden of the PJI patients increased slightly. The proportion of ASA 4-5 patients in 2008-2009 was 13.5% and 16.6% in 2020-2021. Furthermore, this increase was mostly due to the increased comorbidity burden among patients with PJI of the hip, as no remarkable changes were observed among patients with PJI of the knee. (Table 12)

Table 12. Number of ASA ≥4 patients during the study period

Joint, n (%)	2008-09	2010-11	2012-13	2014-15	2016-17	2018-19	2020-21
Total	7 *(13.5)*	8 *(9.4)*	7 *(9)*	13 *(11.1)*	25 *(15)*	25 *(16.3)*	28 *(16.6)*
Hip	2 *(10.5)*	1 *(2.9)*	4 *(12.1)*	7 *(10.9)*	20 *(22)*	14 *(18.4)*	21 *(20)*
Knee	5 *(15.2)*	7 *(14)*	3 *(6.7)*	6 *(11.3)*	3 *(4.8)*	11 *(14.3)*	7 *(10.9)*

5.2 Microbiology of PJI (Studies I and III)

Staphylococcus aureus (S. aureus) was the most identified pathogen, accounting for 273 (40%) infections (Table 13). In total, 37.1% (157 of 423) of PJIs of the hip and 30.5% (116 of 380) of PJIs of the knee, respectively, were caused by *S. aureus*. A total of 189 (23.4%) PJIs were culture-negative, and they were more common among knee infections (30%, 114 of 380) than hip infections (17.7%, 75 of 423).

Table 13. Microbiological results from tissue specimens

	All		Hip		Knee	
Pathogen	**N**	**%**	**N**	**%**	**N**	**%**
Staphylococcus aureus	273	*31.1*	157	*34.1*	116	*27.8*
CNS	186	*21.2*	107	*23.2*	79	*18.9*
Streptococcus beta-hemolyticus	88	*10*	40	*8.7*	48	*11.5*
Other streptococcus species	25	*2.8*	14	*3*	11	*2.6*
Gram-negative aerobic	46	*5.2*	24	*5.2*	22	*5.3*
Enterococcus species	33	*3.8*	20	*4.3*	13	*3.1*
Anaerobic	21	*2.4*	13	*2.8*	8	*1.9*
Other	18	*2*	11	*2.4*	7	*1.7*
Culture-negative	189	*21.5*	75	*16.3*	114	*27.3*

As microbiological findings from the polymicrobial infections are included, the total N is greater than the total N of the surgeries performed.

5.2.1 Early infections

Most of the early infections (43.1%, 188 of 436) were caused by *S. aureus*, both among hip PJIs (40.3%, 116 of 288) and knee PJIs (48.6%, 72 of 148). The CNS were also identified in over 20% of PJIs. The proportion of culture-negative infections was similar between the joints. (Table 14)

Table 14. Microbiological results from tissue specimens after early PJI

	All		Hip		Knee	
Pathogen	**N**	**%**	**N**	**%**	**N**	**%**
Staphylococcus aureus	188	*38.1*	116	*36.4*	72	*41.1*
CNS	117	*23.7*	80	*25.1*	37	*21.1*
Streptococcus beta-hemolyticus	42	*8.5*	28	*8.8*	14	*8*
Other streptococcus species	4	*0.8*	0	*0*	4	*2.3*
Gram-negative aerobic	22	*4.5*	15	*4.7*	7	*4*
Enterococcus species	21	*4.3*	15	*4.7*	6	*3.4*
Anaerobic	9	*1.8*	5	*1.6*	4	*2.3*
Other	14	*2.8*	9	*2.8*	5	*2.9*
Culture-negative	77	*15.6*	51	*16*	26	*14.9*

Early infection was defined as infection occurring within the first 90 postoperative days from the previous aseptic surgery. As microbiological findings from the polymicrobial infections are included, the total N is greater than the total N of the surgeries performed.

5.2.2 Acute hematogenous infections

Staphylococcus aureus was the most prevalent pathogen among acute hematogenous infections, causing 60 (27%) infections. (Table 15) Beta-hemolytic streptococci were the most prevalent amongst acute knee PJIs (22.4%, 33 of 147). Among hip PJIs, *S. aureus* was the most identified pathogen, causing 32 (42.6%) infections. The proportion of culture-negative PJIs was greater among knee PJIs.

Table 15. Microbiological results from tissue specimens after acute hematogenous PJI

	All		Hip		Knee	
Pathogen	**N**	**%**	**N**	**%**	**N**	**%**
Staphylococcus aureus	60	*26.4*	32	*42.1*	28	*18.5*
CNS	21	*9.3*	4	*5.3*	17	*11.3*
Streptococcus beta-hemolyticus	43	*18.9*	10	*13.2*	33	*21.9*
Other streptococcus species	12	*5.3*	6	*7.9*	6	*4*
Gram-negative aerobic	18	*7.9*	6	*7.9*	12	*7.9*
Enterococcus species	5	*2.2*	0	*0*	5	*3.3*
Anaerobic	5	*2.2*	3	*3.9*	2	*1.3*
Other	2	*0.9*	0	*0*	2	*1.3*
Culture-negative	61	*26.9*	15	*19.7*	46	*30.5*

Acute infection was defined as an infection occurring after the first 90 postoperative days from the previous aseptic surgery, with fewer than 28 days of symptoms. As microbiological findings from the polymicrobial infections are included, the total N is greater than the total N of the surgeries performed.

5.2.3 Chronic infections

Most of the chronic infections (32.2%, 48 of 149) were caused by CNS, both after THA (38.3%, 23 of 60) and TKA (28.1%, 25 of 89). (Table 16) The proportion of culture-negative PJIs of the knee was high, as pathogen detection was not possible in 42 (47.2%) knees, and infections were, therefore, categorized as culture-negative.

Table 16. Microbiological results from tissue specimens after chronic PJI

	All		Hip		Knee	
Pathogen	**N**	**%**	**N**	**%**	**N**	**%**
Staphylococcus aureus	25	*15.8*	9	*13.6*	16	*17.4*
CNS	48	*30.4*	23	*34.8*	25	*27.2*
Streptococcus beta-hemolyticus	3	*1.9*	2	*3*	1	*1.1*
Other streptococcus species	9	*5.7*	8	*12.1*	1	*1.1*
Gram-negative aerobic	6	*3.8*	3	*4.5*	3	*3.3*
Enterococcus species	7	*4.4*	5	*7.6*	2	*2.2*
Anaerobic	7	*4.4*	5	*7.6*	2	*2.2*
Other	2	*1.3*	2	*3*	0	*0*
Culture-negative	51	*32.3*	9	*13.6*	42	*45.7*

Chronic infection was defined as an infection occurring after the first 90 postoperative days from the initial aseptic surgery, with at least 28 days of symptoms. As microbiological findings from the polymicrobial infections are included, the total N is greater than the total N of the surgeries performed.

5.2.4 Trends in the microbiology

During the study period, the proportion of PJIs identified to have been caused by *S. aureus* was 30.5% in 2008-2009, whereas the corresponding proportion in 2020-2021 was 37.8%. However, no clear trends were observed, and the proportions were nearly the same at the beginning of the study period as they were at the end of the period.

The proportion of negative cultures remained at around 20% throughout the study period. For hips, the proportion of negative cultures decreased from 31.6% in 2008-2009 to 16.5% in 2021-2021. For knees, the corresponding proportion increased from 20% in 2008-2009 to 25.7% in 2021-2021. In addition, higher proportions of negative cultures were observed among knees than among hips throughout the study period.

5.3 Surgical strategies (Studies I and III)

During our study period, the incidence of one-stage revision increased remarkably. Between 2008 and 2013, it was below 0.25 per 100 primary TJAs, but increased steadily to more than 0.75 per 100 primary TJAs between 2013 and 2020. Incidences of one-stage revision are presented in Figures 12, 13, and 14.

In addition, one-stage revision became the most used surgical strategy at our institution, with more than half (51.5%, 87 of 169) of the revisions in 2021 being one-stage revisions. The strategy became especially common in the management of hip PJIs, as the proportion of hip PJIs managed with one-stage revision increased from 0% in 2008-2009 and 14.3% in 2010-2011 to 56.2% in 2020-2021. The corresponding numbers for knee PJIs were 12.1% in 2008-2009 and 43.8% in 2021-2021. (Tables 17 and 18)

In addition to the observed increase in incidence and the total proportion of one-stage revision, a remarkable decrease among two-stage revision was observed, both among hip and knee PJIs. At the beginning of our study period, two-stage revision was the most used strategy (100% hips, 57.6% knees). However, by the end of the study period, it was the least used strategy for both PJIs of the hip (14.3%) and the knee (6.3%).

The incidence as well as the proportion of DAIR remained at almost the same level throughout the study period. Indeed, between 2020-2021, most of the PJIs were managed by either DAIR (37.3%) or one-stage (51.5%) revision.

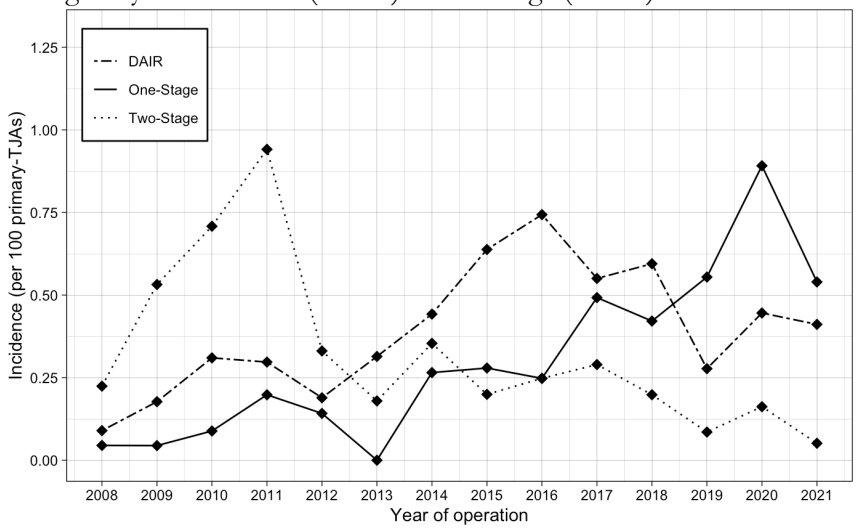

Figure 12. Incidence of PJI after primary THA or TKA at the Coxa Hospital for Joint Replacement between 2008 and 2021, stratified by the type of revision surgery

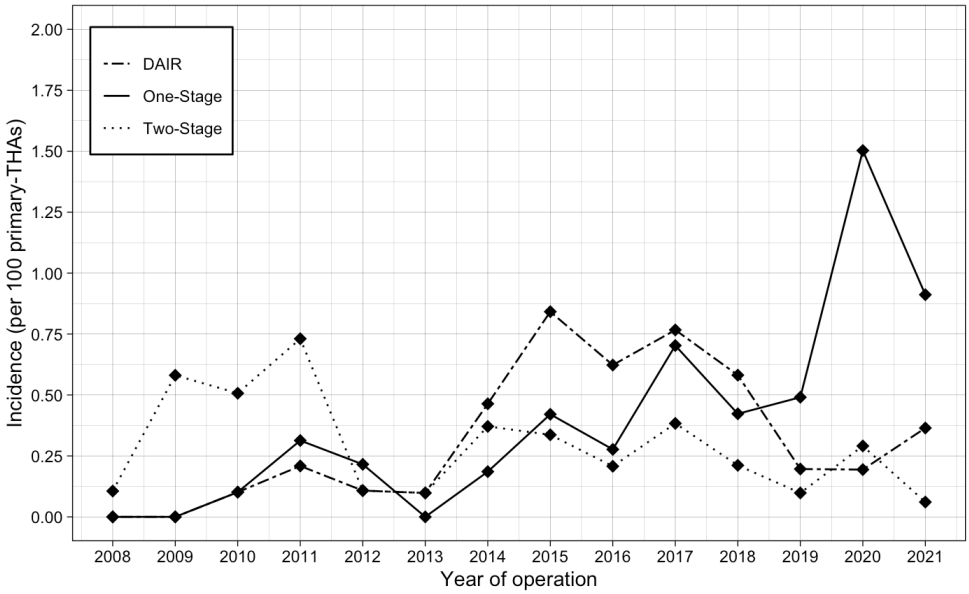

Figure 13. Incidence of PJI after primary THA at the Coxa Hospital for Joint Replacement between 2008 and 2021, stratified by the type of revision surgery

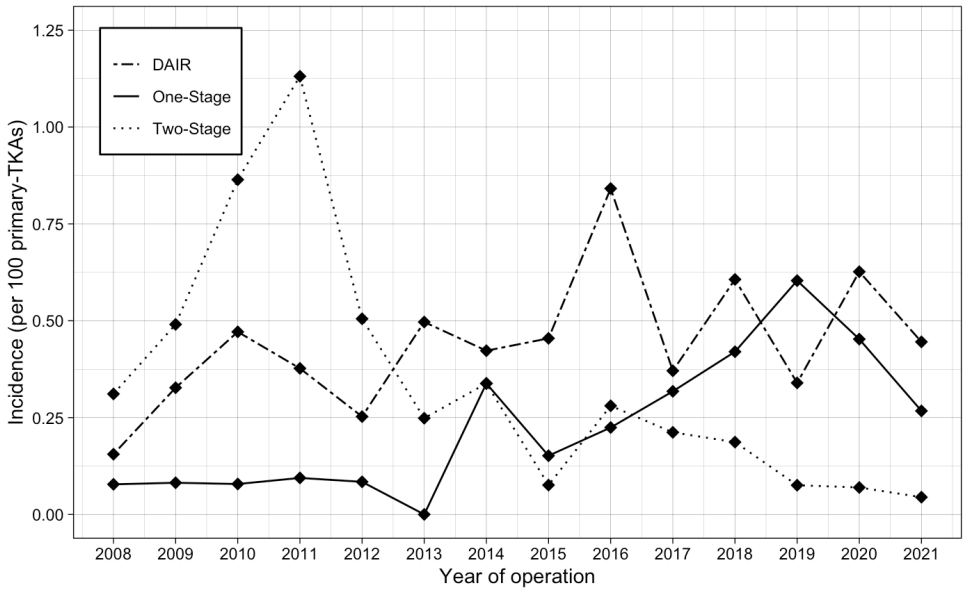

Figure 14. Incidence of PJI after primary TKA at the Coxa Hospital for Joint Replacement between 2008 and 2021, stratified by the type of revision surgery

Table 17. Distribution of the surgical strategies for hip PJI between 2008 and 2021

	2008-09 n = 19	2010-11 n = 35	2012-13 n = 33	2014-15 n = 64	2016-17 n = 91	2018-19 n = 76	2020-21 n = 105
All infections, n (%)							
DAIR	0	8 *(22.9)*	10 *(30.3)*	29 *(45.3)*	41 *(45.1)*	31 *(40.8)*	31 *(29.5)*
One-stage	0	5 *(14.3)*	5 *(15.2)*	11 *(17.2)*	29 *(31.9)*	32 *(42.1)*	59 *(56.2)*
Two-stage	19 *(100)*	22 *(62.9)*	18 *(54.5)*	24 *(37.5)*	21 *(23.1)*	13 *(17.1)*	15 *(14.3)*
Early infections, n (%)							
DAIR	0	6 *(37,5)*	8 *(50)*	19 *(51.4)*	32 *(50.8)*	27 *(43.5)*	25 *(28.7)*
One-stage	0	5 *(31.3)*	2 *(12.5)*	7 *(18.9)*	22 *(34.9)*	28 *(45.2)*	55 *(63.2)*
Two-stage	7 *(100)*	5 *(31.3)*	6 *(37.5)*	11 *(29.7)*	9 *(14.3)*	7 *(11.3)*	7 *(8)*
Acute hematogenous infections n (%)							
DAIR	0	1 *(20)*	0	9 *(50)*	8 *(44.4)*	4 *(50)*	5 *(41.7)*
One-stage	0	0	3 *(37.5)*	4 *(22.2)*	4 *(22.2)*	2 *(25)*	3 *(25)*
Two-stage	6 *(100)*	4 *(80)*	5 *(62.5)*	5 *(27.8)*	6 *(33.3)*	2 *(25)*	4 *(33.3)*
Chronic infections, n (%)							
DAIR	0	1 *(7.1)*	2 *(22.2)*	1 *(11.1)*	1 *(10)*	0	1 *(16.7)*
One-stage	0	0	0	0	3 *(30)*	2 *(33.3)*	1 *(16.7)*
Two-stage	6 *(100)*	13 *(92.9)*	7 *(77.8)*	8 *(88.9)*	6 *(60)*	4 *(66.7)*	4 *(66.7)*

Table 18. Distribution of the surgical strategies for knee PJI between 2008 and 2021

	2008-09 n = 33	2010-11 n = 50	2012-13 n = 45	2014-15 n = 53	2016-17 n = 62	2018-19 n = 77	2020-21 n = 64
All infections, n (%)							
DAIR	10 *(30.1)*	12 *(24)*	14 *(31.1)*	24 *(45.3)*	31 *(50)*	29 *(43.3)*	32 *(50)*
One-stage	4 *(12.1)*	4 *(8)*	4 *(8.9)*	11 *(20.8)*	17 *(27.4)*	36 *(38.8)*	28 *(43.8)*
Two-stage	19 *(57.6)*	34 *(68)*	27 *(60)*	18 *(34)*	14 *(22.6)*	12 *(17.9)*	4 *(6.3)*
Early infections, n (%)							
DAIR	5 *(29.4)*	5 *(33.3)*	2 *(16.7)*	9 *(60)*	16 *(69.6)*	14 *(45.2)*	22 *(62.9)*
One-stage	4 *(23.5)*	1 *(6.7)*	0	2 *(13.3)*	4 *(17.4)*	13 *(41.9)*	11 *(31.4)*
Two-stage	8 *(47.1)*	9 *(60)*	10 *(83.3)*	4 *(26.7)*	3 *(13)*	4 *(12.9)*	2 *(5.7)*
Acute hematogenous infections, n (%)							
DAIR	5 *(45.5)*	7 *(36.8)*	12 *(57.1)*	15 *(62.5)*	15 *(62.5)*	15 *(53.6)*	9 *(45)*
One-stage	0	2 *(10.5)*	1 *(4.8)*	7 *(29.2)*	7 *(29.2)*	11 *(39.3)*	10 *(50)*
Two-stage	6 *(54.5)*	10 *(52.6)*	8 *(38.1)*	2 *(8.3)*	2 *(8.3)*	2 *(7.1)*	1 *(5)*
Chronic infections, n (%)							
DAIR	0	0	0	0	0	0	1 *(11.1)*
One-stage	0	1 *(6.3)*	3 *(25)*	2 *(14.3)*	6 *(40)*	12 *(66.7)*	7 *(77.8)*
Two-stage	5 *(100)*	15 *(93.8)*	9 *(75)*	12 *(85.7)*	9 *(60)*	6 *(33.3)*	1 *(11.1)*

5.4 Outcomes of revision arthroplasty (Studies II and IV)

The overall risk for any-cause failure was 34.4% (CI, 29.4%–39.1%) for PJI of the hip and 26.5% (21.8%–30.9%) for PJI of the knee. At 1-year follow-up, 26.6% (CI, 22.2%–31.2%) of patients with PJI of the hip had undergone a reoperation and 7.9% (CI, 5.2%–10.9%) had died. For patients with PJI of the knee, the corresponding risks were 22.8% (CI, 18.6%–27.3%) for reoperation and 3.6% (CI, 2.0%–5.9%) for death. The highest overall risk for failure after PJI of the hip was observed when DAIR was performed (47%, CI, 37.9%–54.8%). After PJI of the knee, the highest risk for failure was observed when a two-stage revision was performed (30.8%, CI, 22.1%–38.6%).

After hip PJI, the risk for reoperation was highest when DAIR was performed, as 36.6% (CI, 28.5%–44.7%) of patients underwent a reoperation during 1-year follow-up. The risk for reoperation was similar after one-stage (20.2%, CI, 13.4%–28%) and two-stage (21.5%, CI, 14.6%–29.2%) revisions. After knee PJI, the lowest risk for reoperation was after one-stage revision, as 15.3% (CI, 9%–23.2%) of these patients underwent reoperation during 1-year follow-up. The risk for reoperation was similar when DAIR (24.1%, CI, 17.4%–31.5%) or two-stage (27.5%, CI, 19.8%–35.7%) revision was performed.

The risk for death was higher after PJI of the hip, as 7.9% (CI, 5.4%–10.9%) of patients had died after 1-year follow-up, but the corresponding risk was 3.6% (CI, 2.0%–5.9%) after PJI of the knee. For both hip and knee PJIs, the risk for death was highest when DAIR was performed (hip 10.4%, CI, 6%–16.3%; knee 4.3%, CI, 1.7%–8.5%). Although the risk for death after one- and two-stage revisions were similar, the risk was subsequently higher for PJIs of the hip (one-stage 7%, CI, 3.3%–12.7%; two-stage 5.8%, CI, 2.5%–11%) than among PJIs of the knee (one-stage 3.1%, CI, 0.8%–8%; two-stage 3.3%, CI, 1.1%–7.7%). However, the results were imprecise because the confidence intervals of the estimated failure rates overlapped. The risks for reoperation and death are presented in Figures 15 and 16.

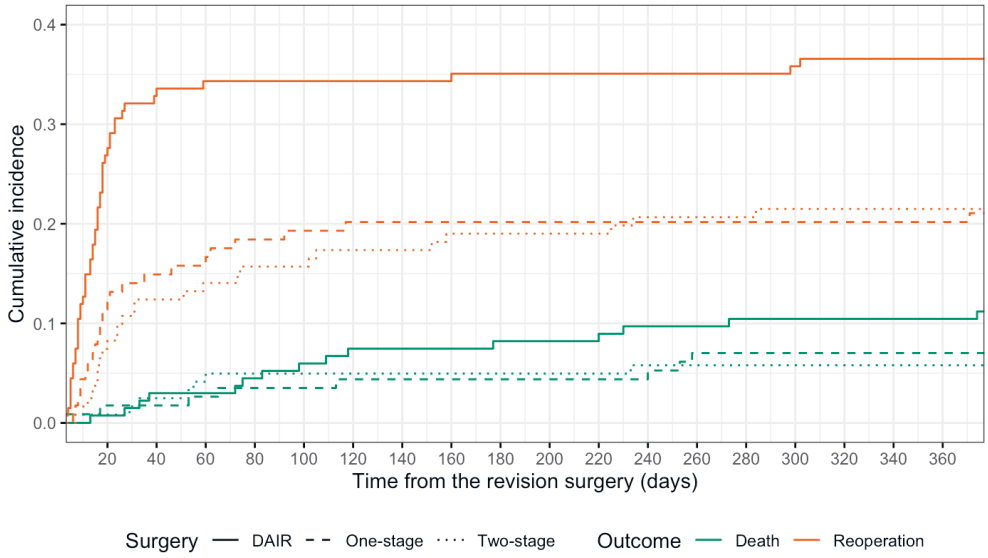

Figure 15. Cumulative incidence of failure after revision for hip PJI, stratified by the type of surgery

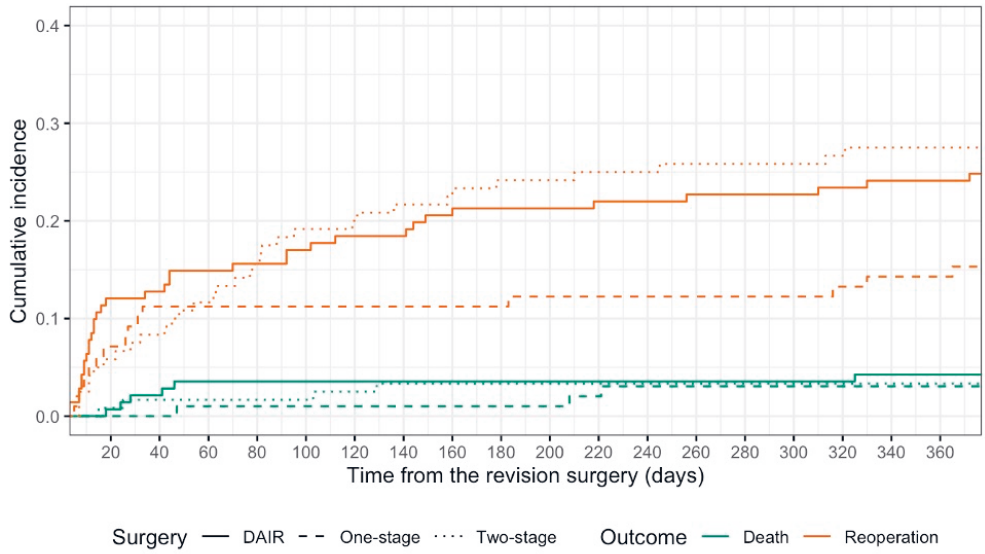

Figure 16. Cumulative incidence of failure after revision for knee PJI, stratified by the type of surgery

5.4.1 Early infections

For early PJIs of the hip, the failure risk was 37.1% (CI, 30.8%–42.9%) during a 1-year follow-up. The risk was highest if DAIR (45.6%, CI, 35.1%–54.4%) was performed. When compared to DAIR, one-stage revision almost halved the risk for reoperation (HR 0.51, CI, 0.31–0.84) with no added mortality risk (HR 1.05, CI, 0.5–2.2). After adjusting the analysis by the type of fixation of the previous prosthesis (cemented/uncemented), the difference between the failure risks remained similar (aHR 0.69, CI, 0.45–1.06); however, the results were imprecise, and the confidence intervals included zero change.

The failure risk was lower after early knee PJI than after early hip PJI, as the risk for failure was 30.9% (CI, 22.8%–38.2%) during 1-year follow-up. In addition, the results after DAIR were superior to other strategies, as 26.1% (CI, 15%–35.8%) failed within 1-year follow-up. However, the results were imprecise, and the confidence intervals overlapped with those from other revision strategies. The largest risk for failure was also observed if a two-stage revision was performed, as 40% (CI, 21.4%–54.2%) of those procedures failed during 1-year follow-up. Further details on the failure risks after early PJI are presented in Table 19.

Table 19. Risk for failure after early PJI

		30-day survival (CI)	1-year survival (CI)
Hips			
	All revisions (n=245)	24.9% *(19.3%–30.1%)*	37.1% *(30.8%–42.9%)*
	DAIR (n=103)	35% *(25.1%–43.5%)*	45.6% *(35.1%–54.4%)*
	One-stage (n=94)	18.1% *(9.9%–25.5%)*	26.6% *(17.1%–35%)*
	Two-stage (n=48)	16.7% *(5.4%–26.6%)*	39.6% *(24%–51.9%)*
Knees			
	All revisions (n=139)	17.3% *(10.7%–23.3%)*	30.9% *(22.8%–38.2%)*
	DAIR (n=69)	15.9% *(6.8%–24.2%)*	26.1% *(15%–35.8%)*
	One-stage (n=35)	20% *(5.6%–32.2%)*	31.4% *(14.2%–45.2%)*
	Two-stage (n=35)	17.1% *(3.7%–28.7%)*	40% *(21.4%–54.2%)*

Early infection was defined as infection occurring within the first 90 postoperative days from the previous aseptic surgery. Failure is defined as a reoperation or death. Failure rates were calculated with the Kaplan-Meier estimator. Results are reported with 95% confidence intervals.

5.4.2 Acute hematogenous infections

The failure rates after acute hematogenous PJI favored one-stage revision, both among hips (13.3%, CI, 0%–28.9%) and knees (8.6, CI, 0%–17.4%), as the failure rates were the lowest within 1-year follow-up when one-stage revision was performed. The risk for failure was the highest after DAIR in both hip and knee PJIs. Further details on the failure risk after acute hematogenous PJIs are presented in Table 20.

Table 20. Risk for failure after acute hematogenous PJI

		30-day survival (CI)	1-year survival (CI)
Hips			
	All revisions (n=68)	23.5% *(12.8%–33%)*	30.9% *(19%–31%)*
	DAIR (n=25)	36% *(14.1%–52.3%)*	48% *(24.2%–64.3%)*
	One-stage (n=15)	6.7% *(0%–18.5%)*	13.3% *(0%–28.9%)*
	Two-stage (n=28)	21.4% *(4.7%–35.2%)*	25% *(7.1%–39.4%)*
Knees			
	All revisions (n=136)	8.8% *(3.9%–13.5%)*	25% *(17.4%–31.9%)*
	DAIR (n=71)	12.7% *(4.6%–20.1%)*	31% *(19.3%–40.9%)*
	One-stage (n=35)	2.9% *(0%–9.2%)*	8.6% *(0%–17.4%)*
	Two-stage (n=30)	6.7% *(0%–15.2%)*	30% *(11.5%–44.6%)*

Acute infection was defined as an infection occurring within the first 90 postoperative days from the previous aseptic surgery, with less than 28 days of symptoms. Failure is defined as a reoperation or death. Failure rates were calculated with the Kaplan-Meier estimator. Results are reported with 95% confidence intervals.

5.4.3 Chronic infections

The failure rates after chronic infections were lowest when compared to the other infection types, as the risk for failure after chronic PJI of the hip was 26.8% (CI, 14.2%–37.5%). After chronic PJI of the knee, 21.4% (CI, 12.1%–29.7%) failed within 1-year follow-up. However, as most of the chronic infections were managed with two-stage revision, the results are not comparable.

Almost all the chronic hip PJIs were managed with two-stage revision, and 15.6% (CI, 4.3%–25.5%) of those revisions failed within 1-year follow-up. Chronic knee PJIs were managed with either one-stage revision or two-stage revision. In total, 28 (26.8%) one-stage and 55 (45.8%) two-stage revisions were performed for chronic

infections. When compared to two-stage revision, the use of one-stage revision was slightly associated with a decreased risk for reoperation (HR 0.52, CI, 0.21–1.29) with no added mortality risk (HR 0.60, CI, 0.17–2.15). Furthermore, the risk for any-cause failure was also lower (HR 0.54, CI, 0.26–1.14) when one-stage revision was performed. The results from these analyses were, however, imprecise, and confidence intervals included zero change. Further details on the failure risks after chronic PJIs are presented in Table 21.

Table 21. Risk of failure after chronic PJI

		30-day survival (CI)	1-year survival (CI)
Hips			
	All revisions (n=56)	1.8% *(0%–5.2%)*	26.8% *(14.2%–37.5%)*
	DAIR (n=6)	0%	76.7% *(0%–89.2%)*
	One-stage (n=5)	0%	80% *(0%–96.5%)*
	Two-stage (n=45)	2.2% *(0%–6.4%)*	15.6% *(4.3%–25.5%)*
Knees			
	All revisions (n=84)	4.8% *(0.1%–9.2%)*	21.4% *(12.1%–29.7%)*
	DAIR (n=1)	-	-
	One-stage (n=28)	3.6% *(0%–10.2%)*	14.3% *(0.3%–26.3%)*
	Two-stage (n=55)	5.5% *(0%–11.3%)*	25.5% *(13%–36.1%)*

Chronic infection was defined as an infection occurring after the first 90 postoperative days from the previous aseptic surgery, with at least 28 days of symptoms. Failure is defined as a reoperation or death. Failure rates were calculated with the Kaplan-Meier estimator. Results are reported with 95% confidence intervals.

5.4.4 Predictors of the outcome

Higher ASA scores increased the risk for death after both hip PJI (aHR 4.54, CI, 2.66–7.77 per 1 unit increase) and knee PJI (aHR 1.66, CI, 1.09–2.53 per 1 unit increase). Higher ASA scores were also predictive of reoperation after hip PJI, as a 1 unit increase in the ASA score represented a 1.63 (CI, 1.19–2.24) times higher risk.

The prediction of reoperation was difficult because in the selected Cox models the C-indexes were 0.63 for hips and 0.64 for knees, with reoperation as the endpoint. The corresponding R^2-values were 0.20 and 0.23, indicating modest prediction capability. ASA class, type of operation, and type of infection were the most important predictors of reoperation after hip PJI, whereas the most important predictors of reoperation after knee PJI were ASA class and CCI.

The prediction of death was less difficult than the prediction of reoperation. In the selected Cox models, the C-indexes were 0.81 for hips and 0.63 for knees, with death as the endpoint. The corresponding R^2-values were 0.74 for hips, indicating good predictive ability, and 0.22 for knees, indicating modest predictive ability. ASA class, BMI, and the presence of diabetes mellitus were the most important predictors of death after hip PJI, whereas CCI and the presence of diabetes mellitus or liver cirrhosis were the most important predictors of death after knee PJI.

5.5 Validation of the KLIC-score (Study V)

A KLIC-score was slightly associated with the risk for failure after DAIR, as a 1-point increase represented a 1.45 (CI, 1.13–1.90) times higher risk for failure. For 1-stage revision, the results were similar but imprecise, as the confidence intervals (OR 1.20, CI, 0.93–1.56) included zero change. Further measures of the prognostic performance of the KLIC-score are presented in Table 22.

Table 22. Prognostic performance of the KLIC-score

	AUC (95% CI)	OR (95% CI)	SEN	SPE	PPV	NPV
DAIR						
KLIC-score*	0.63 *(0.55–0.72)*	1.45 *(1.13–1.90)*	-	-	-	-
KLIC >2	0.50 *(0.46–0.54)*	1.04 *(0.28–3.89)*	0.94	0.06	0.51	0.5
KLIC >3.5	0.53 *(0.48–0.59)*	1.69 *(0.72–4.14)*	0.88	0.19	0.53	0.6
KLIC >4.5	0.64 *(0.57–0.71)*	4.0 *(1.95–8.62)*	0.44	0.82	0.73	0.59
One-stage						
KLIC-score*	0.56 *(0.46–0.66)*	1.20 *(0.93–1.56)*	-	-	-	-
KLIC >2	0.59 *(0.44–0.53)*	0.67 *(0.15–2.95)*	0.92	0.05	0.4	0.5
KLIC >3.5	0.56 *(0.47–0.65)*	1.66 *(0.79–3.57)*	0.68	0.44	0.45	0.67
KLIC >4.5	0.54 *(0.47–0.61)*	1.78 *(0.66–4.84)*	0.2	0.88	0.53	0.62

All the measures were calculated with failure within 60-days as the endpoint. * = 1-unit increase. SEN = sensitivity, SPE = specificity, PPV = positive predictive value, NPV = negative predictive value.

Within 60-day follow-up, the discriminative ability of the KLIC-score was poor, both after DAIR (AUC 0.63, CI, 0.55–0.72) and one-stage revisions (AUC 0.56, CI, 0.46–0.66). The results after 1-year follow-up were similar (DAIR 0.53, CI, 0.44–0.63; one-stage 0.58 CI, 0.46–0.69). The ROC curves and the corresponding AUCs are presented in Figure 17.

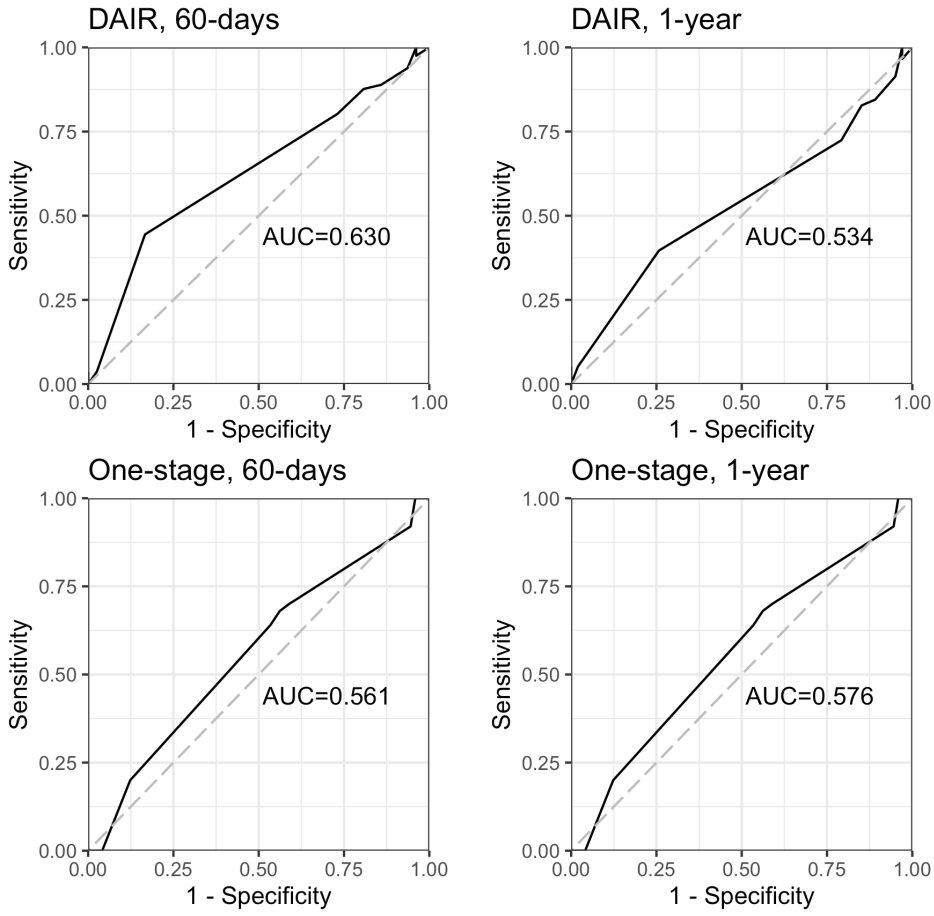

Figure 17. Receiver operating characteristics curves for the KLIC-score stratified by the type of surgery and follow-up time

The calibration curves within 60-day and 1-year follow-ups are presented in Figure 18. On average, the KLIC-score either underestimated or overestimated the risk for failure. However, based on the calibration plots, the predictive capability was better for one-stage revision than DAIR, as the model was almost ideal for predicting failure within 60 days.

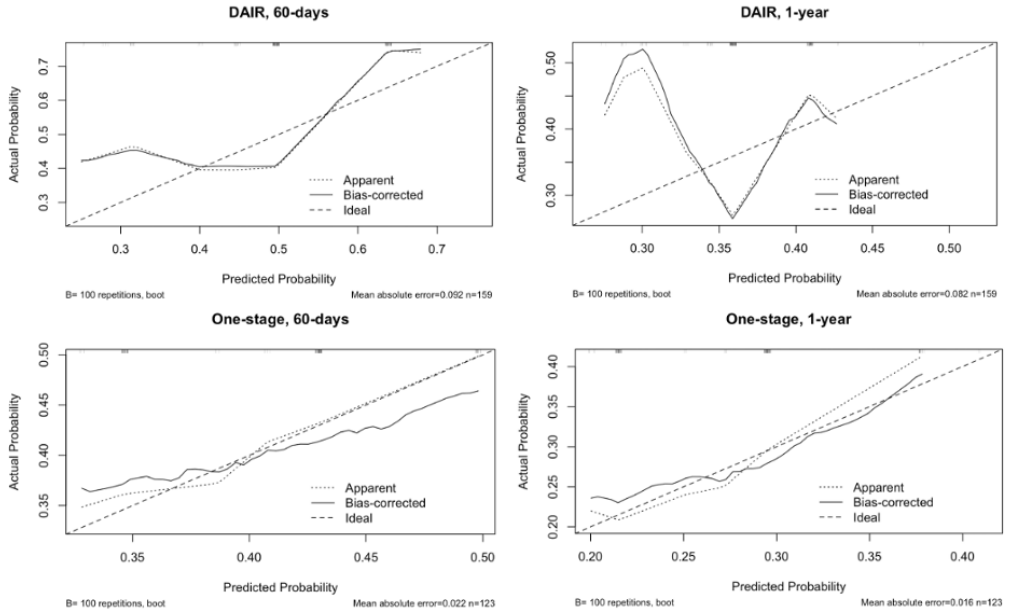

Figure 18. Calibration curves stratified by the type of surgery and follow-up time. On the x-axes are the predicted probabilities and on the y-axes are the observed probabilities. A perfectly calibrated model would follow the straight dashed line referred to as "ideal" in the graph. Calibration was modeled with bootstrapping using 100 repetitions.

The results from the DCA suggested that the model's net benefit did not demonstrate a significant advantage across a wide range of threshold probabilities. Notably, the net benefit curve consistently tracked below both the "Full Treatment" line (representing universal treatment for all patients) and the "No Treatment" line (representing no treatment for any patients) across almost the entire spectrum of threshold probabilities. This indicates that the model's use in guiding treatment decisions did not provide any additional clinical benefit beyond the established baseline strategies. The DCA curves are presented in Figure 19.

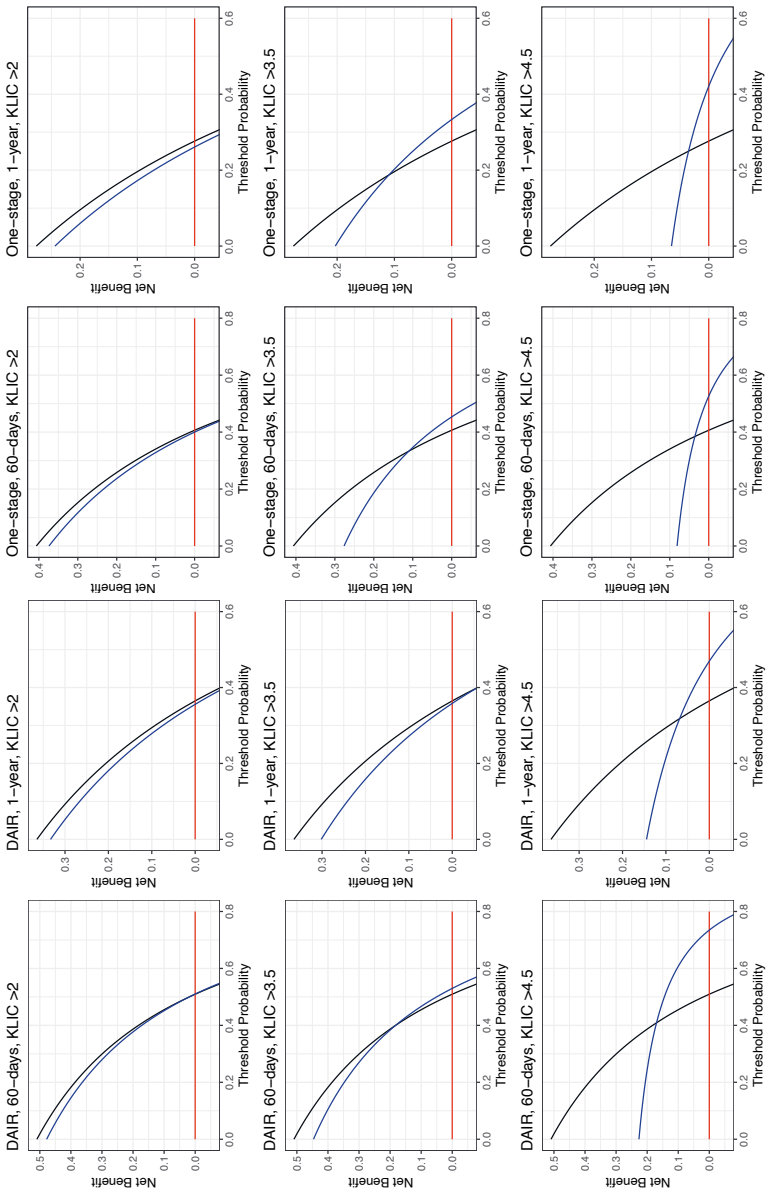

Figure 19. Decision-curve analyses curves. The black line represents the "treat all" scenario, the blue line represents the "treat above specific KLIC-score" scenario. The red line represents the scenario where no patients are treated, and hence the net benefit is zero (no true-positive and no false-positive classifications). The graph gives the expected net benefit per patient relative to no treatment in any patient ("Treat none"). If the model curve is above the no-treatment line, it suggests that using the model is beneficial across a range of threshold probabilities. If the model curve is above the full treatment line, it suggests that the model outperforms treating all patients at some threshold probabilities.

6 DISCUSSION

6.1 Epidemiology

6.1.1 Incidence of PJI

In studies I and III, the incidence of PJI was greater after THA than after TKA. Previously, the incidence has been reported to be higher among TKA patients than among THA patients (Huotari et al., 2015; Premkumar et al., 2021). A possible explanation for this might be anatomical factors, as the protective soft tissue layers surrounding the hip joint are thicker than the layers surrounding the knee joint. Another possible explanation for this difference might be surgical exposure because the surgical incisions in TKA are typically larger, and hence the potential risk for contamination may be increased. However, although the incidence of hip PJIs was greater than knee PJIs, the incidences were similar, which may be due to the effective preventive measures used at our hospital.

During the previous decades, the incidence of PJI has increased (Chang et al., 2020; Dale et al., n.d., 2009; S. M. Kurtz et al., 2018; Lenguerrand et al., 2017; Rupp et al., 2021). In studies I and III, we also observed an increase in the incidence of early infections. This increase was especially present among PJIs of the hip, as the incidence of early infection increased almost 10-fold during our study period. During the same period, the proportion of ASA class 4 patients with hip PJIs more than doubled from approximately 10% to around 20%. O'Toole et al. have also reported a similar trend in increased comorbidity burden. They observed a remarkable increase in the prevalence of obesity and diabetes mellitus among THA patients, which they expected to continue in future (O'Toole et al., 2016). Furthermore, as we also observed an increase in the comorbidity burden, which is a major risk factor for PJI, we might assume that it has had an effect on the observed increase in incidence (Collaborative (MAC)1a*, 2020; Kunutsor, Whitehouse, Blom, et al., 2016; S. M. Kurtz et al., 2018; Ren et al., 2021).

For early knee PJIs, the yearly variation in PJI incidence was large and no clear trends were observed. Previously, the incidence of knee PJIs has been reported to have increased (Chang et al., 2020; Rupp et al., 2021), but decreases in incidence have also been reported (Bozzo et al., 2022; F.-D. Wang et al., 2018). These contradictory results may be explained by the different study periods. For example, during our study period, we would have been able to produce several different conclusions. First, by restricting the study period from 2008 to 2015, we could have declared that the incidence of early knee PJIs has decreased. Second, by restricting the study period from 2015 to 2021, we could have concluded that the incidence of early infections has increased remarkably.

Another factor that might explain the increased incidence of hip PJIs in contrast to the rather steady incidence of knee PJIs, is that the comorbidity burden remained approximately the same throughout the study period among knee PJIs, even though a decreasing trend in the prevalence of major comorbidities, such as DM and rheumatoid arthritis was observed among knee PJI patients, whereas an increasing trend in the comorbidity burden was observed among hip PJIs. However, we can only surmise that the comorbidity burden of PJI patients was approximately the same during our study period, as we did not analyze specific risk factors for PJI.

Philosophically, one might say that the best way to treat PJIs is prevention. However, as the risk for PJI is relatively low nowadays, it might be possible that it cannot be reduced further by only optimizing surgical factors. In addition, it would be almost impossible to reduce the risk for certain complications, such as PJI, to absolute zero. With the number of annual primary TJAs increasing year on year, an increase in the absolute number of PJIs is to be expected. Therefore, in future we should focus more on the prevention of PJIs by optimizing patient-related risk factors such as obesity and DM. In addition, we should focus more on treatment strategies for PJI in future, so that the initial treatment of this complication would be as effective as possible.

6.1.2 Microbiology

Staphylococcus aureus is reported to be the most common pathogen among early infections and is responsible for causing approximately one-third of these infections (Benito et al., 2019; Tai et al., 2022; Triffault-Fillit et al., 2019; Tsaras, Osmon, et al., 2012). Similarly, in studies I and III, *S. aureus* was the most identified pathogen and caused most of the early infections among both hip and knee PJIs. *S. aureus* was also

the most identified pathogen among acute hematogenous hip PJIs. Interestingly, despite their common occurrence, the majority of acute hematogenous knee PJIs were attributed to beta-hemolytic streptococci rather than *S. aureus*. These findings are consistent with those reported by Triffault-Fillit et al. who also observed a higher incidence of acute hematogenous knee PJIs caused by streptococci compared to *S. aureus*. (Triffault-Fillit et al., 2019). The high prevalence of streptococci among acute PJIs could potentially be a knee-specific occurrence. This observation aligns with previous associations linking streptococcal knee PJIs to secondary causation stemming from erysipelas or cellulitis affecting the knee. (Wouthuyzen-Bakker et al., 2018). Furthermore, our results confirm that the microbiological profile might differ between hip and knee infections, and hence joint-specific examination will be warranted in future too (Preobrazhensky et al., 2021).

The proportion of negative cultures has previously been reported to range widely, but the consensus appears to be that the true incidence of culture-negative PJIs is somewhere between 7% and 15% (Lamagni, 2014). In our study, 21.5% of PJIs were culture-negative, and negative cultures were more prevalent amongst knee PJIs. Culture-negative knee PJIs were more common than culture-negative hip PJIs among acute and chronic infections. However, among early infections the proportions were similar.

In addition, it might also be possible that in primary health care, the threshold for consultation of the orthopedic surgeon is lower for patients with hip pain than for knee pain. However, as a significant part of our patients were referrals, and we did not have accurate access to data on any antimicrobial treatment given before arrival at our hospital, the effect of possible preoperative antimicrobial treatment on the cultured tissue specimens can only be hypothesized.

6.2 Recent trends in the use of surgical techniques

During the study period, one-stage revision became the most used revision strategy. This strategy became especially common in the management of early hip PJI, as the proportion of hip PJIs managed with one-stage revision increased from 0% in 2008-2021 to 63.2% in 2020-2021. One-stage revision also became the most popular choice for chronic knee infections, and the corresponding numbers for those were 0% in 2008-2009 and 77.8% in 2021-2021. Previously, Rupp et al. in Germany also reported an increasing proportion of PJIs managed with one-stage revision between 2008 and 2021 (Rupp et al., 2021).

In our study, the one-stage revision became very common, especially for early hip PJIs and chronic knee PJIs. Indeed, at the end of our study period, the majority of such infections were managed with one-stage revision. For hip PJIs, the increase in the incidence of one-stage revisions and the subsequent decrease in the incidence of DAIRs might be considered surprising, as DAIR is less invasive than one-stage revision and is considered a suitable option for the treatment of early PJIs (Karachalios & Komnos, 2021; Zimmerli et al., 2004). Our findings might be explained by the aggressive approach to PJI treatment, as the one-stage operation is also considered a suitable treatment for early and acute infections (Karachalios & Komnos, 2021; Zimmerli et al., 2004). In addition, increased comorbidity might also be a reason why the incidence of one-stage operations has increased. We might, therefore, end up performing one-stage revision rather than DAIR for patients with multiple comorbidities, because the eradication rates of one-stage operations are reported to be better (Karachalios & Komnos, 2021).

For chronic knee PJIs, two-stage revision has traditionally been advocated as the gold standard (Gehrke et al., 2015; Izakovicova et al., 2019). However, previous studies have questioned the superiority of two-stage revision over one-stage revision (Nguyen et al., 2016; van den Kieboom et al., 2021). In our study, one-stage revision became the most common revision strategy for chronic infection. These findings might also be partly explained by the adoption of the "1.5-stage revision", as it has been reported to be a suitable method for treating chronic PJIs of the knee (Hernandez et al., 2021; Siddiqi et al., 2018).

6.3 Outcomes of PJI treatment

Previous studies have reported that mortality after PJI ranges between 3% and 5% within 1-year follow-up (Cancienne et al., 2018; Lum et al., 2018; Natsuhara et al., 2019). Mortality after hip PJI in our study was associated with the type of surgery. For example, 1-year mortality was 10.4% after DAIR, 5.8% after one-stage revision, and 7% after two-stage revision. However, in multivariable analyses, the type of operation was not associated with the risk for death. Hence, the variances in mortality rates primarily stem from patient-related factors influencing the selection of the treatment approach. In study IV, the mortality rates after knee PJI were, however, similar between the different surgical strategies. Previously, mortality has been reported to be highest after DAIR and lowest after one-stage revision (Leta et al., 2019; Urish et al., 2018).

It has also been reported that the increased mortality after PJI is associated with preoperative morbidity, rather than treatment (Drain et al., 2022). This might partly explain our results, as the type of revision surgery was not associated with mortality risk in multivariable analyses, but total comorbidity burden, measured with ASA-class, was. Furthermore, as we observed a trend of increased morbidity among hip PJI patients in study I, the risk for mortality might increase further in future should this increase in comorbidity burden continue. In future, increased comorbidity might not only cause an increased rate of PJIs, but it could also negatively influence an individual's prognosis, making the treatment of PJIs even more difficult.

6.3.1 Early prosthetic joint infections

In study II, the risk for failure after DAIR was surprisingly high after early hip PJIs, as within 1-year follow-up over 40% of these procedures failed. For early knee PJIs, the corresponding risk was remarkably lower, being about 30% in study IV. In fact, the DAIR procedure for early knee PJI was the most effective treatment strategy when compared to the other techniques.

There is still a lack of evidence of the differences between DAIR and one-stage revisions for early PJIs of the hip (Hansen et al., 2013; Riemer & Lange, 2022; Wolf et al., 2014). In 2022, excellent results after one-stage revision for early PJI of the hip were reported by Riemer et al, suggesting that one-stage revision might at least be comparable with DAIR, if not superior, in the treatment of early infections (Riemer & Lange, 2022). However, no direct comparison between these two revision strategies was performed due to the lack of sample size. As revealed by the results from study II, one-stage revision might be at least as effective a treatment method as DAIR for early hip PJIs.

Of course, one-stage revision will not be suitable for anyone. The fixation method used for the previous prosthesis must be considered as an important factor in deciding whether to perform DAIR or one-stage revision for early hip PJIs. In our analysis, where the fixation method was considered, the decreased risk for reoperation was still observed with no increased risk for death. However, the results from these analyses were imprecise, and hence no definitive conclusions can be made. The positive results with one-stage revision for early hip PJIs might also explain the results from study I, as the proportion of early hip PJIs managed with one-stage revision had increased to 50%.

To our knowledge, no prior study has examined the outcomes between DAIR and one-stage revision for certain types of PJI of the hip. Given that one-stage revision did not increase the risk for death compared to DAIR, there is a need for additional investigations into patient selection between these two approaches, preferably through a randomized controlled trial. Additionally, future assessments should explore the effectiveness of non-traditional revision strategies, such as cement-in-cement revisions, compared with traditional methods, because reports have suggested promising outcomes for these alternative approaches (Fishley et al., 2022).

In study IV, the results after DAIR for early PJI of the knee were good, as the best results were achieved with this approach. The DAIR procedure is still considered the primary treatment method for early knee PJIs (Izakovicova et al., 2019), especially when exchange of the modular components is possible (Zaruta et al., 2018). Interestingly, Rupp et al. reported, that a decreasing proportion of all knee PJIs are managed with DAIR in Germany, even though the annual number of primary TKAs and septic revisions is increasing (Rupp et al., 2021), and thus the annual number of early PJIs might also have increased. However, as their study was based solely on registry data, and no classification between the different infection types was performed, a direct comparison with our results from study III is impossible. Furthermore, our results from one-stage revision for early knee PJI were almost as good as the results from DAIR. There is a very limited amount of data on the differences between these two approaches. Therefore, this should be one topic to investigate further in future.

6.3.2 Acute hematogenous prosthetic joint infections

Most of the acute hematogenous PJIs among both hip and knee PJIs were managed with DAIR. The failure rates after DAIR were, however, inferior to other strategies. Among acute hip PJIs, for example, almost 50% of DAIR procedures failed during 1-year follow-up, and among acute knee PJIs more than 30% of DAIR procedures failed during 1-year follow-up. Surprisingly, the results after one-stage revision were superior to other strategies, especially among acute knee PJIs, where one-stage revision was the most used strategy after DAIR. Failure rates after two-stage revision for acute infections were also very high when compared to the failure rates after one-stage revision. This finding might, however, have been due to the selection bias caused by initial patient selection because most patients were managed with either

DAIR or one-stage revision, as suggested by international guidelines (Izakovicova et al., 2019; Zimmerli et al., 2004).

Acute hematogenous PJIs have traditionally been managed with DAIR (Izakovicova et al., 2019; Osmon et al., 2013; Zaruta et al., 2018; Zimmerli, 2000). As DAIR is the least invasive procedure, it is considered a valuable first-line treatment for acute hematogenous PJI, because it does not exclude the possibility of later explantation of the prosthesis and, for example, performing one-stage revision.

In studies I–IV, the infections were categorized as chronic PJIs when symptoms lasted for at least 28 days, and acute hematogenous PJIs when symptoms lasted less than 28 days. It might, however, be difficult to define when the initial symptoms began. It is evident that the type of infection is one of the strongest factors when deciding which type of revision procedure to perform. Furthermore, if the beginning of the symptoms is not correctly defined, we might end up performing DAIRs for chronic PJIs with mature biofilms. As the dichotomization of infections into acute and chronic is difficult, this approach should not be used as the only deciding factor in clinical decision-making. Moreover, if the classification of the PJI is difficult, it might be wise to perform a more throughout revision surgery, such as a one-stage revision, instead of DAIR.

6.3.3 Chronic prosthetic joint infections

Chronic PJIs are usually managed with 2-stage revision because chronic infections might cause significant deficits in the bones and surrounding soft tissues, which may, in turn, need longer durations to heal properly (Zimmerli et al., 2004). However, as 2-stage revision significantly increases the comorbidity burden of the patient as well as the economic burden for the health care system, this approach should only be reserved for cases where no other options are available.

In study II, rather low failure rates were achieved with 2-stage revision, as 15.6% of procedures failed during 1-year follow-up. As the number of other approaches was very low, it was not possible to perform a comparison between surgical strategies. At our hospital, two-stage revision is the preferred treatment option for chronic hip PJI, as demonstrated by the results in study I. A previous meta-analysis compared one- and two-stage revisions and reported similar results in the treatment of chronic PJIs of the hip (Lange et al., 2012). However, the results also shared the common limitation within PJI research in that they concluded that evidence on the differences between these two strategies was limited. In our study, the number of

patients treated with one-stage revision was very low, and thus the results from these analyses were imprecise. We cannot, therefore, make conclusions on whether one-stage revision would be effective for the management of chronic infections.

For chronic knee PJIs, the results from one-stage revisions were almost superior to those observed from two-stage revisions. Previously, one-stage revision has been associated with a similar risk for reoperation when compared to two-stage revision (Leta et al., 2019). A previous randomized controlled trial from the United Kingdom demonstrated no superiority for one-stage revision over two-stage revision (Blom et al., 2022). However, as the patient cohort in that RCT included patients with multiple PJI revisions, our results are not comparable. A meta-analysis from Kunutsor et al. also demonstrated similar results after one-stage and two-stage revisions (Kunutsor, Whitehouse, Lenguerrand, et al., 2016). If no superiority of two-stage over one-stage revision has been reported by recent studies, the indications for two-stage revisions should be discussed carefully. Furthermore, when the added costs and the burden for the patient associated with the second operation of two-stage revision are taken into account, one-stage revision seems to be a viable option for the treatment of PJI of the knee (Blom et al., 2022; Okafor et al., 2023a). However, as one-stage revision might not be suitable for everyone, more research on patient selection is warranted.

6.4 Prediction of the failure after PJI revision

In study V, we aimed to validate the KLIC-score within a Northern European cohort and to assess its predictive ability for early PJIs treated via one-stage revision. A well-validated prediction model would be helpful in making treatment decisions in a clinical setting. For instance, in managing PJI cases, such a model could offer insight into the most favorable revision strategy for an individual patient's prognosis. However, our findings revealed that while a higher KLIC-score is linked to an elevated risk for early failure, its ability to differentiate between outcomes is limited. Moreover, employing the model to guide treatment decisions does not yield any additional benefit beyond existing baseline strategies.

The limited predictive performance of the KLIC-score in our study might be attributed to the rarity of comorbidities that contributed to its calculation within our patient cohort. Specifically, conditions such as liver cirrhosis and renal failure were notably infrequent in our cohort, exerting minimal influence on the overall KLIC-score. When certain conditions included in a predictive score are markedly uncommon, it introduces a bias in the observed results, impacting the assessment of

the model's clinical applicability. Notably, the development of the KLIC-score occurred in Southern Europe (Tornero et al., 2015), where the prevalence of comorbidities differs from that seen in Northern Europe. Hence, this discrepancy in comorbidity burden likely influenced the KLIC-score's accuracy within our cohort.

It is worth contemplating the utility of a prediction model if it only identifies patients at extremely high risk. Furthermore, during the development of prediction models, it is crucial to assess whether the score aids clinical decision-making without potentially causing treatment delays. Future investigations should, therefore, prioritize those identifying factors contributing to failure following procedures, such as DAIR or one-stage revision, for early PJI, because it appears that among a Northern European patient cohort the KLIC-score might not effectively differentiate patients at an elevated risk for failure.

6.5 Strengths and limitations

6.5.1 Strengths

All the studies in this dissertation aimed to investigate and answer clinically relevant topics and questions. At present, there is still a lack of data regarding the trends in the treatment of PJI and differences between treatment methods. In all the studies, the research questions were based on real clinical problems, offering an ideal setting for future clinical implications.

The major strength of our study was the single-center setting. As a high-volume referral center focused fully on joint replacement surgery, the environment at our institution is ideal for research. Moreover, the specific details of every treatment period are prospectively collected in our database, providing an excellent basis for retrospective research.

Another major strength associated with the single-center setting is that the effect of possible selection bias was minimized because all patients are managed in a single institution. Within retrospective research, and within PJI research in particular, selection bias is often prevalent because treatment decisions are not standardized, and study cohorts can be very heterogenic. However, as a public hospital, each of our patients is treated similarly. Therefore, the possible effect of selection bias on the observed result was minimized.

The manual gathering of patient data from the EHRs is another strength of our study. As a single-center study, the sample size is not as large as it might be in muti-center or registry studies, but as the data were completely acquired manually, the completeness and accuracy were maximized. For example, it was possible to collect and analyze the surgical techniques used and other details such as duration of the symptoms. Of course, it would be ideal to perform the data gathering prospectively, but as our institution has its own prospectively maintained database, accurate retrospective data collection was possible.

A major strength in studies II, IV, and V was the diverse methodological analyses. Thanks to these prospectively designed analyses, the completeness of the gathered data was optimized, and common methodological mistakes were avoided. As a result, our analyses were able to answer clinically relevant questions.

6.5.2 Limitations

We are aware that each of our studies may have several potential limitations that warrant consideration. Given the infrequent occurrence of PJI, our findings might be susceptible to selection bias. However, when the substantial number of patients and their treatment under consistent conditions in a single institution, rather than across multiple centers, are considered, the possibility of selection bias was minimized. Moreover, by analyzing surgeries among two-year admission groups instead of yearly groups, we aimed to diminish the impact of patient selection on the observed results and temporal trends. Nevertheless, owing to the retrospective nature of the study, a residual risk of selection bias persists.

As our institution is a referral center, not all patients originate from the Tampere area. Many of our patients come from other areas for their initial TJA, and it is possible that if they developed PJI later, the treatment might have been carried out outside our institution. This potential bias could have introduced inaccuracy to the observed results.

A major limitation that should be considered in interpreting our results is that we did not collect or analyze the effect of antimicrobial therapy on treatment outcomes. Consequently, it is possible that the antimicrobial therapy was not optimal for all patients, potentially leading to inferior outcomes. For instance, since the usage of rifampin was not analyzed and the median duration of antimicrobial treatment after DAIR was less than 12 weeks, these factors may have influenced the observed failure rates, particularly after DAIR. However, since the antimicrobial treatments were

designed by infectious disease specialists within the same institution, the possible bias of heterogeneous treatment regimens was minimized.

Another potential limitation of our study is that in some cases microbiological treatment may have been started before the surgery. Therefore, the intraoperative findings might have been negative, and thus may have affected the results. Moreover, as the definition of PJI does not require positive microbiological cultures (Palan et al., 2019; Zmistowski et al., 2014), and all our PJIs were confirmed with validated criteria, we cannot be sure that some of the PJIs were only culture-negative because of previous antimicrobial treatment. In addition to the potential preoperative microbiological treatment, the effect of the exchange of the modular parts to the failure rates was not examined.

Inaccuracies may exist within the databases used, potentially resulting in, for instance, incomplete records of diagnoses, such as diabetes mellitus or rheumatoid arthritis, for certain patients. However, as we conducted a comprehensive screening of EHRs to capture the history of comorbidities, we aimed to minimize the potential bias in our results arising from any missing information regarding these comorbidities.

In addition, our infection classification relied on a combination of the time elapsed since the previous surgery and the duration of symptoms. It is important to note that using diverse classification strategies might yield varied results. However, this limitation is typical in PJI research, given the absence of a standardized protocol for infection classification. Additionally, our inclusion of multiple operated joints without prior infection-related revisions might have had an impact on our findings.

Another limitation in studies II and IV was our restricting of follow-up time to one year, even though it has been claimed that one year would be long enough to examine the outcomes of PJI treatment (Fillingham et al., 2019). In addition, as we did not analyze concomitant revisions, we cannot conclude, what happened after the first failed revision due to PJI. Furthermore, this is a topic that is at least as complex as the first revision due to PJI, and hence should be investigated further in future.

Another limitation in Studies II and IV is that we did not analyze intraoperative complications, such as intraoperative fractures. Since one-stage and two-stage revisions are significantly more aggressive strategies than DAIR, it is possible that the number of intraoperative complications may have been higher.

6.6 Future considerations

Despite the attempts to prevent PJI, the incidence does not seem to be decreasing. Moreover, as the incidence of early PJIs has increased and is predicted to increase further, the total annual number of early PJIs will also increase in future. In addition, the increased number of prosthetic joints means that more people are continually at risk for developing acute hematogenous or chronic PJIs. The increased number of PJIs will present a huge burden for the whole health care system, and hence future scientific efforts should focus on the treatment of PJIs. Future efforts should also focus further on the prevention of PJIs, especially among patients at high risk for PJI.

If we cannot prevent PJI completely, we should treat it as efficiently as possible. Future research should, therefore, focus more on the differences between the different surgical strategies. Currently, there is a lack of high-quality studies, especially randomized controlled trials, comparing different treatment strategies. In future, a well-designed trial would benefit everybody and aid in clinical decision-making.

It might be possible that no conclusive answers will ever be found to the question of the selection of different surgical strategies. Hence, decisions between different revision strategies should be carefully discussed with the patient.

7 SUMMARY AND CONCLUSIONS

The main findings of the studies are summarized as follows:

1) The comorbidity burden among patients with PJI of the hip increased slightly over the last decade at our institution. This might present a formidable treatment challenge, as comorbidities have a negative effect on the outcomes of PJI treatment. Furthermore, the incidence of revisions due to early infections has increased remarkably, perhaps reflecting a change in the distribution of the pathogens that cause PJIs.
2) By using one-stage revision instead of DAIR in early PJIs of the hip, it might be possible to improve the prognosis by decreasing the risk for reoperation without increasing mortality. However, as patient selection is undeniably difficult, more research is warranted.
3) The comorbidity burden among patients with PJI of the knee remained at the same level showing no obvious trends. DAIR was the most used strategy, but the proportion of one-stage revisions has increased to almost the same level. The incidence of PJI varied between the years, being still relatively low at all periods.
4) Among knee PJIs, one-stage revision might offer benefits to individual patients with no increased risk of infection relapse or mortality. Hence, it could be a viable alternative to two-stage revision for selected patients. However, for early knee PJIs, the results of DAIR were superior to other strategies.
5) The KLIC-score is not a reliable predictor of early failure after early PJI in a Northern European cohort. Using the model to guide treatment decisions does not provide any additional clinical utility beyond the baseline strategies. In future, more research on the prediction of PJI treatment outcomes is warranted.

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10 ORIGINAL PUBLICATIONS

PUBLICATION I

Trends in Revision Hip Arthroplasty for Prosthetic Joint Infection: A Single-Center Study of 423 Hips at a High-Volume Center Between 2008 and 2021

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Complications - Infection

Trends in Revision Hip Arthroplasty for Prosthetic Joint Infection: A Single-Center Study of 423 Hips at a High-Volume Center Between 2008 and 2021

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ABSTRACT

Background: Prosthetic joint infection (PJI) is one of the most devastating complications after total hip arthroplasty (THA), and comorbidities increase the risk. We examined whether there was a temporal change in the demographics, especially regarding comorbidities, of patients who have PJIs and were treated over a 13-year study period at a high-volume academic joint arthroplasty center. In addition, the surgical methods used and the microbiology of the PJIs were assessed.

Methods: Revisions (n = 423, 418 patients) due to PJI of the hip performed at our institution between 2008 and September 2021 were identified. All included PJIs fulfilled the 2013 International Consensus Meeting diagnostic criteria. The surgeries were categorized into one of the following categories: debridement, antibiotics, and implant retention, 1-stage revision, and 2-stage revision. Infections were classified as early, acute hematogenous, and chronic infections.

Results: There was no change in the median age of the patients, but the proportion of ASA-class 4 patients increased from 10.5% to 20%. The incidence of early infections increased from 0.11 per 100 primary THAs in 2008 to 1.09 in 2021. The incidence of 1-stage revisions increased the most, rising from 0.10 per 100 primary THAs in 2010 to 0.91 per 100 primary THAs in 2021. Furthermore, the proportion of infections caused by *Staphylococcus aureus* increased from 26.3% in 2008 to 2009 to 40% in 2020 to 2021.

Conclusion: The comorbidity burden of PJI patients increased during the study period. This increase may present a treatment challenge, as comorbidities are known to have a negative effect on PJI treatment outcomes.

Prosthetic joint infection (PJI) is one of the most devastating complications after total hip arthroplasty (THA). Moreover, PJI is not only a tremendous burden for the individual patient, but also for the global health care industry, as it is associated with recurrent surgeries, increased mortality risks, and inferior patient-reported outcomes [1–3].The incidence of PJI after THA has been reported to range between 0.5% and 0.7% at 1-year follow-up. For late infections, the cumulative incidence has been reported to range from 0.04% to 0.06% per prosthesis-year [4–6]. The incidence of PJI has increased during recent decades [6–10]. Over this period, the comorbidity burden of patients undergoing primary THA has also increased and is expected to increase further [11,12]. Indeed, an increased prevalence of diabetes and obesity, both of which are known risk factors for PJI [13,14], may lead to an even greater increase in the incidence of PJI [11].

Traditionally, the surgical treatment of PJI has been based on treatment algorithms, where early infections are preferably treated with debridement, antibiotics, and retention (DAIR), and delayed

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infections in 2-stage revision surgery [15,16]. Early or acute hematogenous PJIs are mainly caused by *Staphylococcus aureus* and delayed infections by coagulase-negative staphylococci (CNS) [17,18]. However, high rates of CNSs have also been observed in early infections [19]. The proportion of culture-negative infections has been reported to be around 5% to 15% [19,20]. Culture-negative PJIs, in particular, might present a challenge for treatment, as microbiological treatment cannot be targeted [21].

To our best knowledge, no previous study has examined how the demographics of patients with PJI, the strategy for surgical treatment, and the distribution of pathogens have changed during the past decade. In the present study, we aimed to assess the following: (1) Has there has been a change in the demographics of PJI patients? (2) Has there been any change in the surgical treatment of PJI?, and (3) Have microbiological findings changed?

Materials and Methods

Our institution is a high-volume academic referral center focused on joint arthroplasty surgery, with an annual volume of more than 2,500 primary and over 300 revision THAs. In this retrospective cohort study, we identified all revision surgeries performed for PJI at our institution between January 1st, 2008, and September 12th, 2021, by searching the ICD-10 (International Classification of Diseases 10th revision) code T84.5 (Infection and inflammatory reaction due to internal joint prosthesis). After excluding superficial wound infections and 2-stage operations, where the information on the first surgery was not available, the PJI diagnosis was confirmed with 2013 International Consensus Meeting diagnostic criteria [22]. If the criteria were not fulfilled, the hip was excluded. Only the first revisions due to PJI were included and those patients who underwent revision due to PJI in both hips were analyzed as 2 separate operations.

The patient data were obtained using our institution's electronic data lake as well as electronic health records (EHR). Our institution's electronic data lake is a prospectively filled database, where specific details of every treatment period (eg, details of surgery, prosthesis, laboratory results, medication, comorbidities) are collected and documented. The EHRs contain information related to patient care, whereas the data base contains more comprehensive information on surgical details. The following patient demographics were collected from the data lake and EHRs: age, sex, body mass index (BMI), American Society of Anesthesiology (ASA) classification, and comorbidities. Charlson comorbidity indexes (CCI) were calculated separately for each patient [23]. In addition, we also recorded the date of the primary surgery, the date of the last non-infectious operation to the ipsilateral joint, and the date from the beginning of the symptoms before revision surgery. Information on the presence of the fistula and intraoperative microbiological findings from tissue specimens were also collected from the EHRs. All the microbiology analyses were performed in the accredited microbiology laboratory of the local university hospital. In accordance with Finnish legislation, no Institutional Review Board hearing was required because of the retrospective register-based study design and because the patients were not contacted.

The surgeries were categorized into one of the following 3 categories based on the intention to treat principle: Debridement, antibiotics, and implant retention (DAIR); 1-stage revision; or 2-stage revision. The DAIR included all surgeries where the joint capsule was opened, acetabular liner and/or femoral head possibly replaced, but the femoral stem or acetabular component were not replaced or removed. In 1-stage revision, all the components were replaced in 1 operation, whereas in 2-stage revision, the components were sequentially removed and replaced in 2 operations with a period of resection arthroplasty or spacer prosthesis in between. To reflect the pathogenesis of the PJI and to produce results that are applicable in the clinical setting, the infections were classified as early (≤90 days from the previous surgery), acute hematogenous (>90 days from the previous surgery AND <28 days of symptoms), and to chronic infections (>90 days from the previous surgery AND ≥28 days of symptoms) [16,18,24].

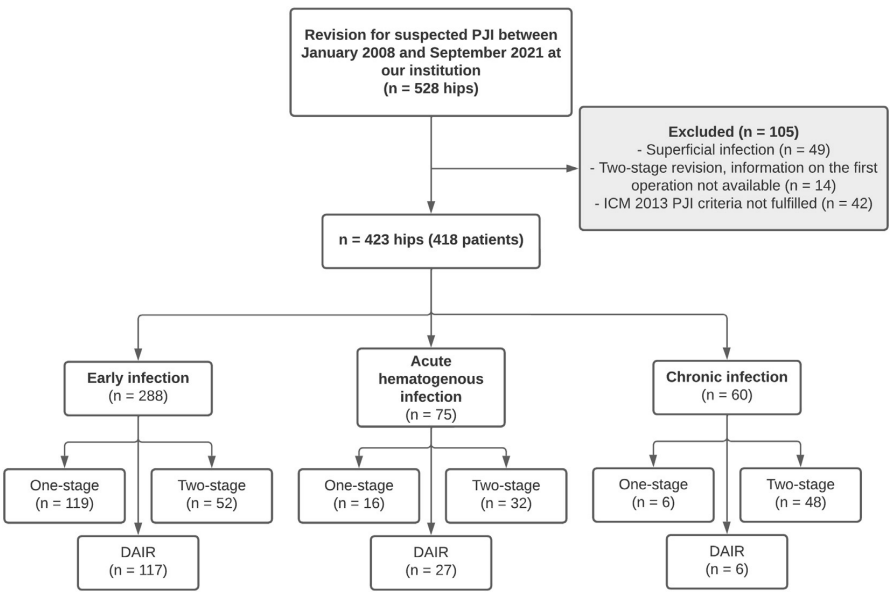

Fig. 1. Infections are classified as early (≤3 months from the previous surgery), acute hematogenous (>3 months from the previous surgery with <28 days of symptoms), and chronic (≥3 months from the previous surgery with ≥28 days of symptoms). PJI, prosthetic joint infection; DAIR, debridement, antibiotics, and implant retention.

Table 1
PJI Patient Characteristics and Preoperative Risk Factors, Stratified by the Type of the Infection.

Variable	Early (n = 288)	Acute Hematogenous (n = 75)	Chronic (n = 60)
Patient characteristics			
Women, n (%)	157/288 (54.5)	38/75 (50.7)	31/60 (51.7)
Age, y, median (IQR)	72 (63-79)	70 (64-78)	75 (63-79)
BMI, mean (sd)	29.3 (6.0)	28.5 (6.5)	26.8 (4.7)
BMI ≥30, n (%)	109/272 (40.1)	23/66 (34.8)	15/54 (27.8)
BMI ≥35, n (%)	49/272 (18)	11/66 (16.7)	3/54 (5.6)
CCI, median (range)	3 (0-7)	3 (0-6)	3 (0-6)
CCI ≥3, n (%)	192/288 (66.7)	43/75 (57.3)	41/60 (68.3)
ASA-class, n (%)			
1	9 (3.1)	2 (2.7)	1 (1.7)
2	68 (23.6)	14 (18.7)	14 (23.3)
3	169 (58.7)	40 (53.3)	34 (56.7)
4	38 (13.2)	19 (25.3)	10 (16.7)
5	2 (0.7)	0	0
NA	2 (0.7)	0	1 (1.7)
Co-morbidities, n (%)			
Diabetes mellitus	59/276 (21.4)	9/65 (13.8)	11/57 (19.3)
Rheumatoid arthritis	23/272 (8.5)	4/65 (6.2)	8/56 (14.3)
Chronic kidney disease	11/275 (4)	0	3/56 (5.4)
Operation type, n (%)			
DAIR	117 (40.6)	27 (36)	6 (10)
One-stage revision	119 (41.3)	16 (21.3)	6 (10)
Two-stage revision	52 (18.1)	32 (42.6)	48 (80)
Spacer usage	12/52 (23.1)	3/32 (9.4)	9/48 (18.8)
Surgical characteristic			
Time since previous operation, median (IQR), d	18 (13-26)	2,163 (891-3,675)	1,133 (392-2441)
Symptom duration, median (IQR), d	14 (7-20)	7 (3-13)	158 (61-369)
Sinus tract, n (%)	208/284 (73.2)	7/74 (9.5)	18/60 (30)

Infections are classified as early (≤3 mo from the previous surgery), acute hematogenous (>3 mo from the previous surgery with <28 d of symptoms), and chronic (>3 mo from the previous surgery with ≥28 d of symptoms).
DAIR, debridement, antibiotics, and implant retention; d, days; y, years; IQR, interquartile range; sd, standard deviation; CCI, charlson comorbidity index; ASA, American Society of Anesthesiology; BMI, body mass index.

Table 2
PJI Patient Characteristics and Preoperative Risk Factors, Stratified by the Operation type.

Variable	DAIR (n = 150)	One-Stage (n = 141)	Two-Stage (n = 132)
Patient characteristics			
Women, n (%)	93/150 (62)	70/141 (49.6)	63/132 (47.7)
Age, median (IQR), y	73 (66-80)	71 (59-79)	72 (64-78)
BMI, mean (sd)	28.9 (6.1)	29.9 (6.6)	27.5 (4.9)
BMI ≥30, n (%)	51/135 (37.8)	59/131 (45)	37/126 (29.4)
BMI ≥35, n (%)	23/135 (17)	27/131 (20.6)	13/126 (10.3)
CCI, median (range)	3 (0-7)	3 (0-7)	3 (0-7)
CCI ≥3, n (%)	105/150 (70)	85/141 (60.3)	86/132 (65.2)
ASA-class, n (%)			
1	4 (2.7)	6 (4.3)	2 (1.5)
2	35 (23.3)	33 (23.4)	28 (21.2)
3	78 (52)	77 (54.6)	88 (66.7)
4	32 (21.3)	23 (16.3)	12 (9.1)
5	1 (0.7)	1 (0.7)	0
NA	0	1 (0.7)	2 (1.5)
Co-morbidities, n (%)			
Diabetes mellitus	27/139 (19.4)	29/133 (21.8)	23/126 (18.3)
Rheumatoid arthritis	14/139 (10.1)	7/129 (5.4)	14/125 (11.2)
Chronic kidney disease	5/140 (3.6)	4/131 (3.1)	5/125 (4)
Infection type, n (%)			
Early	117 (78)	119 (84.4)	52 (39.4)
Acute hematogenous	27 (18)	16 (11.3)	32 (24.2)
Chronic	6 (4)	6 (4.3)	48 (36.4)
Surgical characteristic			
Time since previous operation, median (IQR), d	18 (13-47)	21 (15-37)	248 (34-1733)
Symptom duration, median (IQR), d	12 (6-17)	15 (8-22)	19 (7-80)
Sinus tract, n (%)	92/148 (62.2)	91/138 (65.9)	50/132 (37.9)
Spacer usage, n (%)	-	-	24/132 (18.2)

Infections are classified as early (≤3 mo from the previous surgery), acute hematogenous (>3 mo from the previous surgery with <28 d of symptoms), and chronic (>3 mo from the previous surgery with ≥28 d of symptoms).
DAIR, debridement, antibiotics, and implant retention; d, days; y, years; IQR, interquartile range; sd, standard deviation; CCI, charlson comorbidity index; ASA, American Society of Anesthesiology; BMI, body mass index.

Table 3
Patient Demographics Within Our Study Period, Stratified by the Year of Operation Infections are Classified as Early (≤3 mo From the Previous Surgery), Acute Hematogenous (>3 mo From the Previous Surgery With <28 d of Symptoms), and Chronic (>3 mo From the Previous Surgery With ≥28 d of Symptoms).

Variable	2008-09 (n = 19)	2010-11 (n = 35)	2012-13 (n = 33)	2014-15 (n = 64)	2016-17 (n = 91)	2018-19 (n = 76)	2020-21 (n = 105)
Patient characteristics							
Female, n (%)	10/19 (52.6)	19/35 (54.3)	19/33 (57.6)	33/64 (51.6)	51/91 (56)	39/76 (51.3)	55/105 (53.4)
Age, median (IQR), y	71 (64-79)	69 (62-77)	75 (70-78)	73 (64-80)	73 (66-80)	72 (63-79)	70 (60-78)
BMI, mean (sd)	25.6 (3.6)	28.2 (4.5)	25.9 (3.8)	29.4 (6.4)	28.7 (6.3)	29.6 (6.2)	29.4 (6.3)
BMI ≥30, n (%)	4/18 (22.2)	15/34 (44.1)	3/23 (13)	23/62 (37.1)	33/84 (39.3)	27/73 (37)	42/98 (42.9)
BMI ≥35, n (%)	0	2/34 (5.9)	1/23 (4.3)	13/62 (21)	13/84 (15.5)	13/73 (17.8)	21/98 (21.4)
CCI, median (range)	3 (1-6)	3 (1-6)	3 (1-6)	3 (0-7)	3 (0-7)	3 (0-6)	3 (0-7)
CCI ≥3, n (%)	12/19 (63.2)	19/35 (54.3)	26/33 (78.8)	42/64 (65.6)	64/91 (70.3)	47/76 (61.8)	66/105 (62.9)
ASA-class, n (%)							
1	0	0	1 (3)	2 (3.1)	3 (3.3)	2 (2.6)	4 (3.8)
2	6 (31.6)	10 (28.6)	5 (15.2)	16 (25)	23 (25.3)	14 (18.4)	22 (21)
3	9 (47.4)	24 (68.6)	23 (69.7)	39 (60.9)	45 (49.5)	45 (59.2)	58 (55.2)
4	2 (10.5)	1 (2.9)	4 (12.1)	7 (10.9)	19 (20.9)	13 (17.1)	21 (20)
5	0	0	0	0	1 (1.1)	1 (1.3)	0
NA	2 (10.5)	0	0	0	0	1 (1.3)	0
Comorbidities, n (%)							
Diabetes mellitus	1/17 (5.9)	5/34 (14.7)	11/32 (34.4)	11/61 (18)	17/86 (19.8)	13/67 (19.4)	21/101 (20.8)
Rheumatoid arthritis	2/17 (11.8)	4/34 (11.8)	3/31 (9.7)	6/61 (9.8)	8/86 (9.3)	5/65 (7.7)	7/99 (7.1)
Chronic kidney disease	1/17 (5.9)	2/34 (5.9)	0	3/61 (4.9)	4/86 (4.7)	2/67 (3)	2/100 (2)
Infection type, n (%)							
Early	7 (36.8)	16 (45.7)	16 (48.5)	37 (57.8)	63 (69.2)	62 (81.6)	87 (82.9)
Acute hematogenous	6 (31.6)	5 (14.3)	8 (24.2)	18 (28.1)	18 (19.8)	8 (10.5)	12 (11.4)
Chronic	6 (31.6)	14 (40)	9 (27.3)	9 (14.1)	10 (11)	6 (7.9)	6 (5.7)
Operation type, n (%)							
DAIR	0	8 (22.9)	10 (30.3)	29 (45.3)	41 (45.1)	31 (40.8)	31 (29.5)
One-stage revision	0	5 (14.3)	5 (15.2)	11 (17.2)	29 (31.9)	32 (42.1)	59 (56.2)
Two-stage revision	19 (100)	22 (62.9)	18 (54.5)	24 (37.5)	21 (23.1)	13 (17.1)	15 (14.3)
Spacer usage	3 (15.8)	4 (18.2)	2 (11.1)	10 (41.7)	4 (19)	0	1 (6.7)

DAIR, debridement, antibiotics, and implant retention; d, days; y, years; IQR, interquartile range; sd, standard deviation; CCI, charlson comorbidity index; ASA, American Society of Anesthesiology; BMI, body mass index.

Patient and Surgical Demographics

A total of 423 PJI revisions (418 patients) were performed at our institution between January 1st, 2008 and September 12th, 2021. Of these, 288 (68.1%) were early infections, 75 (17.7%) acute hematogenous infections, and 60 (14.2%) chronic infections (Fig. 1). A total of 150 (35.5%) DAIRs, 141 (33.3%) 1-stage revisions, and 132 (31.2%) 2-stage revisions were performed. Most of the DAIRs (n = 117, 78%) and 1-stage operations (n = 119, 84.4%) were performed for early infections. Most of the 2-stage revisions were performed because of early (n = 52, 39.4%) or chronic infection (n = 48, 36.4%). The median age of the patients was 72 years (range, 34 to 94) and 53.9% (n = 226) were women. Further details on the demographics and surgical treatments are presented in Tables 1 and 2.

Data Analyses

Means with standard deviations (SD) were presented for normally distributed variables and medians with interquartile ranges (IQRs) for variables with non-Gaussian population. Categorical variables were presented as counts and percentages. To examine the changes during our study period, patient demographics and microbiology of the PJIs were compared in a longitudinal setting using descriptive statistics. Moreover, to avoid selection bias, patient demographics and microbiology of the PJIs were compared in 2-year admission groups, rather than in yearly groups.

As our institution is a tertiary referral center, not all revisions were performed on patients whose primary-THA was performed at our institution. Therefore, incidences were calculated based on the number of primary THAs performed at our institution, and the number of PJIs of which the primary arthroplasty was performed at our institution. Referral PJIs, and PJIs that occurred after revision THA, were not included in the incidence calculations. All analyses were performed using R (version 4.1.2; R Foundation for Statistical Computing, Vienna, Austria). The results of this study are reported according to the STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) guidelines [25].

Results

Trends in Demographics and Surgical Treatment

While the median age of the patients did not change during the study period, the comorbidity burden of the patients increased markedly; the proportion of ASA-class 4 patients increased from 10.5% in 2008 to 2009 to over 20% in 2016 to 2017 and remained approximately that level till the end of the study period (Table 3).

Furthermore, the incidence of PJI operations increased over 12-fold: from 0.11 per 100 primary THAs in 2008 to 1.34 per 100 primary THAs in 2021. The largest increase was observed in early infections. In 2008, the incidence of early infection was 0.11 per 100 primary THAs, whereas in 2021 it was 1.09 per 100 primary THAs. During our study period, 1-stage revision became the most common surgical treatment. In the years 2008 to 2009, no 1-stage revisions were performed, but in the years 2020 to 2021, the proportion of 1-stage revisions was 56.2% (n = 59). (Tables 3 and 4, Figs. 2 and 3).

Microbial Findings

Staphylococcus aureus was the most identified pathogen, accounting for 157 (37.1%) infections. A further 107 (25.3%) infections were caused by coagulase-negative staphylococci (CNS), 10 (9.3%) of which were further identified as *Staphylococcus lugdunensis*. There were 75 culture-negative infections (17.7%), which were the most common among acute hematogenous infections, with 19.7%

Table 4
Yearly Incidence of the PJI Revisions at Our Institution Between 2008 and 2021.

Variable	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
Operation type, n														
Primary THA	944	1,033	986	958	928	1,020	1,078	1,188	1,445	1,565	1,892	2,038	2,063	1,646
PJI revision	1	6	7	12	4	2	11	19	16	29	23	16	41	22
Infection type, n														
Early	1	3	4	6	0	1	6	10	12	21	20	14	37	18
Acute hematogenous	0	3	0	2	3	0	5	6	2	5	0	1	2	3
Chronic	0	0	3	4	1	1	0	3	2	3	3	1	2	1
Type of the revision, n														
DAIR	0	0	1	2	1	1	5	10	9	12	11	4	4	6
One-stage revision	0	0	1	3	2	0	2	5	4	11	8	10	31	15
Two-stage revision	1	6	5	7	1	1	4	4	3	6	4	2	6	1
Incidence per 100 primary THAs														
Overall	0.11	0.58	0.71	1.25	0.43	0.20	1.02	1.60	1.11	1.85	1.22	0.79	1.99	1.34
Early infections	0.11	0.29	0.41	0.63	0	0.10	0.56	0.84	0.83	1.34	1.06	0.69	1.79	1.09
Acute hematogenous infections	0	0.29	0	0.21	0.32	0	0.46	0.51	0.14	0.32	0	0.05	0.10	0.18
Chronic infections	0	0	0.30	0.42	0.11	0.10	0	0.25	0.14	0.19	0.16	0.05	0.10	0.06
DAIR	0	0	0.10	0.21	0.11	0.10	0.46	0.84	0.62	0.77	0.58	0.20	0.19	0.36
One-stage revision	0	0	0.10	0.31	0.22	0	0.19	0.42	0.28	0.70	0.42	0.49	1.50	0.91
Two-stage revision	0.11	0.58	0.51	0.73	0.11	0.10	0.37	0.34	0.21	0.38	0.21	0.10	0.29	0.06

The number of PJI revisions are calculated based on the number of PJIs, whose previous operation was primary arthroplasty performed at our institution. Therefore, referral PJIs or PJIs that occurred after revision arthroplasty are not included. infections are classified as early (≤3 mo from the previous surgery), acute hematogenous (>3 mo from the previous surgery with <28 d of symptoms), and chronic (≥3 mo from the previous surgery with ≥28 d of symptoms).
THA, total hip arthroplasty; DAIR, debridement, antibiotics, and implant retention.

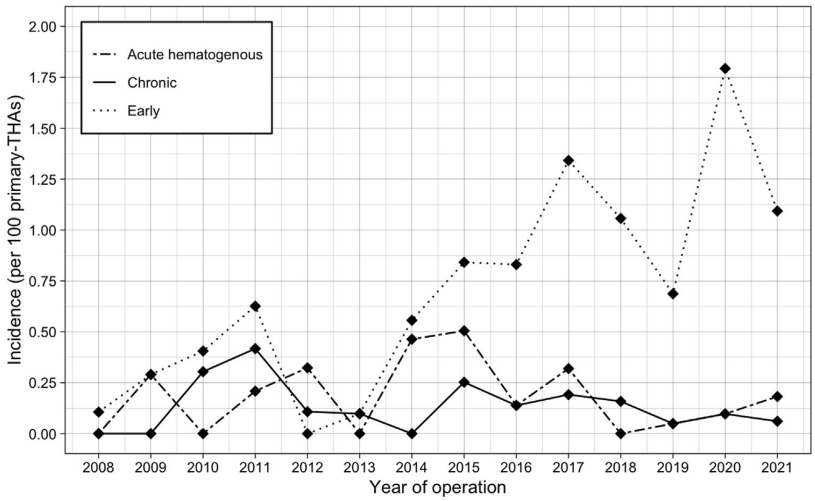

Fig. 2. Infections are classified as early (≤3 months from the previous surgery), acute hematogenous (>3 months from the previous surgery with <28 days of symptoms), and chronic (≥3 months from the previous surgery with ≥28 days of symptoms). Incidences are calculated based on the number of primary THAs at our institution and number of PJI revisions, whose previous operation was primary arthroplasty performed at our institution. Therefore, referral PJIs or PJIs that occurred after revision arthroplasty are not included. THA, total hip arthroplasty.

(n = 15) of them identified as culture negative. In addition, a total of 38 (9%) infections were polymicrobial. (Tables 5 and 6).

During the study period, the proportion of *S. aureus* increased the most. In 2008 to 2009, the proportion of *S. aureus* was 26.3% (n = 5). However, in 2020 to 2021, the proportion had increased to 40% (n = 46). The proportion of negative cultures decreased remarkably in this period. Also, the proportion was 31.6% (n = 6) in 2008 to 2009, but only 16.5% (n = 19) in 2020 to 2021 (Table 7).

Discussion

The results of the present study reveal that there was a notable increase in the comorbidity burden of patients with PJI during the study period. At the beginning of our study period, 2-stage revision was the most performed surgical procedure. However, 1-stage revision became the most performed procedure later. In addition, we also observed a more than 10-fold increase in the incidence of early infections and, perhaps reflecting this increase, the proportion of PJIs caused by *S. aureus* also increased notably.

The median age of the patients did not change during the study period. However, the proportion of ASA-class 4 patients more than doubled from approximately 10 to around 20%. The same trend was observed for patients with ASA-class 3 or greater, as the proportion increased from 57.9% to 75.2%. The same trend of increased comorbidity burden has previously been reported by O'Toole et al. They reported that rates of obesity and diabetes in THA patients has

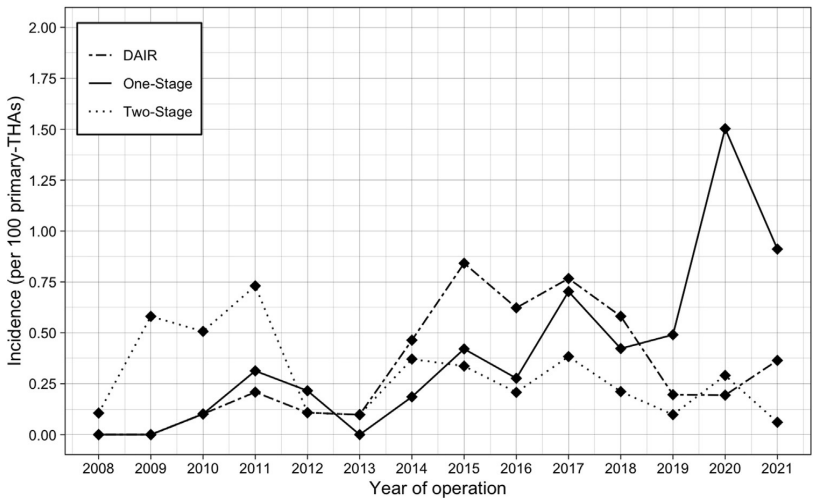

Fig. 3. Incidences are calculated based on the number of primary THAs performed at our institution and number of PJI revisions, whose previous operation was primary arthroplasty performed at our institution.

Table 5
Microbiological Results From Tissue Specimens, Stratified by the Type of the Infection.

Pathogen	All (n = 461)		Early (n = 319)		Acute Hematogenous (n = 76)		Chronic (n = 66)	
	N	%	N	%	N	%	N	%
Staphylococcus aureus	157	*34.1*	116	*36.4*	32	*42.1*	9	*13.6*
CNS	107	*23.2*	80	*25.1*	4	*5.3*	23	*34.8*
Streptococcus beta-hemolyticus	40	*8.7*	28	*8.8*	10	*13.2*	2	*3*
Other streptococcus species	14	*3*	0	*0*	6	*7.9*	8	*12.1*
Gram-negative aerobic	24	*5.2*	15	*4.7*	6	*7.9*	3	*4.5*
Enterococcus species	20	*4.3*	15	*4.7*	0	*0*	5	*7.6*
Anaerobic	13	*2.8*	5	*1.6*	3	*3.9*	5	*7.6*
Other	11	*2.4*	9	*2.8*	0	*0*	2	*3*
Negative culture	75	*16.3*	51	*16*	15	*19.7*	9	*13.6*

Microbiological findings from the polymicrobial infections (n = 38) are included, and therefore the total N is greater than the total N of the surgeries performed (n = 423). *Bacillus cereus* (n = 2), *Candida parapsilosis* (n = 1) and *Corynebacterium species* (n = 8) are included in the other group.
Italics: No statistical testing of significance (eg, T-Test or Mann-Whitney U) were performed, as described in the methods section "microbiology of the PJIs were compared in a longitudinal setting using descriptive statistics".
CNS, Coagulase-Negative Staphylococci.

increased significantly and was projected to increase even more [11]. This increase in the comorbidity burden can be partly explained by the increases in the proportion of patients who had diabetes or BMI over 35. Furthermore, as the increased comorbidity burden is a risk factor for PJI, we might assume that it has had an effect on the observed increase in the incidence of PJIs [6,13,14,26].

In addition to the increase in the incidence of early infection, there was also an over 120% increase in the proportion of early infections over the study period. During the same period, the number of primary THAs in our institution increased from 944 in 2008 to 2,063 in 2020, an increase of 118.5%. Therefore, the observed increase in the proportion of early PJIs is at least partly due to the increased number of primary THAs performed. In addition to that, as our institution is a tertiary referral center, not all revisions were performed on patients, whose primary THA was performed at our institution. This might be the reason why the number of revisions due to early infections performed at our institution increased more than the number of primary THAs.

The increase in the incidence of 1-stage revisions and the subsequent decrease in the incidence of DAIRs might be considered surprising because DAIR is less invasive than 1-stage revision and is considered as a suitable option for the treatment of early or acute hematogenous infections [16,27]. The differences in incidence rates can be explained by the adoption of a more aggressive approach to PJI treatment, as the 1-stage operation is also considered as a suitable treatment for early and acute infections [16,27]. In addition, our institution is a high-volume center, and we currently prefer to perform 1-stage revision to as many patients as possible. Increased comorbidity might also be a reason, why the incidence of 1-stage operations has increased. We might, therefore, end up performing the 1-stage revision rather than DAIR for patients with multiple comorbidities, because the eradication rates of 1-stage operations have been reported to be better [27]. With 2-stage revisions, we observed no trend in the number of operations or in the incidences, as both remained at approximately the same level during the entire study period.

Staphylococcus aureus is reported to cause between 24 and 28% of PJIs, and the most common pathogen among early infections and responsible for causing approximately one-third of them [17–19,28]. Similarly, in our study, *S. aureus* was the most isolated pathogen and the most prevalent among early and acute hematogenous infections. In contrast, chronic PJI was most commonly caused by CNS. The proportion of *S. aureus* had a temporal trend, however, and it became the most common pathogen during our study period. At the same time, the proportion of early infections increased from 36.8 to 82.9%. Furthermore, the proportion of acute hematogenous infections caused by *S. aureus* was also high in our study, which is in line with the findings of Benito et al. (2019) [17].

The proportion of negative cultures also decreased during the study period from 31.6% to 16.5%. This finding might be explained by the more accurate microbiological diagnostic techniques used. Furthermore, an increasing trend in the mean number of

Table 6
Microbiological Results From Polymicrobial Infections (n = 38) Stratified by the Type of the Infection.

Pathogen	All (n = 76)		Early (n = 62)		Acute Hematogenous (n = 2)		Chronic (n = 12)	
	N	%	N	%	N	%	N	%
Staphylococcus aureus	11	*14.5*	10	*16.1*	0	*0*	1	*8.3*
CNS	26	*34.2*	22	*35.5*	0	*0*	4	*33.3*
Streptococcus beta-hemolyticus	8	*10.5*	7	*11.3*	0	*0*	1	*8.3*
Other streptococcus species	3	*3.9*	0	*0*	1	*50*	2	*16.7*
Gram-negative aerobic	10	*13.2*	9	*14.5*	0	*0*	1	*8.3*
Enterococcus species	4	*5.3*	3	*4.8*	0	*0*	1	*8.3*
Anaerobic	5	*6.6*	3	*4.8*	1	*50*	1	*8.3*
Other	9	*11.8*	8	*12.9*	0	*0*	1	*8.3*

Bacillus cereus (n = 1), *Candida parapsilosis* (n = 1) and *Corynebacterium species* (n = 7) are included in the other group.
Italics: No statistical testing of significance (eg, T-Test or Mann-Whitney U) were performed, as described in the methods section "microbiology of the PJIs were compared in a longitudinal setting using descriptive statistics".
CNS, Coagulase-Negative Staphylococci.

Table 7
Microbiological Results From Tissue Specimens During Our Study Period.

Pathogen	2008-09 (n = 19)		2010-11 (n = 36)		2012-13 (n = 35)		2014-15 (n = 67)		2016-17 (n = 101)		2018-19 (n = 88)		2020-21 (n = 115)	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Staphylococcus aureus	5	*26.3*	8	*22.2*	13	*37.1*	19	*28.4*	32	*31.7*	34	*38.6*	46	*40*
CNS	6	*31.6*	10	*27.8*	6	*17.1*	17	*25.4*	23	*22.8*	18	*20.5*	27	*23.5*
Streptococcus beta-hemolyticus	0	*0*	4	*11.1*	3	*8.6*	5	*7.5*	11	*10.9*	8	*9.1*	9	*7.8*
Other streptococcus species	1	*5.3*	2	*5.6*	0	*0*	4	*6*	3	*3*	2	*2.3*	2	*1.7*
Gram-negative aerobic	1	*5.3*	1	*2.8*	1	*2.9*	3	*4.5*	7	*6.9*	6	*6.8*	5	*4.3*
Enterococcus species	0	*0*	1	*2.8*	3	*8.6*	5	*7.5*	6	*5.9*	4	*4.5*	1	*0.9*
Anaerobic	0	*0*	2	*5.6*	1	*2.9*	2	*3*	3	*3*	2	*2.3*	3	*2.6*
Other	0	*0*	0	*0*	0	*0*	1	*1.5*	2	*2*	5	*5.7*	3	*2.6*
Negative culture	6	*31.6*	8	*22.2*	8	*22.9*	11	*16.4*	14	*13.9*	9	*10.2*	19	*16.5*

Microbiological findings from the polymicrobial infections (n = 38) are included, and therefore the total N is greater than the total N of surgeries performed (n = 423).
Italics: No statistical testing of significance (eg, T-Test or Mann-Whitney U) were performed, as described in the methods section "microbiology of the PJIs were compared in a longitudinal setting using descriptive statistics".
DAIR, debridement, antibiotics, and implant retention; CNS, Coagulase-Negative Staphylococcus.

intraoperative tissue specimens per patient was observed. In the years 2008 to 2009, the mean number was 5.26, but the corresponding number had increased to 5.90 in 2020 to 2021. This arguably decreases the risk of "false-negative" diagnosis. The decreased proportion of acute hematogenous infections may also be the reason, as the largest proportion of culture-negative infections was among those. Sepsis is often presented within patients with acute infection, and therefore the antimicrobial treatment may have been started before the revision surgery, thus causing the intraoperative tissue cultures being negative.

Our study has several potential limitations that should be considered. Due to the rare nature of PJI, our findings might be prone to selection bias. However, as the total number of patients was over 400 and each patient was treated in the same institution by the same surgeons, rather than in a multicenter setting, we believe that the potential risk for selection bias was minimized. Furthermore, as we analyzed the surgeries in 2-year admission groups, rather than in yearly groups, we managed to minimize the effect of patient selection on the observed results and temporal trends. Another potential limitation of our study is that in some cases microbiological treatment may have started before the surgery. Therefore, the intraoperative findings might have been negative, and thus may have affected the results. Moreover, as the definition of PJI does not require positive microbiological cultures [20,22], and all our PJIs were confirmed with validated criteria, we cannot be sure whether some of the PJIs were culture-negative only because of previous antimicrobial treatment. In addition, there might be inaccuracy in the used databases, and therefore for example, the diagnosis of diabetes mellitus or rheumatoid arthritis might have been missing in some patients. However, as the EHRs were screened thorough for the history of comorbidities, we believe, that this possible bias that missing information regarding the comorbidities might have to our results, was minimized. Furthermore, the classification of the infection was based on the combination of time from the previous surgery and duration of symptoms, and it is evident, that different classification strategies might have produced different results. However, this limitation is common in PJI research, as there is no standardized protocol for the infection classification. In addition, we also included multiply operated hips, if no infection-related revisions were performed previously, and this might also have effected to our results. The strengths of our study are the large number of patients combined with accurate records from our high-quality prospectively maintained datalake. In addition, the length of the study period made it possible to examine temporal trends in a single-center setting.

In conclusion, the comorbidity burden among PJI patients increased markedly over the last decade at our institution. This clearly presents a formidable treatment challenge, as comorbidities have a negative effect on PJI treatment outcomes. Furthermore, the incidence of revisions due to early infections has increased remarkably, perhaps reflecting the change in the distribution of the pathogens that cause PJIs.

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PUBLICATION II

Clinical Outcomes After Revision Hip Arthroplasty due to Prosthetic Joint Infection - A Single-Center Study of 369 Hips at a High-Volume Center with a Minimum of One Year Follow-Up

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Complications - Infection

Clinical Outcomes After Revision Hip Arthroplasty due to Prosthetic Joint Infection—A Single-Center Study of 369 Hips at a High-Volume Center With a Minimum of One Year Follow-Up

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ABSTRACT

Background: Prosthetic joint infection (PJI) treatment decisions are traditionally based on treatment algorithms. There is, however, a lack of evidence to support the choice of these treatment algorithms. Therefore, we aimed to assess the one-year survival after PJI revision and compared different surgical strategies in a single-center setting.

Methods: Revisions of the hip due to PJI performed at our institution between January 2008 and September 2021 with at least one-year of follow-up were identified. In total, 134 debridement, antibiotics, and implant retentions (DAIRs), 114 one-stage revisions, and 121 two-stage revisions were performed. Infections were classified as early, acute hematogenous, and chronic. Survival was calculated using the Kaplan-Meier method and cumulative incidence function. Predictors of outcomes were examined with Fine-Gray regressions and Cox proportional hazards regressions. Subdistribution hazard ratios and hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated.

Results: At one-year follow-up, 26.6% (CI 22.2 to 31.2%) of the patients had undergone reoperation and 7.9% (CI 5.4 to 10.9%) had died. The risk for reoperation was highest after DAIR (36.6%, CI 28.5 to 44.7%) and lowest after one-stage revision (20.2%, CI 13.4 to 28%). Within the early infections, the one-stage revision almost halved the risk of reoperation (HR 0.51, CI 0.31 to 0.84) with no added mortality risk (HR 1.05, CI 0.5 to 2.2), when compared to DAIR.

Conclusion: By utilizing 1-stage revision over DAIR in early infections, it might be possible to improve the prognosis by decreasing the risk of reoperation without increasing mortality. However, as the patient selection is undeniably difficult, more research is warranted.

Prosthetic joint infection (PJI) is one of the most devastating complications after total hip arthroplasty (THA). The key to successful treatment of PJI is a thorough debridement with the removal of all infected material and the eradication of any possible biofilm [1]. Prosthetic joint infection can also be treated surgically with debridement, antibiotics, and implant retention (DAIR), where the implant is retained in the joint, but the acetabular liner and femoral head are replaced [1,2]. If DAIR is not considered appropriate, the components can be removed and replaced either in a one-stage operation or in 2 separate operations [1,2].

The decision on which type of operation to perform has traditionally been based on treatment algorithms [1–3]. However, there is a lack of clear scientific evidence to support the choice of the treatment algorithm, and no universal consensus on the optimal

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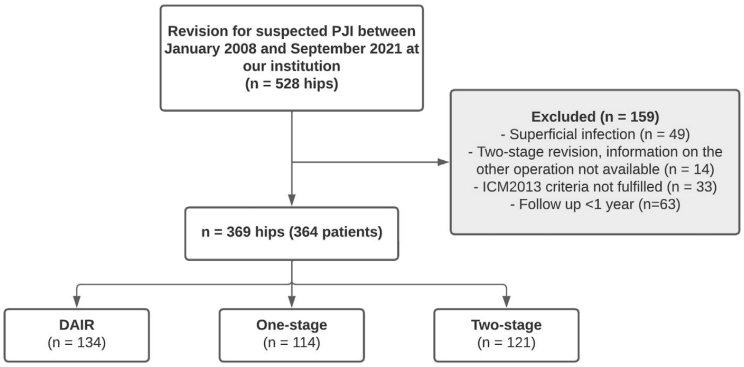

Fig. 1. Flowchart of the patients at our institution between January 2008 and September 2021. PJI, prosthetic joint infection, DAIR, debridement, antibiotics, and implant retention.

method exists [3–5]. Previous clinical studies have been based on case series of small heterogenous cohorts where patients have either been treated in a multi-center setting or no comparison between surgical strategies has been performed [6–14]. Furthermore, the outcomes of PJI revisions have not improved over time and a definitive consensus for treatment selection has not been achieved [4,15].

To be able to plan future treatment strategies, more evidence on the differences between surgical strategies is needed. In the present study, we assessed: (1) What is the short-term survival after PJI revision? and (2) How do the outcomes of the surgical strategies differ?

Materials and Methods

In this retrospective study, we identified all revision surgeries performed for PJI of the hip at our institution between January 1, 2008, and September 12, 2021, by searching the ICD-10 (International Classification of Diseases 10th revision) code T84.5 (Infection and inflammatory reaction due to internal joint prosthesis). Superficial wound infections and two-stage operations, where information on the first operation was not available, were excluded. Only the first revisions due to PJI were included, and those patients who underwent revision due to PJI in both hips were analyzed as having undergone 2 separate operations. The 2013 International Consensus Diagnostic Criteria [16] were used to confirm the PJI diagnosis. In addition, all patients with less than one year of follow-up were excluded (Figure 1).

Our institution's electronic data lake and electronic health records (EHRs) were used to obtain the patient data. The EHRs contain information related to patient care, whereas the data lake contains more comprehensive information on surgical details (eg, details of the surgery and prosthesis). The following patient demographics were collected: age, sex, body mass index, American Society of Anesthesiology (ASA) classification, and comorbidities. In addition, the date of the last noninfectious operation to the ipsilateral joint, and the date the symptoms started before the revision surgery were recorded. Detailed information on the presence of a fistula and intraoperative microbiological findings acquired from tissue specimens were also collected from the EHRs. All the microbiology analyses were performed in the accredited laboratory of the local university hospital. In accordance with Finnish legislation, no institutional review board hearing was required because of the retrospective register-based study design and because the patients were not contacted.

The surgeries were categorized into one of the following 3 categories: DAIR, one-stage revision, or two-stage revision. The infections were classified as early ($\leq$90 days from the previous surgery), acute hematogenous (>90 days from the previous surgery AND <28 days of symptoms), and chronic infections (>90 days from the previous surgery AND $\geq$28 days of symptoms) [2,17,18].

The treatment decisions were based on international consensuses, where the early and hematogenous infections are preferably treated with either DAIR or one-stage revision [1,2,19]. Within those, the one-stage revision was the preferred method if the hip was uncemented or if the time from the previous operation was on the edge of the optimal timeframe (within the first 3 to 4 postoperative weeks from the index procedure) for DAIR. For chronic infections, the two-stage revision was the preferred treatment method. If the two-stage revision was contraindicated, then the one-stage ($n = 5$) or even DAIR ($n = 6$) was utilized. In addition, each of the hips were evaluated individually and treated according to the up-to-date consensuses.

According to the microbiological results from the preoperative and intraoperative tissue specimens, postoperative antimicrobial treatments were designed by infectious-disease specialists. Since 2014, the usual practice has been to administer postoperative antibiotic therapy intravenously for 2 weeks followed by 4 weeks of oral therapy regardless of the surgical modality. From 2008 to 2014, total duration of treatment may have been longer; up to 3 months. However, parenteral treatment very rarely exceeded 4 weeks if highly bioavailable oral treatment could be used. The antibiotic-free interval before the 2nd stage operation has been variable, but most often not less than 2 weeks. Also, antibiotics have been discontinued after the 2nd stage operation with negative intraoperative cultures and no patient-specific indication for prolonged suppressive antibiotic treatment. In staphylococcal infections, a rifampin-based combination was used when not contraindicated (drug interactions or high risk of adverse reactions) except in two-stage revisions without any foreign material left *in situ*.

Primary and Secondary Outcomes

Follow-up started from the day of the revision surgery due to PJI and ended when the patient was lost to our institution's regular follow-up program (eg, death or patient moved to another area) or on the date of data collection, whichever came first. Reoperation was defined as a new surgical procedure on the previously operated joint. Furthermore, the outcomes of the revision surgeries were categorized according to the Musculoskeletal Infection Society

(MSIS) categorization scheme [20]. In the case of two-stage revision, the first operation was the starting point for the follow-up period, as recommended by the MSIS [20]. In survival analyses, our primary outcome was reoperation due to any reason (MSIS tiers 3A to 3E). It has been suggested that aseptic revision performed within one year from the initial surgery for the treatment for PJI represents a failure secondary due to PJI. Therefore, these revisions were also included [20]. Death from any cause (MSIS tiers 4A and 4B) was considered as a competing risk, as we did not have access to the causes of death, and it was not possible to classify whether the death was PJI-related or not [21,22].

Data Analyses

Means with standard deviations were presented for normally distributed variables and medians with ranges or interquartile ranges for variables with non-Gaussian populations. Cumulative incidences of reoperations and deaths were calculated as described by Scrucca et al. [23]. The risk of any-cause failure was calculated using the Kaplan-Meier estimator. Results are presented with 95% confidence intervals (CIs).

A Fine-Gray regression model was used to identify potential predictors for reoperation or death, as the model has been reported to be more accurate than cause-specific Cox regression when estimating a single patient's clinical prognosis [24]. However, the cause-specific Cox models for both reoperation and death were calculated and the results from those analyses are also presented [25]. In the Cox models, the proportional hazards assumptions were tested using Schoenfeld's residuals, and the assumptions were not violated in any tested model.

To assess the effect of confounding factors and to predict the outcomes more accurately, multivariable analyses were performed. Due to the many possible predictors of outcome, variable selection processes were performed (Appendix 1). First, global models were formed based on known risk factors and clinically relevant factors (Appendix 2). The variables included in these global models were selected for the final Fine-Gray regression models using backward elimination with a significance level of 0.157 (Akaike Information Criteria selection). For the cause-specific Cox regression models, the variables were selected based on the combination of backward elimination with $P < .10$ as a level of significance. Thereafter, model stabilities were assessed by bootstrap stability investigation with 200 repetitions. Based on these 2 investigations, the final variables for the regression analyses were selected. Results from multivariable analyses were presented with either adjusted subdistributed hazard ratios (sdHRs) or adjusted hazard ratios (aHRs). All analyses were performed using R (version 4.1.2; R Foundation for Statistical Computing, Vienna, Austria).

Patient Demographics

A total of 369 revisions (364 patients) with at least one year of follow-up were identified. Of these, 134 (36.3%) were DAIRs, 114 (30.9%) were one-stage revisions, and 121 (32.8%) were two-stage revisions (Figure 1). Most of the PJIs were early infections (245 of 369, 66.4%). A total of 103 (42%) DAIRs and 94 (38.4%) one-stage revisions were performed for early infections. *S. aureus* was the most frequently identified pathogen, causing 134 infections (36.3%). The median age of the patients was 72 years (range, 34 to 94) and 53.4% (n = 197) were women. Further details on patient demographics are presented in Table 1.

Results

Outcomes after PJI Revision

At one-year follow-up, 26.6% (CI 22.2 to 31.2%) of the patients had undergone a reoperation and 7.9% (CI 5.2 to 10.9%) had died. The risk for reoperation and death was highest after DAIR (reoperation 36.6%, CI 28.5 to 44.7%; death 10.4%, CI 6 to 16.3%). However, the risk for death between one-stage (7%, CI 3.3 to 12.7%) and two-stage (5.8%, CI 2.5 to 11%) revisions was nearly the same. Compared to the other strategies, time to failure was the shortest when DAIR was performed (Figure 2). When the MSIS criteria were applied, the highest rate of optimal outcome was after one-stage revision (53.5%), and the lowest after DAIR (34.3%) (Table 2, Appendix 3, and Figure 2).

Type of PJI and Risk for Failure

The risk for failure within one year after PJI was highest after early infection (37.1%, CI 30.8 to 42.9%) and lowest after chronic infection (26.8%, CI 14.2 to 37.5%). The risk for failure was highest when DAIR was performed, both after early (45.6%, CI 35.1 to 54.4%) and acute hematogenous infections (48%, CI 24.2 to 64.3%). The risks for failure after one-stage or two-stage revision due to early infections were comparable within the first 30 postoperative days. However, after one year of follow-up, the one-stage revision was superior to the other strategies. Further details of the failure risks are presented in Table 3.

Risk Factors for Failure

Compared to DAIR, one-stage revision more than halved the risk for reoperation (adjusted subdistribution hazard ratios [sdHRs] 0.44, CI 0.26 to 0.75; aHR 0.48, CI 0.29 to 0.79). For early infections, the one-stage revision almost halved the risk of reoperation (HR 0.51, CI 0.31 to 0.84) with no added mortality risk (HR 1.05, CI 0.5 to 2.2) (Appendix 4). The effect of two-stage revision on the risk for reoperation compared with DAIR was similar (adjusted sdHR 0.72, CI 0.43 to 1.19; aHR 0.55, CI 0.34 to 0.89), but the results were imprecise and CIs included the zero change.

Higher ASA scores increased both the risk for reoperation (adjusted sdHR 1.55, CI 1.16 to 2.05; aHR 1.63, CI 1.19 to 2.24 per one-unit increase) and the risk for death (adjusted sdHR 2.98, CI 1.86 to 4.77; aHR 4.54, CI 2.66 to 7.77) (Table 4, and Appendices 5 and 6.

Discussion

The results of the present study revealed that treatment of PJIs is associated with a high risk for reoperation and death. The risk for reoperation was associated with the type of operation, being lowest after one-stage revision and highest after DAIR.

A previous meta-analysis reported that mortality after PJI revision is approximately 4.2% at one-year follow-up [26]. However, only two-stage revisions were included in that analysis. In the present study, one-year mortality differed according to the type of surgery. For example, after a two-stage revision, one-year mortality was 5.8%, whereas after a one-stage revision, it was 7% and, interestingly, after DAIR it was the highest at 10.4%. In multivariable analyses, the type of operation was not related to the risk for death, so the differences between the mortality rates are mostly due to the patient-related factors that contributed to the choice of treatment modality. In addition, as the higher ASA-class was associated to the increased mortality, with the groups not similar regarding the distribution of ASA-classes, this might partly explain this difference between the

Table 1
PJI Patient Characteristics and Preoperative Risk Factors Stratified by the Surgical Technique.

Variable	DAIR n = 134, (%)	One-Stage n = 114, (%)	Two-Stage n = 121, (%)
Patient characteristics			
Women, n	83/134 (61.9)	54/114 (47.4)	60/121 (49.6)
Age, median (range), y	73 (36 to 94)	70 (37 to 93)	72 (34 to 88)
BMI, mean (range)	29.1 (18 to 46)	30.0 (15 to 50)	27.5 (18 to 41)
CCI, median (range)	3 (0 to 7)	3 (0 to 7)	3 (0 to 7)
ASA-class, n			
1	4 (3)	6 (5.3)	2 (1.7)
2	35 (26.1)	29 (35.4)	27 (22.3)
3	67 (50)	63 (55.3)	78 (64.5)
4	27 (20.1)	14 (12.3)	12 (9.9)
5	1 (0.7)	1 (0.9)	0
NA	0	1 (0.9)	2 (1.7)
Comorbidities, n			
Diabetes mellitus	25/124 (20.2)	22/106 (20.8)	22/115 (19.1)
Rheumatoid arthritis	13/125 (10.4)	5/104 (4.8)	12/104 (11.5)
Chronic kidney disease	4/125 (3.2)	3/105 (2.9)	5/114 (4.4)
Infection type, n			
Early	103 (76.9)	94 (82.5)	48 (39.7)
Acute hematogenous	25 (18.7)	15 (13.2)	28 (23.1)
Chronic	6 (4.5)	5 (4.4)	45 (37.2)
Surgical characteristic			
Time since previous operation, median (IQR), d	18 (12 to 50)	21 (15 to 37)	230 (34 to 1,620)
Symptom duration, median (IQR), d	11 (6 to 16)	15 (8 to 22)	20 (7 to 77)
Sinus tract, n	83 (61.9)	72 (63.2)	45 (37.1)
Spacer usage, n	-	-	24 (19.8)
Duration of the antibiotic treatment, mean (SD), wk	7.8 (3.7)	8.0 (5.2)	8.1 (3.2)
Rifampin usage, n	55/130 (42.3)	60/111 (54.1)	41/119 (34.5)
Previous indication, n			
Osteoarthritis	60 (44.8)	85 (74.5)	76 (62.8)
Aseptic revision	41 (30.6)	12 (10.5)	27 (22.3)
Fracture	30 (22.4)	16 (14)	14 (11.6)
Other	3 (2.2)	1 (0.9)	4 (3.3)
Cemented prosthesis	91 (67.9)	60 (52.6)	55 (45.4)
Unstable prosthesis	0	17 (12.3)	20 (16.5)
Microbial findings, n (%)[a]			
Staphylococcus aureus	41 (26.6)	50 (40.3)	43 (33.9)
CNS	37 (24)	26 (21)	33 (26)
Streptococcus beta-hemolyticus	15 (9.7)	14 (11.3)	8 (6.3)
Other streptococcus species	3 (1.9)	3 (2.4)	7 (5.5)
Gram-negative aerobic	11 (7.1)	7 (5.6)	4 (3.1)
Enterococcus species	6 (3.9)	8 (6.5)	6 (4.7)
Anaerobic	6 (3.9)	2 (1.6)	4 (3.1)
Other	6 (3.9)	0	2 (1.6)
Negative culture	29 (18.8)	14 (11.3)	20 (15.7)
Polymicrobial	20 (14.9)	10 (8.8)	6 (5)

Infections were classified as early (≤90 d from the previous surgery), acute hematogenous (>90 d from the previous surgery AND <28 d of symptoms), and chronic infections (>90 d from the previous surgery AND ≥28 d of symptoms).
ASA, American Society of Anesthesiology; BMI, body mass index; CCI, Charlson comorbidity index; d, days; DAIR, debridement, antibiotics, and implant retention; IQR, interquartile range; SD, standard deviation; wk, weeks; y, years.
[a] Microbiological findings from the polymicrobial infections (n = 36) are included; therefore, the total N is greater than the total N of surgeries performed (n = 369).

observed mortalities. There is a scarcity of previously published data on the differences between mortality rates after different PJI revision strategies. Tirumala et al. reported that 90-day mortality rates do not differ between one-stage and two-stage revisions [10]. Our results were similar, but we had a larger sample size.

A two-stage revision has been advocated to be the most successful method for the treatment of PJI [1,3]. However, there is a lack of data in the literature for a comparison between the one-stage and two-stage approaches [27]. In our study, one-stage revision had as high a risk for reoperation and death as two-stage revision. The risk for any-cause failure after chronic infection was the lowest after two-stage revision. However, as the findings from the one-stage revisions were imprecise due to the small number of patients, we cannot make definitive conclusions on whether the one-stage revision is effective for chronic infection.

After early infection, the risk for failure at one-year follow-up was lowest after one-stage revision and highest after DAIR. There is still a scarcity of data available on the differences between DAIR and one-stage revisions [28–30]. In a recent study, Riemer et al. reported excellent results after one-stage revision for early PJI, suggesting that one-stage revision might be at least comparable with DAIR in the treatment of early infections [28]. However, their study had a small sample size and no direct comparison between treatment strategies was performed. In addition to the high risk for failure after DAIR, the mean time to failure was remarkably short when DAIR was performed since most of the failures occurred within the first 40 days. Some studies have reported that 6 to 8 weeks of antimicrobial treatment is noninferior to twelve weeks of antimicrobial treatment [31–33]. This finding is in accordance with our results, as most of the failures occurred within the first weeks.

Table 2
Risk for Failure After PJI Revision Surgery Stratified by the Surgical Technique.

Revision Type	30 d Survival (CI)	1 y Survival (CI)
Any-cause failure		
All revisions (n = 369)	21.1% (16.9 to 25.2%)	34.4% (29.4 to 39.1%)
DAIR (n = 134)	33.6% (25.1 to 41.1%)	47% (37.9 to 54.8%)
One-stage (n = 114)	15.8% (8.8 to 22.2%)	27.2% (18.5 to 34.9%)
Two-stage (n = 121)	12.4% (6.3 to 18.1%)	27.3% (18.9 to 34.8%)
Reoperation		
All revisions (n = 369)	19.5% (15.6 to 23.7%)	26.6% (22.2 to 31.2%)
DAIR (n = 134)	32.1% (24.3 to 40.1%)	36.6% (28.5 to 44.7%)
One-stage (n = 114)	14% (8.4 to 21.1%)	20.2% (13.4 to 28%)
Two-stage (n = 121)	10.7% (6 to 17%)	21.5% (14.6 to 29.2%)
Death		
All revisions (n = 369)	1.6% (0.7 to 3.4%)	7.9% (5.4 to 10.9%)
DAIR (n = 134)	1.5% (0.3 to 4.8%)	10.4% (6 to 16.3%)
One-stage (n = 114)	1.8% (0.3 to 5.6%)	7% (3.3 to 12.7%)
Two-stage (n = 121)	1.7% (0.3 to 5.3%)	5.8% (2.5 to 11%)

Any-cause failure rates were calculated with the Kaplan-Meier estimator, and cause-specific failure rates using cumulative incidences. Results are presented with 95% confidence intervals.
DAIR, debridement, antibiotics, and implant retention.

Thus, prolonging the duration of the antimicrobial treatment would not have affected the outcome.

We observed a high risk for reoperation and death after DAIR. To our best knowledge, no previous study has compared outcomes between DAIR and one-stage revision [3]. The one-stage strategy is not suitable for everyone. Indeed, when the femoral stem is well-cemented and the overall situation is suitable for DAIR, it might not be worth risking intraoperative complications. Furthermore, as one-stage revision did not increase the risk for death compared to DAIR, further research on patient selection between these 2 strategies is warranted, preferably in a randomized controlled trial setting. In addition, in the future it would be necessary to evaluate how the results from the nontraditional revision strategies, such as cement-in-cement revisions, compared to the traditional strategies, as the results from those have been reported to be rather good [34].

We are aware that our study has several potential limitations that are mainly due to the retrospective setting of the study. It should be noted about the rare and diverse nature of PJI and that the patient selection process between the different treatment strategies is not completely definitive, possibly resulting in selection bias. However, this is a common limitation in the field of PJI research, and it can only be addressed in a prospective setting. In addition, the patient profile might have changed during our long study period, hence affecting the selection processes and distribution of used techniques [35]. Furthermore, all patients were managed by the same surgeons in a single-center setting, and we believe that the potential selection bias was as low as possible. Another limitation is that we did not examine the effect of antimicrobial therapy on the outcomes because some of the PJIs were referrals and information on treatments was not accurate in all cases. In contrast, a clear advantage of the present

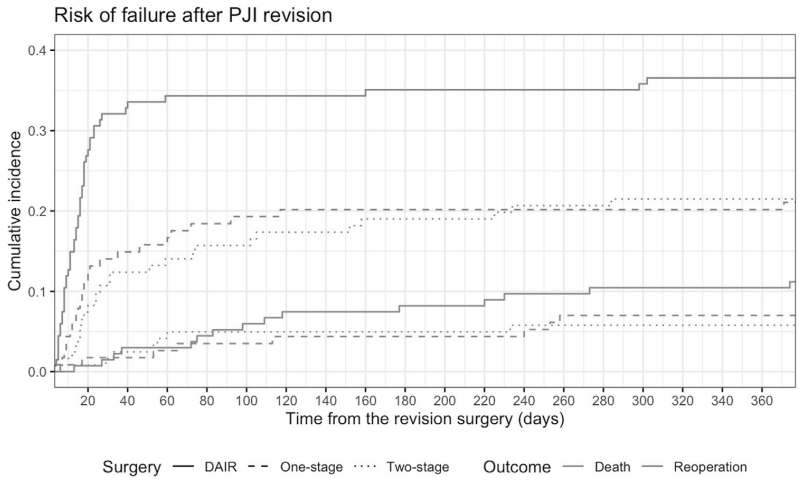

Fig. 2. The surgical technique stratified cumulative incidences of different failure types after prosthetic joint infection revision surgery. DAIR, debridement, antibiotics, and implant retention.

Table 3
Risk for Any-Cause Failure After PJI Revision Surgery Stratified by the Surgical Technique and Infection Type.

Revision Type	30 d Survival (CI)	1 y Survival (CI)
Early infection		
All revisions (n = 245)	24.9% (19.3 to 30.1%)	37.1% (30.8 to 42.9%)
DAIR (n = 103)	35% (25.1 to 43.5%)	45.6% (35.1 to 54.4%)
One-stage (n = 94)	18.1% (9.9 to 25.5%)	26.6% (17.1 to 35%)
Two-stage (n = 48)	16.7% (5.4 to 26.6%)	39.6% (24 to 51.9%)
Acute hematogenous infection		
All revisions (n = 68)	23.5% (12.8 to 33%)	30.9% (19 to 31%)
DAIR (n = 25)	36% (14.1 to 52.3%)	48% (24.2 to 64.3%)
One-stage (n = 15)	6.7% (0 to 18.5%)	13.3% (0 to 28.9%)
Two-stage (n = 28)	21.4% (4.7 to 35.2%)	25% (7.1 to 39.4%)
Chronic infection		
All revisions (n = 56)	1.8% (0 to 5.2%)	26.8% (14.2 to 37.5%)
DAIR (n = 6)	0%	76.7% (0 to 89.2%)
One-stage (n = 5)	0%	80% (0 to 96.5%)
Two-stage (n = 45)	2.2% (0 to 6.4%)	15.6% (4.3 to 25.5%)

Failure is determined as a reoperation or death. Failure rates were calculated with the Kaplan-Meier estimator. Results are presented with 95% confidence intervals.
DAIR, debridement, antibiotics, and implant retention.

study was the large study sample. Previous PJI studies have been mainly based on small case series or heterogenous multicenter cohorts. Although the sample size might be larger in a multicenter setting, if the treatment decisions are not made by the same surgeons, the risk for selection bias will be higher than in a single-center setting. Moreover, because our study had a large sample size, we were also able to perform diverse methodological analyses to compare different treatment strategies and to further examine patient-specific factors that can be used in future decision-making.

In conclusion, revision arthroplasty for PJI of a primary total hip arthroplasty is a complex operation with a high risk of reoperation and mortality. However, by preferring 1-stage revision over DAIR in early infections, it might be possible to improve the prognosis by decreasing the risk of reoperation without increasing mortality. However, as the patient selection is undeniably difficult, more research is warranted.

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Table 4
Cox Proportional Hazard Regression Hazard Ratios for Failure With 95% Confidence Intervals.

Cox Cause-specific Regression (n = 295)	
	Adjusted HR (95% CI)
Hazard ratios for reoperation	
Age	0.98 *(0.96 to 0.99)*
ASA-score	1.63 *(1.19 to 2.24)*
One-stage revision[a]	0.48 *(0.29 to 0.79)*
Two-stage revision[a]	0.55 *(0.34 to 0.89)*
Hazard ratios for death	
Age	1.02 *(0.98 to 1.06)*
ASA-score	4.54 *(2.66 to 7.77)*
Diabetes mellitus	1.77 *(0.94 to 3.34)*
BMI	0.91 *(0.85 to 0.97)*

Italics values indicate, if the confidence intervals exclude the 1.0 value, the result is statistically significant.
ASA, American Society of Anesthesiologists; BMI, body mass index; CI, confidence interval; DAIR, debridement, antibiotics, and implant retention; HR, hazard ratio.
[a] DAIR was used as the reference.

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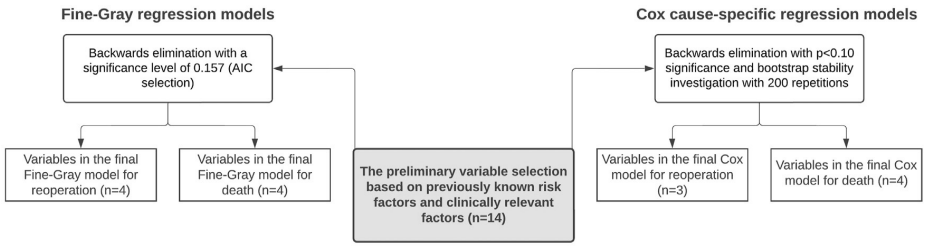
Appendix

Appendix 1



Supplementary Fig. 1. The flow chart summarizing the predictor variable choice for Fine-Gray and Cox regression models. AIC, Akaike Information Criteria.

Appendix 2

Supplementary File 1. Variables included in the global models before variable selection processes applied.
Previously known risk factors and clinically relevant factors included in the global models

1. Age
2. Sex
3. Charlson's comorbidity index
4. Diabetes mellitus
5. ASA score
6. C-reactive protein (serum)
7. Presence of fistula
8. Indication of the previous surgery (primary THA/revision THA)
9. Rheumatoid arthritis
10. Chronic kidney disease
11. Body mass index
12. Pathogen
13. Type of the revision (DAIR/1-stage revision/2-stage revision)
14. Type of the infection (early/acute hematogenous/chronic)

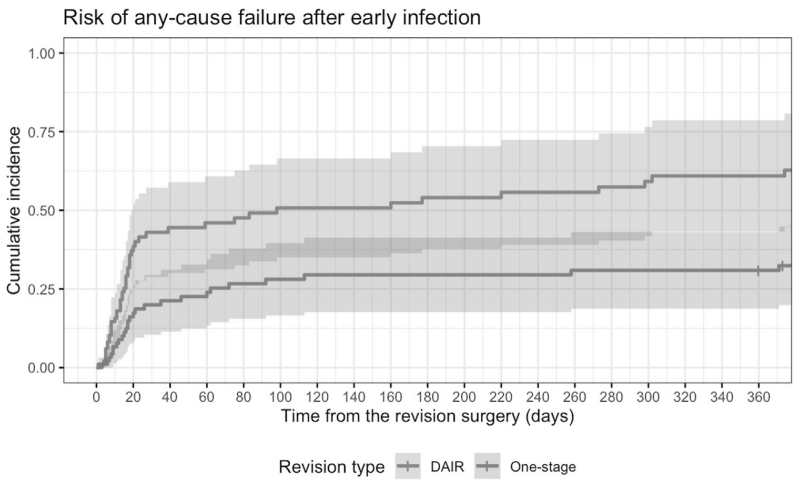
Appendix 3

Supplementary Table 1
Prosthetic Joint Infection Treatment Outcomes According to Musculoskeletal Infection Society Categorization Scheme.

Outcome	All Revisions (n = 369)		DAIR (n = 134)		One-Stage (n = 114)		Two-Stage (n = 121)	
	N	%	N	%	N	%	N	%
Tier 1: Infection control with no continued antibiotic therapy	166	*45*	46	*34.3*	61	*53.5*	59	*48.8*
Tier 2: Infection control with the patient on suppressive antibiotic therapy	14	*3.8*	8	*6*	5	*4.4*	1	*0.8*
Tier 3: Need for reoperation and/or revision and/or spacer retention								
3A: Aseptic revision at >1 y from initiation of PJI treatment	6	*1.6*	1	*0.7*	1	*0.9*	4	*3.3*
3B: Septic revision (including DAIR) at >1 y from initiation of PJI treatment	2 *(50)*[a]	*0.5*	1 *(0)*[a]	*0.7*	0	*0*	1 *(100)*[a]	*0.8*
3C: Aseptic revision at ≤1 y from initiation of PJI treatment	16	*4.3*	5	*3.7*	4	*3.5*	7	*5.8*
3D: Septic revision (including DAIR) at ≤1 y from initiation of PJI treatment	41 *(54)*[a]	*11.1*	20 *(60)*[a]	*14.9*	4 *(25)*[a]	*3.5*	17 *(53)*[a]	*14*
3E: Amputation, resection arthroplasty, or arthrodesis	46	*12.5*	27	*20.1*	16	*14*	3	*2.5*
3F: Retained spacer	2	*0.5*	-	-	-	-	2	*1.7*
Tier 4: Death								
4A: ≤1 y from initiation of PJI treatment	29	*7.9*	14	*10.4*	8	*7*	7	*5.8*
4B: >1 y from initiation of PJI treatment	47	*12.7*	12	*9*	15	*13.2*	20	*16.5*

DAIR, debridement, antibiotics, and implant retention.
[a] Percentage of cases that are reinfected with the same initial organism.

Appendix 4



Supplementary Fig. 2. The risk of any-cause failure after early infection. DAIR, debridement, antibiotics, and implant retention.

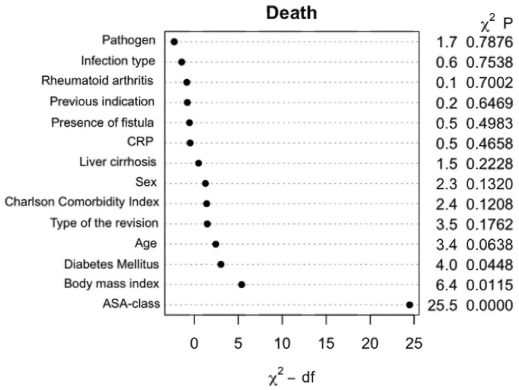
Appendix 5

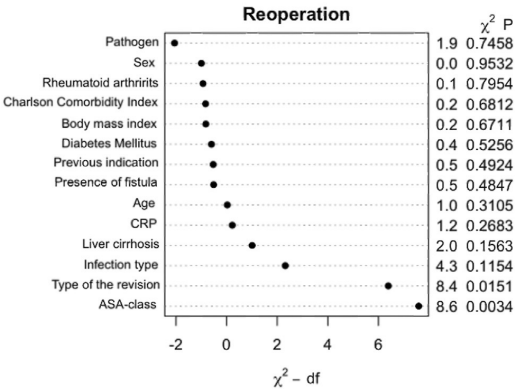
Supplementary Table 2
Fine-Gray Regression Subdistribution Hazard Ratios for Failure With 95% Confidence Intervals.

Fine-Gray Regression (n = 295)	
	Adjusted sdHR (95% CI)
Subdistribution hazard ratios for reoperation[a]	
Age	0.97 *(0.96 to 0.99)*
ASA-score	1.55 *(1.16 to 2.05)*
One-stage revision[b]	0.44 *(0.26 to 0.75)*
Two-stage revision[b]	0.72 *(0.43 to 1.19)*
Subdistribution hazard ratios for death	
Age	1.05 *(1.01 to 1.09)*
ASA-score	2.98 *(1.86 to 4.77)*
Diabetes mellitus	1.80 *(0.97 to 3.35)*
BMI	0.91 *(0.86 to 0.98)*

DAIR, debridement, antibiotics, and implant retention; HR, hazard ratio; sdHR, subdistribution hazard ratio.
[a] DAIR was used as the reference.
[b] Type of infection is adjusted for this model.

Appendix 6





Supplementary Fig. 3. The *Chi*-squared regression coefficients for the predictors in the Cox regression models. The American Society of Anesthesiologists (ASA) -class was the most important predictor of reoperation and death. ASA, American Society of Anesthesiology; BMI, body mass index; CCI, Charlson comorbidity index; DM, diabetes mellitus.

PUBLICATION III

Trends in Revision Knee Arthroplasty for Prosthetic Joint Infection: A Single-Center Study of 384 Knees at a High-Volume Center between 2008 and 2021

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Complications - Infection

Trends in Revision Knee Arthroplasty for Prosthetic Joint Infection: A Single-Center Study of 384 Knees at a High-Volume Center Between 2008 and 2021

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ABSTRACT

Background: Prosthetic joint infection (PJI) is one of the most devastating complications after total knee arthroplasty (TKA), and comorbidities increase the risk. We examined whether a temporal change has occurred in the demographics, especially regarding comorbidities, of patients who have PJI and were treated at our institution over a 13-year study period. In addition, we assessed the surgical methods used and the microbiology of the PJIs.

Methods: Revisions (n = 384, 377 patients) due to PJI of the knee performed at our institution between 2008 and September 2021 were identified. All included PJIs fulfilled the 2013 International Consensus Meeting diagnostic criteria. The surgeries were categorized into one of the following categories: debridement, antibiotics, and retention (DAIR), 1-stage revision, and 2-stage revision. Infections were classified as early, acute hematogenous, and chronic.

Results: No changes in the median age of the patients nor comorbidity burden were observed during the study period. However, the proportion of 2-stage revisions decreased remarkably from 57.6% in 2008 to 2009 to 6.3% in 2020 to 2021. A DAIR was the most used treatment strategy, but the proportion of 1-stage revisions increased the most. In 2008 to 2009, 12.1% of the revisions were 1-stage, but in 2020 to 2021, the proportion was 43.8%. The most common pathogen was *Staphylococcus aureus* (27.8%).

Conclusion: The comorbidity burden remained at the same level with no trends. A DAIR was the most used strategy, but the proportion of 1-stage revisions rose to almost the same level. The incidence of PJI varied between the years, but remained relatively low.

Prosthetic joint infection (PJI) is one of the most devastating complications after total knee arthroplasty (TKA). Moreover, PJI is not only a tremendous burden for individual patients, but also for global health care systems because it is associated with recurrent surgeries, increased mortality risks, and inferior patient-reported outcomes [1–3].

The risk for developing PJI after TKA has been reported to be under 2% within 2-year follow-up [4,5]. In a longer follow-up period, the cumulative incidence has been reported to range between 0.06% and 0.08% per prosthesis-year [6]. During the last decades, decreasing incidences of PJI of the knee have been reported [7,8]. However, increases in the incidences of PJIs have also been reported [9], and these increases are expected to continue [10]. In addition, the comorbidity burden of patients undergoing primary TKA has also increased and is expected to increase further [11]. An increase in the prevalence of diabetes and obesity among TKA patients [11] may lead to an even greater increase in the incidence of PJI, as they are both known risk factors [12].

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Traditionally, the surgical treatment of PJI has been based on treatment algorithms, where early infections are preferably treated with debridement, antibiotics, and retention (DAIR) and late infections with 2-stage revision surgery [13,14]. However, spacer retention after the first stage of an intended 2-stage revision has become a viable treatment option (a so-called "1.5-stage exchange arthroplasty"), as both clinical outcomes and reinfection rates have also been reported to be acceptable with chronic infections [15,16]. Furthermore, 1-stage revisions have also become more popular in recent years [9].

The microbiology of PJI of the knee has been reported to be associated with the time after prosthesis implantation and the route of acquisition. Thus, early and acute hematogenous infections are mainly caused by *Staphylococcus aureus* and delayed infections by coagulase-negative staphylococci (CNS) [17,18]. However, high rates of CNSs have also been observed in early infections [19].

To our best knowledge, no previous study has examined how the demographics of patients who have PJI of the knee, the surgical treatment strategies for PJI, and the distribution of pathogens have changed during the past decade. Therefore, in the present study, we aimed to assess (1) whether there has been a change in the demographics of patients who have a PJI; (2) whether there has been a change in the surgical treatment of PJI; and (3) whether there has been a change in microbiological findings.

Materials and Methods

Our institution is a high-volume academic referral center focused on joint arthroplasty surgery, with an annual volume of more than 3,000 primary and over 200 revision TKAs. In this retrospective cohort study, we identified all revision surgeries performed for PJI of the knee at our institution between January 1st, 2008, and September 12th, 2021, by searching the ICD-10 (International Classification of Diseases 10th revision) code T84.5 (Infection and inflammatory reaction due to internal joint prosthesis). After excluding superficial wound infections and 2-stage operations where information on the first surgery was not available, the PJI diagnosis was confirmed with 2013 International Consensus Meeting diagnostic criteria [20]. If the criteria were not fulfilled, the case was excluded. Only the first revisions due to PJI were included, and those patients who underwent revision due to PJI in both knees were analyzed as 2 separate operations.

The patient data were obtained using our institution's electronic data lake as well as electronic health records (EHR). Our institution's electronic data lake is a prospectively filled database, where specific details of every treatment period (eg, details of surgery, prosthesis, laboratory results, medication, comorbidities) are collected and documented. The EHRs contain information related to patient care, whereas the data lake contains more comprehensive information on the surgical details. The following patient demographics were collected from the data lake and the EHRs: age, sex, body mass index (BMI), American Society of Anesthesiology (ASA) classification, and comorbidities. Charlson comorbidity index (CCI) scores were calculated separately for each patient [21]. In addition, we also recorded the date of the primary surgery, the date of the last noninfectious operation to the ipsilateral joint, and the date from the beginning of the symptoms before revision surgery. Information on the presence of a fistula and intraoperative microbiological findings from tissue specimens were also collected from the EHRs. All the microbiology analyses were performed in the accredited microbiology laboratory of the local university hospital. In accordance with Finnish legislation, no institutional review board hearing was required because of the retrospective register-based study design and because the patients were not contacted.

The surgeries were categorized into 1 of the following 3 categories: DAIR; 1-stage revision; or 2-stage revision. The DAIR included all surgeries where the joint capsule was opened and the tibial liner possibly replaced, but neither the tibial nor the femoral component were replaced or removed. In 1-stage revision, all the components were replaced in 1 operation, whereas in 2-stage revision, the components were sequentially removed and replaced in 2 operations with a period of spacer prosthesis or static spacer in between. If the planned second stage was not performed due to a satisfactory outcome from the first-stage operation, the surgery was categorized as 1-stage revision, as suggested by the Musculoskeletal Infection Society [22].

To reflect the pathogenesis of the PJI and to produce results that are applicable in a clinical setting, the infections were classified as early ($\leq$90 days from the previous surgery), acute hematogenous (>90 days from the previous surgery AND <28 days of symptoms), and chronic (>90 days from the previous surgery AND $\geq$28 days of symptoms) [14,18,23].

Patient and Surgical Demographics

A total of 384 PJI revisions (377 patients) were performed at our institution. Of these, 148 (38.5%) were early infections, 147 (38.3%) acute hematogenous infections, and 89 (32.2%) chronic infections (Fig. 1). In total, 152 (39.6%) DAIRs, 104 (27.1%) 1-stage revisions, and 128 (33.3%) 2-stage revisions were performed. Of the 1-stage revisions, 21 (20.2%) were originally planned to be 2-stage revisions, but the second stage was not performed due to the satisfactory outcome from the first stage. Most of the DAIRs (n = 78, 51.3%) and 1-stage revisions (n = 38, 36.5%) were performed for acute hematogenous infections, whereas most of the 2-stage revisions (n = 57, 44.5%) were performed for chronic infections. The median age of the patients was 72 years (range, 37 to 94) and 50.5% (n = 194) were women (See Tables 1 and 2).

Data Analyses

Means with standard deviations (SD) were presented for normally distributed variables and medians with interquartile ranges (IQR) for variables with non-Gaussian populations. Categorical variables were presented as counts and percentages. To examine the changes during our study period, patient demographics and the microbiology of the PJIs were compared in a longitudinal setting using descriptive statistics. Moreover, to avoid selection bias, patient demographics and the microbiology of the PJIs were compared in 2-year admission groups, rather than in yearly groups.

As our institution is a tertiary referral center, not all revisions were performed on patients who had undergone their primary TKA at our institution. Therefore, incidences were calculated based on the number of primary TKAs performed at our institution, and the number of PJIs of which the primary arthroplasty was performed at our institution. Referral PJIs and those PJIs that occurred after revision TKA were not included in the incidence calculations. All analyses were performed using R (version 4.1.2; R Foundation for Statistical Computing, Vienna, Austria). The results of this study are reported according to the STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) guidelines [24].

Results

Trends in Demographics and Surgical Treatment

Neither the median age of the patients nor the comorbidity burden changed during the study period. The proportion of ASA-class 4 patients was between 4.8% and 14.3% with no trends, and

Table 1
PJI Patient Characteristics and Preoperative Risk Factors Stratified by Type of Infection.

Variable	Early (n = 148)	Acute Hematogenous (n = 147)	Chronic (n = 89)
Patient characteristics			
Women, n (%)	65 (43.9)	72 (49)	57 (64)
Age, in years, median (IQR)	70 (62–77)	74 (65–81)	73 (62–78)
BMI, mean (range)	30.9 (42 to 89)	30.3 (48 to 94)	30.8 (37 to 93)
BMI ≥30, n (%)	84/145 (57.9)	64/127 (50.4)	44/84 (52.4)
BMI ≥35, n (%)	40/145 (27.6)	35/127 (27.6)	17/84 (20.2)
CCI, median (range)	3 (0–6)	3 (0–7)	3 (0–8)
CCI ≥3, n (%)	92/148 (62.2)	99/147 (67.3)	64/89 (71.9)
ASA-class, n (%)			
1	3 (2)	3 (2)	2 (2.2)
2	33 (22.3)	23 (15.6)	17 (19.1)
3	100 (67.6)	90 (61.2)	62 (69.7)
4	8 (5.4)	26 (17.7)	6 (6.7)
5	0	2 (1.4)	0
NA	4 (2.7)	3 (2)	2 (2.2)
Co-morbidities, n (%)			
Diabetes mellitus	32/143 (22.4)	33/119 (27.7)	14/83 (16.9)
Rheumatoid arthritis	12/137 (8.8)	12/119 (10.1)	14/80 (17.5)
Chronic kidney disease	1/141 (0.7)	6/118 (5.1)	2/82 (2.4)
Operation type, n (%)			
DAIR	73 (49.3)	78 (53.1)	1 (1.1)
One-stage revision	35 (23.6)	38 (25.9)	31 (34.8)
Two-stage revision	40 (27)	31 (21.1)	57 (64)
Static spacer	2 (5)	1 (3.2)	6 (10.5)
Surgical characteristic			
Time since previous operation, median (IQR), d	22 (16–29)	1,242 (357–3,240)	686 (284–1,555)
Symptom duration, median (IQR), d	12 (4–20)	5 (3–9)	100 (64–264)
Sinus tract, n (%)	107/146 (73.3)	5/147 (3.4)	10/86 (11.6)

Infections are classified as early (≤3 mo From the previous Surgery), Acute Hematogenous (>3 mo From the previous Surgery With <28 d of Symptoms) and Chronic (>3 mo From the previous Surgery With ≥28 d of Symptoms).
DAIR, debridement, antibiotics, and implant retention; d, days; y, years; IQR, interquartile range; CCI, charlson comorbidity index; ASA, American Society of Anesthesiology; BMI, body mass index.

Table 2
PJI Patient Characteristics and Preoperative Risk Factors, Stratified by the Operation type.

Variable	DAIR (n = 152)	One-Stage (n = 104)	Two-Stage (n = 128)
Patient characteristics			
Women, n (%)	70 (46.1)	51 (49)	73 (57)
Age, in years, median (IQR)	70 (63–77)	74 (66–81)	70 (62–78)
BMI, mean (range)	31.1 (42 to 94)	29.2 (37 to 94)	31.3 (45 to 93)
BMI ≥30, n (%)	80/144 (55.6)	39/91 (42.9)	73/121 (60.3)
BMI ≥35, n (%)	45/144 (31.3)	17/91 (18.7)	30/121 (24.8)
CCI, median (range)	3 (0–7)	3 (0–8)	3 (0–6)
CCI ≥3, n (%)	94 (61.8)	79 (76)	82 (64.1)
ASA-class, n (%)			
1	3 (2)	3 (2.9)	2 (1.6)
2	33 (21.7)	13 (12.5)	27 (21.1)
3	101 (66.4)	68 (65.4)	83 (64.8)
4	11 (7.2)	17 (16.3)	12 (9.4)
5	1 (0.7)	1 (1)	0
NA	3 (2)	2 (1.9)	4 (3.1)
Co-morbidities, n (%)			
Diabetes mellitus	34/132 (25.8)	16/96 (16.7)	29/117 (24.8)
Rheumatoid arthritis	12/132 (9.1)	11/95 (11.6)	18/112 (16.1)
Chronic kidney disease	4/132 (3)	3/95 (3.2)	2/114 (1.8)
Infection type, n (%)			
Early	73 (48)	35 (33.7)	40 (31.3)
Acute hematogenous	78 (51.3)	38 (36.5)	31 (24.2)
Chronic	1 (0.7)	31 (29.8)	57 (44.5)
Surgical characteristic			
Time since previous operation, median (IQR), d	127 (19–1,272)	312 (34–1,304)	296 (42–1,420)
Symptom duration, median (IQR), d	5 (3–13)	13 (5–29)	21 (6–78)
Sinus tract, n (%)	51 (33.6)	28 (26.9)	43 (33.6)
Static spacer, n (%)	-	-	9 (20.9)

Infections are Classified as early (≤3 mo From the previous Surgery), Acute Hematogenous (>3 mo From the previous Surgery With <28 d of Symptoms) and Chronic (>3 mo From the previous Surgery With ≥28 d of Symptoms).
DAIR, debridement, antibiotics, and implant retention; d, days; y, years; IQR, interquartile range; CCI, charlson comorbidity index; ASA, American Society of Anesthesiology; BMI, body mass index.

Table 3
Patient Demographics During Our Study Period, Stratified by the Year of Operation.

Variable	2008-09 (n = 33)	2010–11 (n = 50)	2012–13 (n = 45)	2014–15 (n = 53)	2016–17 (n = 62)	2018–19 (n = 77)	2020–21 (n = 64)
Patient characteristics							
Women, n (%)	16 (48.5)	30 (60)	26 (57.8)	24 (45.3)	37 (59.7)	35 (45.5)	26 (40.6)
Age, median (IQR), y	70 (64–79)	72 (62–78)	69 (60–80)	73 (66–79)	72 (65–81)	72 (63–79)	72 (62–77)
BMI, mean (sd)	29.7 (5.5)	30.5 (6.2)	31.9 (6.7)	30.8 (7.3)	29.4 (5.5)	31.6 (5.3)	30.6 (6.4)
BMI ≥30, n (%)	16/31 (51.6)	26/44 (59.1)	24/41 (58.5)	20/49 (40.8)	27/60 (45)	43/70 (61.4)	36/61 (59)
BMI ≥35, n (%)	7/31 (22.6)	11/44 (25)	9/41 (22)	13/49 (26.5)	10/60 (16.7)	26/70 (37.1)	16/61 (26.2)
CCI, median (range)	3 (1–5)	3 (0–7)	3 (0–6)	3 (1–6)	3 (0–8)	3 (0–7)	3 (0–5)
CCI ≥3, n (%)	24 (72.7)	36 (72)	23 (51.1)	36 (67.9)	42 (67.7)	52 (67.5)	42 (65.6)
ASA-class, n (%)							
1	0	0	2 (4.4)	1 (1.9)	2 (3.2)	1 (1.3)	2 (3.1)
2	6 (18.2)	13 (26)	9 (20)	8 (15.1)	13 (21)	9 (11.7)	15 (23.4)
3	14 (42.4)	30 (60)	31 (68.9)	38 (71.7)	44 (71)	55 (71.4)	40 (62.5)
4	4 (12.1)	7 (14)	3 (6.7)	5 (9.4)	3 (4.8)	11 (14.3)	7 (10.9)
5	1 (3)	0	0	1 (1.9)	0	0	0
NA	8 (24.2)	0	0	0	0	1 (1.3)	0
Co-morbidities, n (%)							
Diabetes mellitus	9/30 (30)	10/48 (20.8)	7/42 (16.7)	15/46 (32.6)	13/53 (24.5)	11/64 (17.2)	14/62 (22.6)
Rheumatoid arthritis	6/30 (20)	7/49 (14.3)	4/40 (10)	5/41 (12.2)	9/53 (17)	3/64 (4.7)	7/62 (11.3)
Chronic kidney disease	0	4/49 (8.2)	0	1/43 (2.3)	1/53 (1.9)	3/64 (4.7)	0
Infection type, n (%)							
Early	17 (51.5)	15 (30)	12 (26.7)	15 (28.3)	23 (37.1)	31 (40.3)	35 (54.7)
Acute hematogenous	11 (33.3)	19 (38)	21 (46.7)	24 (45.3)	24 (38.7)	24 (31.2)	20 (31.3)
Chronic	5 (15.2)	16 (32)	12 (26.7)	14 (26.4)	15 (24.2)	18 (23.4)	9 (14.1)
Operation type, n (%)							
DAIR	10 (30.3)	12 (24)	14 (31.1)	24 (45.3)	31 (50)	29 (37.7)	32 (50)
One-stage revision	4 (12.1)	4 (8)	4 (8.9)	11 (20.8)	17 (27.4)	36 (46.8)	28 (43.8)
Two-stage revision	19 (57.6)	34 (68)	27 (60)	18 (34)	14 (22.6)	12 (15.6)	4 (6.3)
Static spacer	0	3 (8.8)	1 (3.7)	2 (11.1)	1 (7.1)	1 (8.3)	1 (25)

Infections are Classified as early (≤3 mo From the previous Surgery), Acute Hematogenous (>3 mo From the previous Surgery With <28 d of Symptoms), and Chronic (>3 mo From the previous Surgery With ≥28 d of Symptoms).
DAIR, debridement, antibiotics, and implant retention; d, days; y, years; IQR, interquartile range; sd, standard deviation; CCI, charlson comorbidity index; ASA, American Society of Anesthesiology; BMI, body mass index.

the median Charlson's comorbidity index score was 3 throughout the study period (Table 3).

The incidence of PJI or infection types did not show a clear trend, but the yearly changes in the incidences were large. The smallest incidence, 0.54 per 100 primary TKAs, was in 2008, whereas the largest incidence, 1.60 per 100 primary TKAs, was in 2011. The incidence of early infections was between 0.15 and 0.70 per 100 primary TKAs throughout the study period, but the yearly variation was large within those as well (Table 4, and Fig. 2).

During our study period, the proportion of 2-stage revisions decreased remarkably. In 2008 to 2009, for example, 57.6% (19 of 33) of the operations were 2-stage operations. In 2020 to 2021,

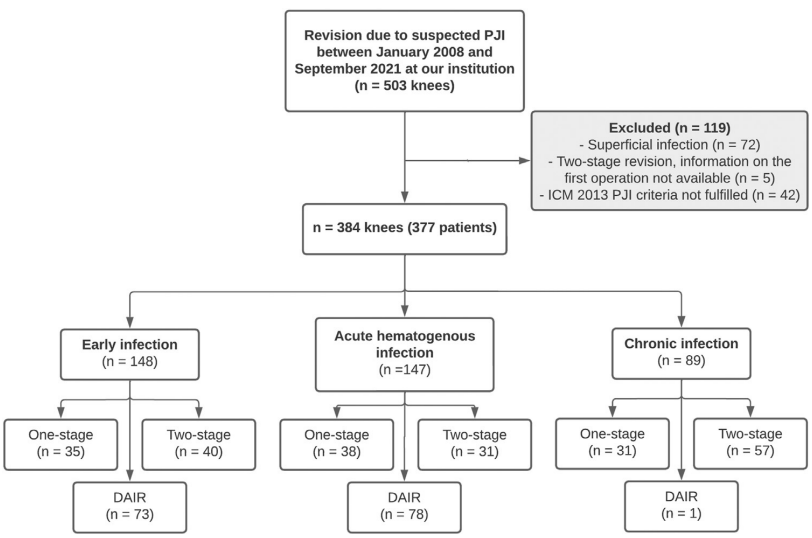

Fig. 1. Flowchart of the patients treated at our institution between January 2008 and September 2021.

Table 4
Yearly Incidence of the PJI Revisions Performed at Our Institution Between 2008 and 2021.

Variable	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
Operation type, n														
Primary TKA	1,286	1,223	1,273	1,061	1,188	1,208	1,183	1,320	1,783	1,888	2,143	2,651	2,873	2,245
PJI revision	7	11	18	17	10	9	13	9	24	17	26	27	33	17
Infection type, n														
Early	5	5	5	5	3	2	3	2	9	10	8	15	20	11
Acute hematogenous	1	3	10	5	4	7	5	6	12	3	14	5	9	3
Chronic	1	3	3	7	3	0	5	1	3	4	4	7	4	3
Type of the revision, n														
DAIR	2	4	6	4	3	6	5	6	15	7	13	9	18	10
One-stage revision	1	1	1	1	1	0	4	2	4	6	9	16	13	6
Two-stage revision	4	6	11	12	6	3	4	1	5	4	4	2	2	1
Incidence per 100 primary TKAs														
Overall	0.54	0.90	1.41	1.60	0.84	0.75	1.10	0.68	1.35	0.90	1.21	1.02	1.15	0.76
Early infections	0.39	0.41	0.39	0.47	0.25	0.17	0.25	0.15	0.50	0.53	0.37	0.57	0.70	0.49
Acute hematogenous infections	0.08	0.25	0.79	0.47	0.34	0.58	0.42	0.45	0.67	0.16	0.65	0.19	0.31	0.13
Chronic infections	0.08	0.25	0.24	0.66	0.25	0	0.42	0.08	0.17	0.21	0.19	0.26	0.14	0.13
DAIR	0.16	0.33	0.47	0.38	0.25	0.50	0.42	0.45	0.84	0.37	0.61	0.34	0.63	0.45
One-stage revision	0.08	0.08	0.08	0.09	0.08	0	0.34	0.15	0.22	0.32	0.42	0.60	0.45	0.27
Two-stage revision	0.31	0.49	0.86	1.13	0.51	0.25	0.34	0.08	0.28	0.21	0.19	0.08	0.07	0.04

The Number of PJI Revisions is Calculated Based on the Number of PJIs Whose Primary Knee Arthroplasty was Performed at Our Institution. Infections are Classified as early (≤3 mo From the previous Surgery), Acute Hematogenous (>3 mo From the previous Surgery With <28 d of Symptoms) and Chronic (>3 mo From the previous Surgery With ≥28 d of Symptoms).
TKA, total knee arthroplasty; DAIR, debridement, antibiotics, and implant retention.

however, the proportion had decreased to 6.3% (4 of 64). The proportion of 1-stage revisions increased the most. In 2008 to 2009, 12.1% (4 of 33) of the revisions were 1-stage, but in 2020 to 2021 the proportion was 43.8% (28 of 64) (Table 3 and Fig. 3)

Microbial Findings

Staphylococcus aureus was the most identified pathogen, accounting for 116 (27.8%) infections. Most of the early infections were caused by *S. aureus* (72 of 175, 41.1%), most chronic infections by coagulase-negative staphylococci (CNS) (25 of 92, 27.2%), and most common pathogens causing acute hematogenous PJIs were beta-hemolytic streptococci (22 of 151, 21.9%) (Tables 5 and 6).

The proportion of infections caused by CNS decreased from 25% (10 of 40) in 2008 to 2009 to 11.4% (8 of 70) in 2020 to 2021. However, the proportion of infections caused by *S. aureus* remained at the same level throughout the study period. The proportion of negative cultures increased slightly. In 2008 to 2009, 20% (8 of 45) of the infections were culture-negative, whereas the proportion had increased to 25.7% (18 of 70) in 2020 to 2021 (Table 7).

Discussion

To better understand the demographics and trends in the treatment of PJI of the knee, we analyzed all revision surgeries due to PJI performed at our institution between January 2008 and September 2021. The results revealed that the comorbidity burden among patients who had a PJI remained at the same level, with no clear trends. However, surgical strategies changed during the study period. For example, in addition to DAIR, 1-stage revision has

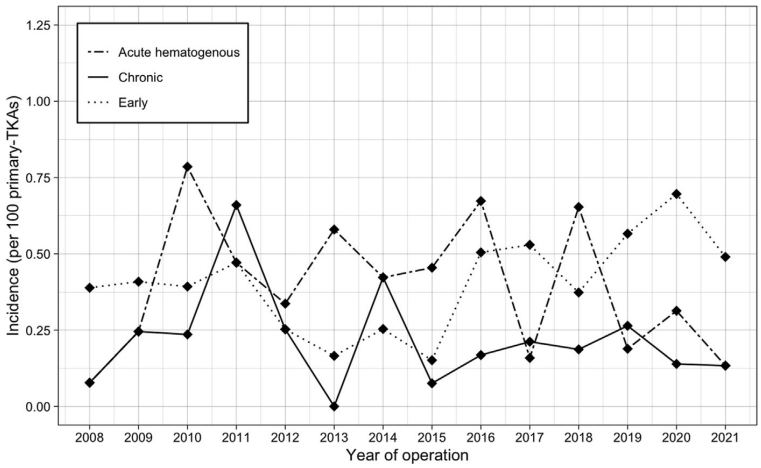

Fig. 2. Incidence of revision surgeries due to prosthetic joint infection at our institution stratified by the type of infection between 2008 and 2021.

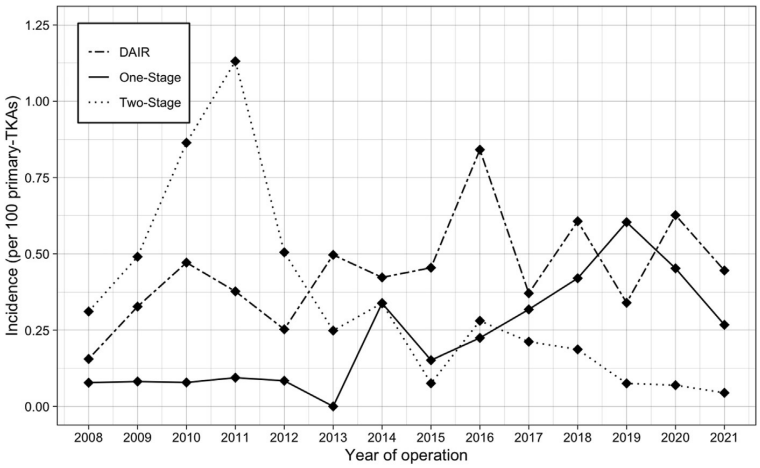

Fig. 3. Incidence of revision surgeries due to prosthetic joint infection at our institution stratified by the type of operation between 2008 and 2021.

become the most used strategy, and the proportion of 2-stage revisions has decreased remarkably. Furthermore, we found that there are rather large yearly variations in incidences, but with no clear trends. Interestingly, we also found that acute hematogenous PJIs are mostly caused by beta-hemolytic streptococci and not *S. aureus*.

Traditionally, 2-stage revision has been the gold standard for the treatment of PJI, especially for late infections [3,13]. However, recent studies have questioned the superiority of 2-stage revision compared to 1-stage revision [25,26]. During our study period, the proportion of 2-stage revisions decreased from over 50% to under 10%, whereas the proportion of 1-stage revisions performed increased from 12.1% to 43.8%. However, the proportion of DAIRs was over 30% for most of the study period, and it remained as the most performed surgical treatment. A similar increasing trend in 1-stage revisions in Germany between 2008 and 2021 has been reported by Rupp *et al.* [9]. In contrast to the findings of our study, they observed an increase in the proportion of 2-stage revisions and a decrease in the proportion of DAIRs. However, as they did not categorize infection types, it remains unclear whether there were any changes in infection types during the study period, which could have possibly affected the distribution of the surgical strategies.

Our findings can be partly explained by the adoption of the so called "1.5-stage revision", where the PJI is managed in a 1-stage manner with the retention of an articulating spacer, since this has been reported to be a reasonable method for treating PJI of the knee [16,27]. In addition, as our institution is a high-volume center, we currently prefer to perform 1-stage revision on as many patients as possible because there are less costs included than in 2-stage revisions [28].

Although an increase in the incidence of PJI of the knee has been reported [9,10], decreases in the incidence of PJI have also been reported [7,8]. However, as the demand for primary TKAs is rapidly increasing [29], the absolute number of early infections is expected to scale up accordingly. In the present study, we did not observe a remarkable increase in the incidence of PJI, but the yearly variation was large. Early infections were the most common infection type, which might be due to the increased number of primary TKAs performed at our institution. Indeed, the number of primary TKAs performed at our institution more than doubled between 2008 and 2020.

Table 5
Microbiological Results From Tissue Specimens Stratified by the Type of Infection.

Pathogen	All (n = 418)		Early (n = 175)		Acute Hematogenous (n = 151)		Chronic (n = 92)	
	N	%	N	%	N	%	N	%
Staphylococcus aureus	116	27.8	72	41.1	28	18.5	16	17.4
CNS	79	18.9	37	21.1	17	11.3	25	27.2
Streptococcus beta-hemolyticus	48	11.5	14	8	33	21.9	1	1.1
Other streptococcus species	11	2.6	4	2.3	6	4	1	1.1
Gram-negative aerobic	22	5.3	7	4	12	7.9	3	3.3
Enterococcus species	13	3.1	6	3.4	5	3.3	2	2.2
Anaerobic	8	1.9	4	2.3	2	1.3	2	2.2
Other	7	1.7	5	2.9	2	1.3	0	0
Negative culture	114	27.3	26	14.9	46	30.5	42	45.7

Infections are Classified as early (≤3 mo From the previous Surgery), Acute Hematogenous (>3 mo From the previous Surgery With <28 d of Symptoms), and Chronic (>3 mo From the previous Surgery With ≥28 d of Symptoms). Microbiological Findings From the Polymicrobial Infections (n = 29, 34 Additional Pathogens) are Included, and Therefore the Total N is Greater Than the Total N of the Surgeries Performed (n = 384). Corynebacterium Species (n = 4), Listeria Monocytogenes, Gemella Species and Kocuria Rhizophila are Included in the Other Group.
CNS, coagulase-negative staphylococci.

Table 6
Microbiological Results From Polymicrobial Infections (n = 29) Stratified by the Type of Infection.

Pathogen	All (n = 63)		Early (n = 50)		Acute Hematogenous (n = 6)		Chronic (n = 7)	
	N	%	N	%	N	%	N	%
Staphylococcus aureus	11	17.5	10	20	0	0	1	14.3
CNS	22	34.9	15	30	2	33.3	5	71.4
Streptococcus beta-hemolyticus	10	15.9	7	14	3	50	0	0
Other streptococcus species	4	6.3	2	4	1	16.7	1	14.3
Gram-negative aerobic	4	6.3	4	8	0	0	0	0
Enterococcus species	4	6.3	4	8	0	0	0	0
Anaerobic	3	4.8	3	6	0	0	0	0
Other	5	7.9	5	10	0	0	0	0

Infections are Classified as early (≤3 mo From the previous Surgery), Acute Hematogenous (>3 mo From the previous Surgery With <28 d of Symptoms), and Chronic (>3 mo From the previous Surgery With ≥28 d of Symptoms).
CNS, coagulase-negative staphylococci.

We observed no trends in the comorbidity burden of patients. This is a surprising finding since the number of comorbidities of primary TKA patients has been observed to be high, with an increasing trend [30]. Moreover, a decreasing trend in the prevalence of diabetes mellitus and rheumatoid arthritis was observed. However, as we did not analyze the specific risk factors for PJI after TKA, we can only state that the comorbidity burden of patients who have a PJI was approximately the same during our study period. In addition, the yearly variation was large due to the selection bias that the rare nature and small numbers of PJI can cause.

Previous studies have usually analyzed the microbiological findings of PJIs without stratifying them by joint [17–19]. However, as it has been reported that the microbiology might differ between joints, a joint-specific examination is warranted [31]. The proportion of PJIs caused by CNS decreased, but since CNS was the most common of the chronic infections and the proportion of chronic infections was approximately the same at the beginning and the end of the study period, this decrease might be due to a decrease among early or acute infections. Furthermore, the proportion of *S. aureus* was approximately 30% throughout the study period, which might reflect the steady proportions of early infections, as *S. aureus* has been reported to be the most common pathogen among early infections [17,18].

Surprisingly, acute hematogenous PJIs were commonly caused by beta-hemolytic streptococci and not *S. aureus*, even though both were common. Similar results were reported by Triffault-Fillit et al. who also reported that a higher number of acute hematogenous PJIs was caused by streptococci than by *S.aureus* [18]. The high proportion of streptococci's among acute PJIs might also be a knee-specific phenomenon since streptococcal knee PJIs have previously been associated with erysipelas or cellulitis of the knee [32].

The present study has several potential limitations that must be addressed. Due to the rare nature of PJI, our findings might be prone to selection bias, which is a common concern in PJI research. However, because we have a total of almost 400 patients, we believe the risk of selection bias has been minimized. Furthermore, as the same surgeons managed all the patients in the same institution, the potential risk was also as minimal as possible. We also analyzed the surgeries in 2-year admission groups, which served to reduce the risk of selection bias. Also, due to the retrospective nature of the study, we did not have access to accurate antimicrobial treatment history. Therefore, treatment may have started before surgery, and thus affected the results from the tissue specimens. Conversely, since the diagnosis of PJI does not require positive intraoperative cultures [20,33], we believe that this potential limitation did not affect the interpretation of our results. Another limitation of our study is that we did not have accurate access to information on those intraoperative factors that might have affected the decision on surgical technique, such as bone stock or soft tissue condition. However, as all patients were managed by the same surgeons at the same institution with similar guidelines, we believe that possible bias to our results was minimized. The strengths of this study were the large sample size with accurate records from our high-quality prospectively maintained data lake. In addition, the large sample size combined with the length of the study period made it possible to examine temporal trends in a single-center setting.

Table 7
Microbiological Results From Tissue Specimens During Our Study Period.

Pathogen	2008-09 (n = 40)		2010–11 (n = 54)		2012–13 (n = 47)		2014–15 (n = 57)		2016–17 (n = 66)		2018–19 (n = 84)		2020–21 (n = 70)	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Staphylococcus aureus	13	32.5	7	13	14	29.8	13	22.8	13	19.7	32	38.1	24	34.3
CNS	10	25	16	29.6	8	17	15	26.3	12	18.2	10	11.9	8	11.4
Streptococcus beta-hemolyticus	3	7.5	7	13	5	10.6	5	8.8	8	12.1	10	11.9	10	14.3
Other streptococcus species	1	2.5	1	1.9	1	2.1	3	5.3	2	3	2	2.4	1	1.4
Gram-negative aerobic	2	5	1	1.9	1	2.1	5	8.8	5	7.6	4	4.8	4	5.7
Enterococcus species	2	5	1	1.9	1	2.1	2	3.5	1	1.5	6	7.1	0	0
Anaerobic	1	2.5	4	7.4	2	4.3	0	0	0	0	0	0	1	1.4
Other	0	0	1	1.9	0	0	0	0	1	1.5	1	1.2	4	5.7
Negative culture	8	20	16	29.6	15	31.9	14	24.6	24	36.4	19	22.6	18	25.7

Microbiological Findings From the Polymicrobial Infections (n = 29, 34 Additional Pathogens) are Included, and Therefore the Total N is Greater Than the Total N of the Surgeries Performed (n = 384).
DAIR, debridement, antibiotics, and implant retention; CNS, coagulase-negative staphylococcus.

In conclusion, the comorbidity burden among patients who have PJI remained at the same level with no clear trends. A DAIR was the most used treatment strategy, but the proportion of 1-stage revisions performed rose to almost the same level. The incidence of PJI varied between years, remaining relatively low at all times.

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PUBLICATION IV

Clinical Outcomes After Revision Knee Arthroplasty due to Prosthetic Joint Infection - A Single-Center Study of 359 Knees at a High-Volume Center with a Minimum of One Year Follow-Up

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Submitted manuscript

PUBLICATION V

KLIC Score Does Not Predict Failure After Early Prosthetic Joint Infection: An External Validation with 153 Knees and 130 Hips

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KLIC Score Does Not Predict Failure After Early Prosthetic Joint Infection: An External Validation With 153 Knees and 130 Hips

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ABSTRACT

Background: A preoperative risk score, the KLIC score (chronic renal failure [K], liver cirrhosis [L], indication of the index surgery [I], cemented prosthesis [C], and C-reactive protein >115 mg/L), has been developed to predict the risk of treatment failure after early prosthetic joint infection (PJI). This study aimed to validate the KLIC score for the debridement, antibiotics, and implant retention (DAIR) procedure and one-stage revisions in a Northern European cohort.

Methods: Revisions due to early PJI of the hip or knee between January 1, 2008, and September 12, 2021, were identified retrospectively. The primary outcome was early failure, which was considered when the patient needed an unscheduled surgery, the patient died, or the patient was prescribed long-term suppressive antibiotics. To examine the association between KLIC score and failure risk, univariable logistic regression with area under the curve (AUC) was used. In addition, models were calibrated to assess prognostic ability and clinical utility was examined with decision-curve analyses.

Results: An increase in KLIC score had a moderate predictive value for early failure after DAIR (odds ratio [OR] 1.45; confidence interval [CI] 1.13 to 1.90). For one-stage revision, it was only slightly predictive of failure (OR 1.20; CI 0.93 to 1.56). After 60 days, the AUC for DAIR was 0.63 (CI 0.55 to 0.72) and 0.56 (CI 0.46 to 0.66) for one-stage revisions, indicating poor discriminative ability. The decision-curve analyses revealed that the model did not offer a remarkable net benefit across a range of threshold probabilities.

Conclusions: We demonstrated that the KLIC score is not a reliable predictor of early failure after early PJI in a Northern European cohort. Using the model to guide treatment decisions does not provide any additional clinical utility beyond the baseline strategies.

Early prosthetic joint infections (PJIs) are preferably treated with the debridement, antibiotics, and implant retention (DAIR) procedure, where the implant is retained in the joint, but the mobile components (tibial/acetabular liner, femoral head) are replaced [1–3]. However, failure rates after DAIR have previously been reported to be more than 50% in under one-year follow-up [4,5]. In addition to DAIR, one-stage revision has been reported to be a comparable or an even more preferable surgical treatment method for early infections [6].

To preoperatively predict the risk of failure Tornero et al (2015) developed a preoperative prediction model known as the KLIC score (chronic renal failure [K], liver cirrhosis [L], indication of the index surgery [I], cemented prosthesis [C], and C-reactive protein >115 mg/L) [7]. Since then, the KLIC score has been externally validated by several cohorts and is reported to be a valid and clinically applicable method for predicting the prognosis of an individual before undergoing DAIR for early PJI [8–10]. Furthermore, the 2019 international consensus on orthopedic infections also declared that the KLIC score may aid in risk stratification [11]. Some studies, however, have questioned the clinical applicability of the

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KLIC score [12,13]. In addition, the quality of the previous validation studies was not optimal, as advanced analyses, such as calibration and decision-curve analyses (DCA), were not performed [14].

A well-validated prediction model would be helpful in the clinical setting, as it would assist in making treatment decisions. For example, in the treatment of PJI, such a model would be helpful when discussing which revision strategy would have the best prognosis for an individual's treatment. To the best of our knowledge, no previous study has validated the KLIC score in a Northern European cohort. In addition, the predictive ability of the KLIC score with one-stage revisions has not previously been investigated. Therefore, the aims of the present study were 1) to externally validate the KLIC score in a Northern European cohort and 2) to examine the predictive ability of the KLIC score among patients treated with one-stage revision.

Materials and Methods

Study Setting and Participants

In this retrospective cohort study, we identified patients who had early PJI of the hip or knee arthroplasty who were treated with either DAIR or one-stage revision at our institution between January 1, 2008, and September 12, 2021, by searching the ICD-10 (International Classification of Diseases 10th Revision) code T84.5 (infection and inflammatory reaction due to internal joint prosthesis). Early PJI was defined as infection occurring within the first 90 postoperative days after previous aseptic surgery to the ipsilateral joint. The PJI diagnoses were confirmed with the 2013 International Consensus Diagnostic Criteria [15]. Only first revisions due to PJI were included, and those patients who underwent revisions in multiple joints were analyzed as having undergone separate operations. In addition, patients with less than a one-year follow-up were excluded (Supplementary Figure 1). In accordance with Finnish legislation (the Act on the Secondary Use of Health and Social Data [552/2019]), no ethical committee approval or informed written consent was required due to the retrospective register-based study design and because patients were not contacted.

To manually obtain data for each patient, we used our institution's electronic data lake and electronic health records. Age, sex, body mass index, American Society of Anesthesiologists classification, comorbidity, and the length of time from the initial operation to the ipsilateral joint were collected for each patient. The results of intraoperative microbiological findings acquired from tissue specimens were also collected from the electronic health records. All the microbiology analyses were performed in the accredited laboratory of the local university hospital.

Treatment Strategies

All patients were managed by a multidisciplinary team comprising orthopedic surgeons specialized in joint arthroplasty surgery and infectious diseases specialists. According to the microbiological results from the preoperative and intraoperative tissue specimens, postoperative antimicrobial treatments were designed by infectious diseases specialists.

The surgeries were categorized into DAIR or one-stage revision. The DAIR procedures included all surgeries where the joint capsule was opened, the acetabular/tibial liner and/or femoral head replaced, but the prosthetic components were not replaced or removed. In one-stage revision, all the components were replaced in one operation. The treatment decisions were based on international consensus, where early infections are preferably treated with either DAIR or one-stage revision [1,2,16]. If the index prosthesis was unstable or uncemented, or if the time from the initial operation was approaching the limits of the optimal time frame (within the first 3 to 4 postoperative weeks from the index procedure) for DAIR, one-stage revision was the preferred option. Moreover, the proportion of one-stage revisions at our institution has increased steadily within the last decade, and the majority of early PJIs are nowadays managed with one-stage revision [17,18].

Primary and Secondary Outcomes

The follow-up period began from the day of the revision surgery for PJI. The primary outcome was early failure which was considered when: 1) the patient needed an unscheduled surgery, that was not planned before the initial revision (eg, septic re-revision), within 60 days of the initial revision; 2) the patient died within 60 days of the initial revision; or 3) the patient was prescribed long-term suppressive antibiotics within 60 days of the initial revision because the patient's condition contraindicated further surgeries. The secondary outcome was failure within the first postoperative year.

Data Analyses

Categorical variables were reported with counts and percentages, and continuous variables with either means with standard deviations or medians with interquartile ranges. A KLIC score was calculated separately for each patient from the preoperative variables described by Tornero et al [7] (Table 1). If the required variables were not available, the patient was excluded from the analyses. Patients were then categorized into groups according to their KLIC score ($\leq$2, 2.5 to 3.5, 4 to 4.5, $\geq$5).

All the analyses were performed separately for DAIRs and one-stage revisions. The risk of failure was calculated using the Kaplan-Meier estimator. Univariable logistic regressions were used to examine the effect of the KLIC score on the risk of failure. The KLIC score was analyzed as a continuous variable as well as a categorized variable. To assess the discriminatory ability, area under the curve (AUC) was calculated for each of the logistic regression analyses, and the results were presented with receiver operating characteristics curves. Categorized KLIC scores were analyzed with binary logistic regressions, and the sensitivity, specificity, and positive and negative predictive values were then calculated for those analyses. Results were presented with odds ratios (ORs) and corresponding 95% confidence intervals (CIs).

In addition, the model calibrations were assessed with calibration plots, and the clinical utility of the KLIC score was examined with DCA [14,19]. The Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) guidelines were followed in the reporting of the results [20]. All analyses were performed using R (version 4.1.2; R Foundation for Statistical Computing, Vienna, Austria).

Table 1
KLIC Score As Described by Tornero et al. (2015).

Variable	Explanation	Score
K	Chronic renal failure (kidney)	2
L	Liver failure	1.5
I	Index surgery = Revision surgery or prosthesis to treat femoral neck fracture	1.5
C	Cemented prosthesis	2
C	C-reactive protein (CRP >115 mg/L)	2.5
	Total	Max 9.5

Patient and Microbiological Demographics

A total of 283 patients who had an early PJI and had been treated with DAIR or one-stage revision were identified. Of these, 159 (56.2%) had been treated with DAIR. Most of the revisions were performed due to PJI of the knee (n = 153, 54.1%), and most of the PJIs occurred after primary arthroplasty (n = 193, 68.2%). The mean age of the patients was 69.3 years (range 37 to 94) and most of the patients (n = 149, 52.7%) were women. *Staphylococcus aureus* was the most identified pathogen, causing 121 (42.8%) infections (Table 2 and Supplementary Table 1).

Results

Survival After PJI Revision

At 60-day follow-up, 28.9% (CI 22.7 to 36.9%) of the DAIR procedures had failed, and the corresponding failure rate at one-year follow-up was 36.5% (CI 29.7 to 44.8%). For one-stage revision, the failure rate was 23.6% (CI 17.2 to 32.4%) after 60 days and 27.6% (20.8 to 36.8%) after one year. The risk for failure was highest in patients with a KLIC score ≤2; however, the results from these groups were imprecise and CIs overlapped with those of the other groups (Table 3).

Prognostic Performance of the KLIC Score

KLIC score had a moderate predictive value for early failure after DAIR for early PJI, as a one-point increase in KLIC score represented a 1.45 (CI 1.13 to 1.90) times higher risk of failure. For one-stage revision, an increase in KLIC score was slightly predictive of failure; however, the CIs (OR 1.20, CI 0.93 to 1.56) included the zero change. At one-year follow-up, no association between KLIC score and risk of failure was observed (Table 4).

The AUC of the KLIC score for DAIR was 0.63 (CI 0.55 to 0.72) after 60-day follow-up and 0.53 (CI 0.44 to 0.63) after one-year follow-up, indicating low discriminative ability. For one-stage revisions, the AUCs were similar to those for DAIR, being 0.56 (CI 0.46 to 0.66) after 60-day follow-up and 0.58 (CI 0.46 to 0.69) after one-year follow-up (Table 4 and Figure 1).

In bivariate logistic regression analyses for categorized KLIC score, a score higher than 4.5 showed the best predictive ability after PJI treated with DAIR, as the risk of failure was 4-fold (OR 4.0, CI 1.95 to 8.62) among those patients in 60-day follow-up. However, the sensitivity of this model was only 0.44 (Table 4).

The calibration curves for each of the models are presented in Figure 2. On average, the prognostic performance for failure after DAIR was poor after both 60 days and 1 year because the KLIC score either underestimated or overestimated the risk of failure. However, the predictive capability was better for one-stage revision, as the model was almost ideal for predicting failure within 60 days, especially among patients who had a risk of failure higher than 40% (Figure 2).

The DCA results indicated that the model did not offer a remarkable net benefit across a range of threshold probabilities. Indeed, the model's net benefit curve consistently remained below both the “full treatment” line (representing treating all patients) and the “no treatment” line (representing treating none of the patients) within almost the full range of threshold probabilities. This suggests that using the model to guide treatment decisions does not provide any additional clinical utility beyond the baseline strategies (Supplementary Figures 2 and 3).

Table 2
Background Characteristics of the Study Sample.

Variable	DAIR (n = 159)	One-Stage (n = 123)
Patient characteristics		
Age, mean (SD)	69.7 (10.4)	68.8 (13.1)
BMI, mean (SD)	30.2 (5.7)	29.9 (6.0)
Female, n (%)	89 (60.0)	60 (48.8)
Joint, n (%)		
Knee	64 (40.3)	89 (72.4)
Hip	95 (59.7)	34 (27.6)
Comorbidities, n (%)		
ASA score, mean (SD)	2.8 (0.7)	2.8 (0.7)
ASA score ≥4	16 (10.1)	12 (9.8)
Renal failure	5 (3.1)	3 (2.4)
Liver cirrhosis	<3[a]	0
CRP, mg/L		
≥115 mg/L, n (%)	144 (90.6)	112 (91.1)
Previous surgery type, n (%)		
Primary	94 (59.1)	99 (80.5)
Revision	36 (22.6)	12 (9.8)
Fracture	29 (18.2)	12 (9.8)
Age of the prosthesis, d, mean (SD)	18.5 (10.7)	24.9 (16.7)
Cemented prosthesis, n (%)	132 (83.0)	79 (64.2)
KLIC score, n (%)		
Mean (SD)	4.6 (1.4)	3.9 (1.4)
≤2	10 (6.3)	8 (6.5)
2.5–3.5	15 (9.4)	40 (32.5)
4–4.5	85 (53.5)	56 (45.5)
5–6	44 (27.7)	16 (13.0)
>6	5 (3.1)	3 (2.4)

DAIR, debridement, antibiotics, and implant retention; d, days; SD, standard deviation; ASA, American Society of Anesthesiology; CRP, C-reactive protein; BMI, body mass index.
[a] Due to Finish legislation, <3 frequencies cannot be reported as exact values.

Table 3
Risk of Failure After PJI Revision Surgery Stratified by the Surgical Technique.

Group	60 d	1 y
DAIR		
All revisions	28.9% (22.7 to 36.9%)	36.5% (29.7 to 44.8%)
KLIC score ≤2	40% (18.7 to 85.4%)	60% (26.9 to 92.9%)
KLIC score 2.5–3.5	33% (16.3 to 68.2%)	33% (16.3 to 68.2%)
KLIC score 4–4.5	24.7% (17.0 to 35.8%)	29.4% (21.2 to 40.9%)
KLIC score >4.5	32.7% (21.8 to 48.8%)	46.9% (34.9 to 63.2%)
One-stage		
All revisions	23.6% (17.2 to 32.4%)	27.6% (20.8 to 36.8%)
KLIC score ≤2	37.5% (15.3 to 91.7%)	50% (25.0 to 100%)
KLIC score 2.5–3.5	12.5% (5.5 to 28.4%)	12.5% (5.5 to 28.4%)
KLIC score 4–4.5	26.8% (17.4 to 41.3%)	30.4% (20.4 to 45.1%)
KLIC score >4.5	31.6% (16.3 to 61.2%)	42.1% (24.9 to 71.3%)

Failure rates were calculated with the Kaplan-Meier estimator. Results are presented with 95% confidence intervals. DAIR, debridement, antibiotics, and implant retention.

Discussion

In the present study, we aimed to externally validate the KLIC score in a Northern European cohort and to examine whether the KLIC score is predictive for early PJIs treated with one-stage revision. Our results reveal that although an increase in the KLIC score is associated with an increased risk of early failure, its discriminative ability is poor. Furthermore, using the model to guide treatment decisions does not provide any additional value beyond the baseline strategies.

There are three separate studies that have previously reported that the KLIC score is valid and clinically useful [8–10]. In two of the studies [8,10], however, the definition of failure differed from that in the original development study of the KLIC score [7]. Furthermore, acute hematogenous infections were included in one of the studies [10]. In the third study, Löwik et al examined early failures

Table 4
Prognostic Performance of the KLIC Score.

Group	60-d Outcomes						1-y Outcomes					
	AUC (95% CI)	OR (95% CI)	SEN	SPE	PPV	NPV	AUC (95% CI)	OR (95% CI)	SEN	SPE	PPV	NPV
DAIR												
KLIC score, one-unit increase	0.63 (0.55 to 0.72)	1.45 (1.13 to 1.90)	-	-	-	-	0.53 (0.44 to 0.63)	1.14 (0.90 to 1.46)	-	-	-	-
KLIC >2	0.50 (0.46 to 0.54)	1.04 (0.28 to 3.89)	0.94	0.06	0.51	0.5	0.48 (0.44 to 0.52)	0.55 (0.14 to 2.07)	0.91	0.05	0.35	0.5
KLIC >3.5	0.53 (0.48 to 0.59)	1.69 (0.72 to 4.14)	0.88	0.19	0.53	0.6	0.49 (0.48 to 0.59)	0.83 (0.35 to 2.06)	0.83	0.15	0.36	0.6
KLIC >4.5	0.64 (0.57 to 0.71)	4.0 (1.95 to 8.62)	0.44	0.82	0.73	0.59	0.57 (0.49 to 0.65)	1.90 (0.95 to 3.79)	0.40	0.74	0.47	0.68
One-stage												
KLIC score, one-unit increase	0.56 (0.46 to 0.66)	1.20 (0.93 to 1.56)	-	-	-	-	0.58 (0.46 to 0.69)	1.26 (0.95 to 1.69)	-	-	-	-
KLIC >2	0.59 (0.44 to 0.53)	0.67 (0.15 to 2.95)	0.92	0.05	0.4	0.5	0.46 (0.40 to 0.52)	0.35 (0.08−1.58)	0.88	0.04	0.26	0.5
KLIC >3.5	0.56 (0.47 to 0.65)	1.66 (0.79 to 3.57)	0.68	0.44	0.45	0.67	0.59 (0.50 to 0.68)	2.17 (0.93 to 5.39)	0.74	0.44	0.33	0.81
KLIC >4.5	0.54 (0.47 to 0.61)	1.78 (0.66 to 4.84)	0.2	0.88	0.53	0.62	0.56 (0.48 to 0.64)	2.18 (0.77 to 5.99)	0.24	0.88	0.42	0.75

DAIR, debridement, antibiotics, and implant retention; CI, confidence interval; AUC, area under the curve; SEN, sensitivity; SPE, specificity; PPV, positive predictive value; NPV, negative predictive value.

after DAIR in a Southern European cohort and reported a 38.3% risk of failure within the first 60 postoperative days [9]. In their study, a one-unit increase in KLIC score increased the risk of failure by 1.32-fold, which is in line with the results of our study. They also reported a sensitivity of 52.2% and a specificity of 70.9% for patients with a KLIC score $\geq$6. In our study, the specificity for patients who had a KLIC score $\geq$5 had a 44% sensitivity and 82% specificity. Moreover, when it comes to the AUC of the continuously analyzed KLIC score, our results were also similar, as Löwik et al reported an AUC of 0.64. Interestingly, the cohort in the study by Löwik et al was also similar to ours in terms of prevalence of liver cirrhosis, indications of the index surgery, and the proportion of cemented prostheses in the index operation. The biggest difference between the cohorts was that the prevalence of kidney failure was less common in our cohort, although the microbiological profiles between the cohorts were similar.

Chalmers et al and Bernaus et al have previously reported that the KLIC score is not a useful method for predicting early failure after the DAIR procedure [12,13]. However, although the AUC from Chalmers et al was 0.637, which is the same as the AUC reported by Löwik et al, the conclusion they made was completely different [9,12]. These studies clearly demonstrated that the discrimination abilities of the KLIC score are not remarkable, as AUCs between 0.6 and 0.7 are generally considered poor [21]. In addition, AUCs should

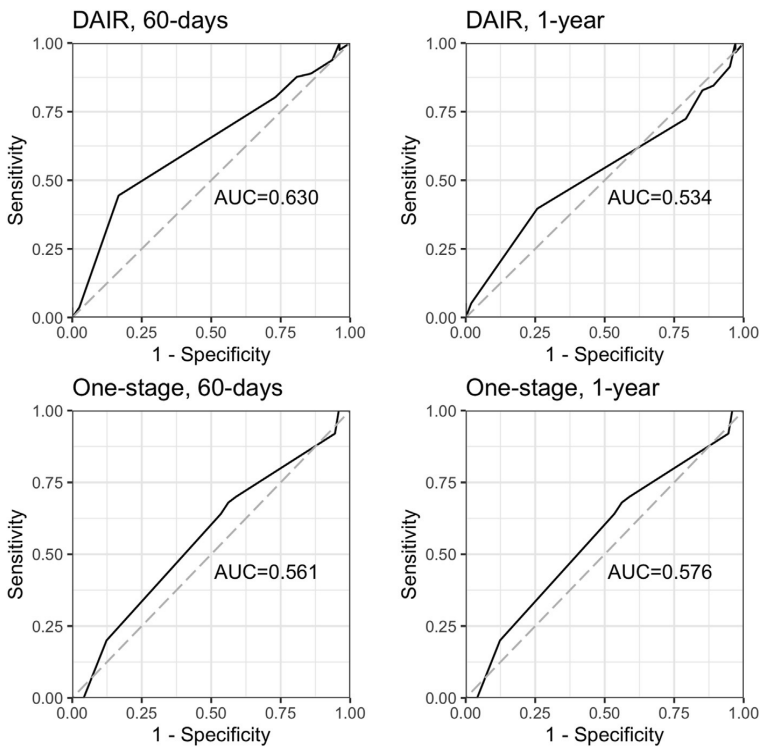

Fig. 1. Receiver operating characteristics (ROC) curves for the KLIC score stratified by the type of surgery and follow-up time. DAIR, debridement, antibiotics, and implant retention; AUC, area under the curve.

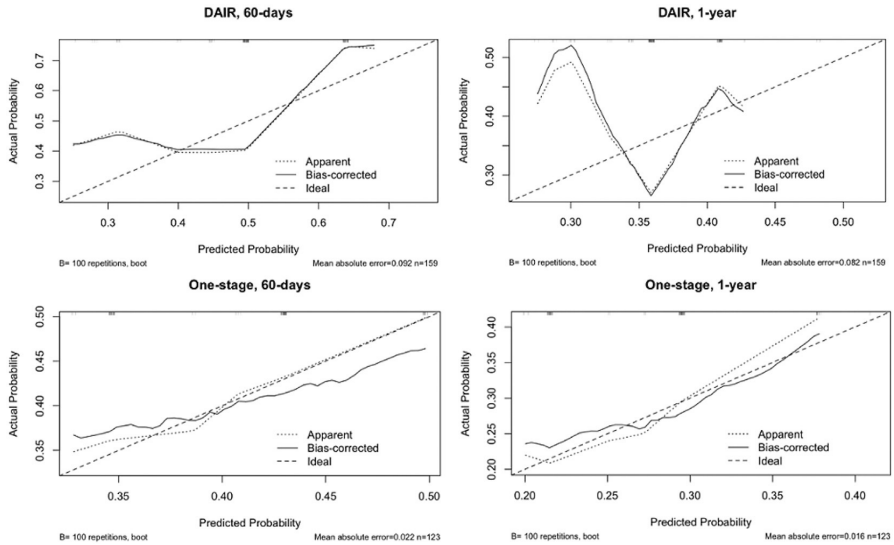

Fig. 2. Calibration curves stratified by the type of surgery and follow-up time. On the x-axis are the predicted probabilities and on the y-axis are the observed probabilities. A perfectly calibrated model would follow the straight dashed line referred to as "ideal" in the graph. Calibration was modeled with bootstrapping using 100 repetitions. DAIR, debridement, antibiotics, and implant retention.

not be used alone to evaluate the prognostic ability of a certain prediction model, as it is only a measure of the discriminative validity of the model and not a measure of the clinical validity [22]. In addition to the AUC, the sensitivity and specificity of the prediction models are important when assessing the clinical utility because they provide additional information on clinical capabilities.

Therefore, the poor predictive ability of the KLIC score might have been because the comorbidities that affect the KLIC score were rare in our patient cohort. Indeed, the prevalence of both liver cirrhosis and renal failure in our cohort was very low, and thus their effect on the total KLIC score was minimal. When the prevalence of a certain condition measured by the prediction score is very low, it produces a selection bias to the observed results and affects the interpretation of the clinical utility of the model. The KLIC score was developed in Southern Europe [7] where the comorbidity burden differs from that seen in Northern Europe. It is likely, therefore, that this influenced the accuracy of the KLIC score in our cohort.

One might consider whether a prediction score is useful in clinical practice if it only identifies those patients who are at very high risk. In other words, when developing prediction models, we should consider whether the prediction score provides additional value to clinical decision-making without increasing the risk of delaying treatment. Future research should focus on the predictors of failure after DAIR or one-stage revision due to early PJI, as it seems the KLIC score is not a valid method for discriminating those patients who have an increased risk of failure in a Northern European patient population.

Potential Limitations

The present study has some potential limitations. Our results were obtained from a single center; therefore, we cannot be sure about its applicability to other centers. It is evident that reoperation indications might differ between centers, which can have a direct impact on the observed failure rates, and hence, the validity assessments of the KLIC score. However, as our institution is a public hospital where patients from all socioeconomic backgrounds are treated, our patient cohort can be considered a representative sample of the Northern European population. Also, due to the retrospective setting of the study, the patient selection process for treatment strategies might not have been entirely conclusive, raising the possibility of introducing selection bias. This is a prevalent concern in PJI research and can only be adequately resolved through a prospective study. Nevertheless, all patients were treated according to institutional guidelines at a single institution, which aimed to mitigate any potential selection bias. In addition, due to a rather healthy cohort and the single-center setting, our subgroup analyses for certain groups were small in sample size and lacked statistical power. However, whereas a multicenter setting could have resulted in a larger sample size, the risk of selection bias is increased if treatment decisions are not made by the same surgeons, especially in a retrospective study setting. Furthermore, the distribution of previous surgery types differed between hips and knees, evidently influencing the choice of revision strategies, which might introduce confounding bias to our results.

Conclusions

In conclusion, we have demonstrated that the KLIC score is not a reliable predictor of early failure after early PJI in a Northern European cohort. Furthermore, its predictive ability is simply not high enough for clinical application. Therefore, further studies on patient-specific prognosis after early PJI are warranted.

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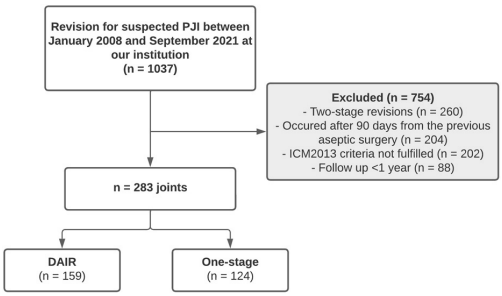
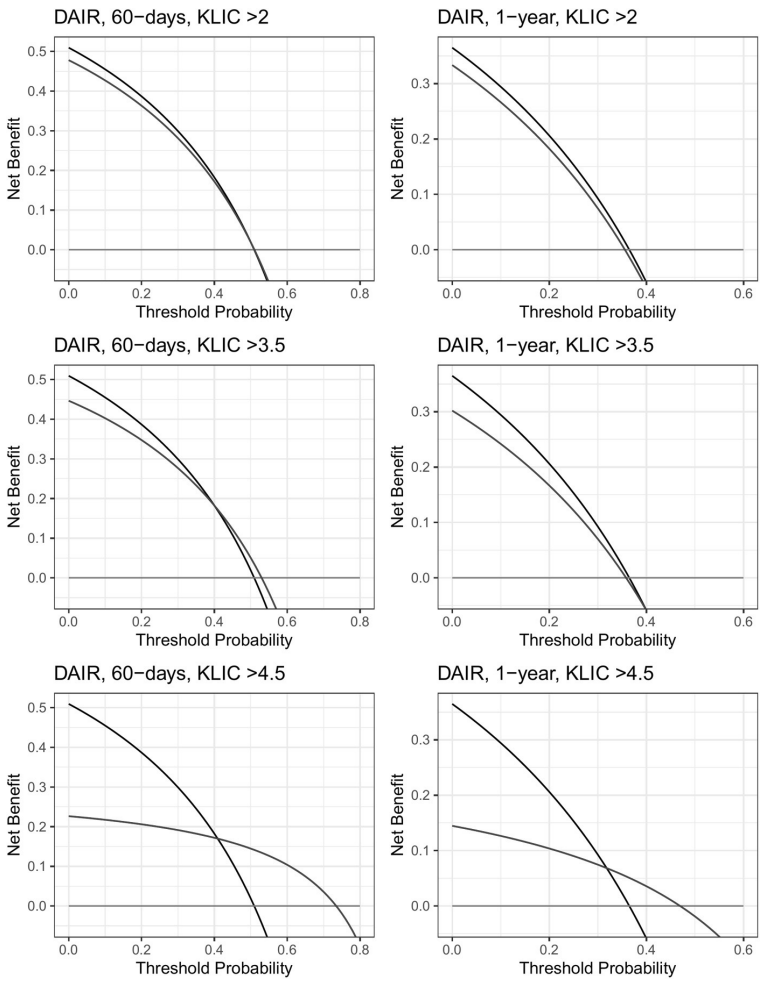
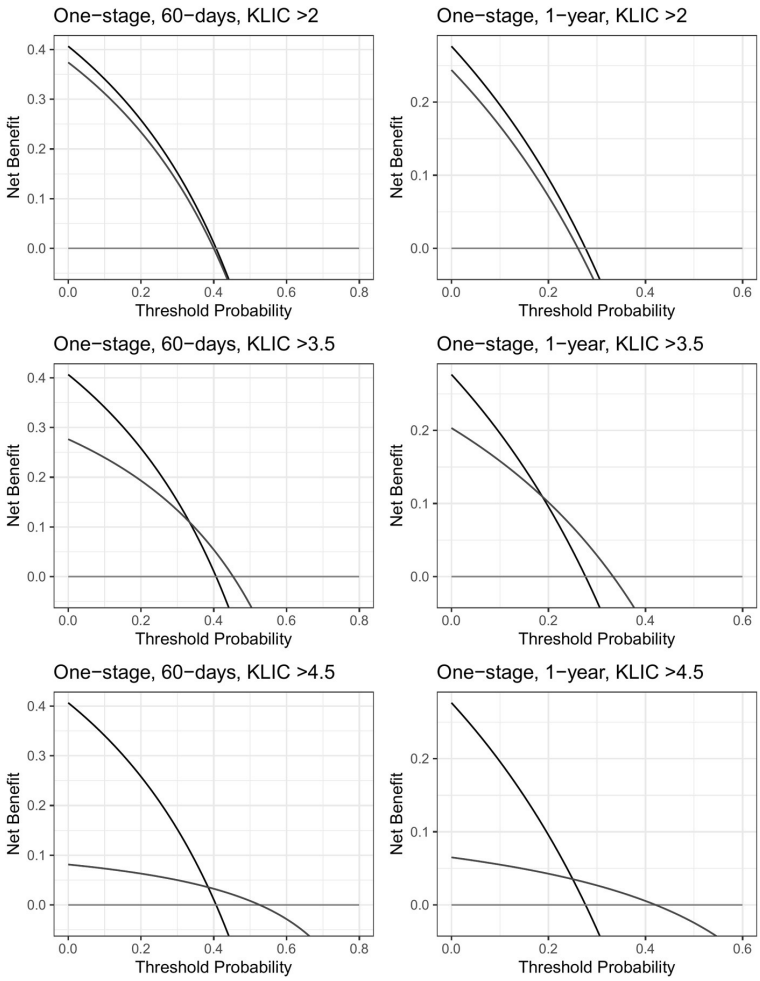


Supplementary Figure 1. Flowchart of the patients at our institution between January 2008 and September 2021. PJI, prosthetic joint infection; DAIR, debridement, antibiotics, and implant retention.



Supplementary Figure 2. Decision-curve analysis curves for DAIR stratified by the type of the surgery and length of follow-up time. The black line represents the "treat all" scenario, the blue line represents the "treat above specific KLIC-score" scenario. The red line represents the scenario where no patients are treated, and hence the net benefit is zero (no true-positive and no false-positive classifications). The graph gives the expected net benefit per patient relative to no treatment in any patient ("Treat none"). If the model curve is above the no treatment line, it suggests that using the model is beneficial across a range of threshold probabilities. If the model curve is above the full treatment line, it suggests that the model outperforms treating all patients at some threshold probabilities. DAIR, debridement, antibiotics, and implant retention.



Supplementary Figure 3. Decision-curve analysis curves for one-stage revisions stratified by the type of the surgery and length of follow-up time. The black line represents the "treat all" scenario, the blue line represents the "treat above specific KLIC-score" scenario. The red line represents the scenario where no patients are treated, and hence the net benefit is zero (no true-positive and no false-positive classifications). The graph gives the expected net benefit per patient relative to no treatment in any patient ("Treat none"). If the model curve is above the no treatment line, it suggests that using the model is beneficial across a range of threshold probabilities. If the model curve is above the full treatment line, it suggests that the model outperforms treating all patients at some threshold probabilities.

Supplementary Table 1
Microbiological Findings from Intraoperative Tissue Specimens.

Microbe	DAIR (n = 159), n (%)[a]	One-Stage (n = 123), n (%)[a]
Staphylococcus aureus	63 (39.6)	58 (47.2)
Coagulase negative *Staphylococcus*	61 (38.4)	29 (23.6)
Beta-haemolytic streptococci	12 (7.5)	18 (14.6)
Other streptococcus species	<3[b]	0
Gram-negative aerobic	9 (5.7)	9 (7.3)
Enterococcus species	7 (4.4)	8 (6.5)
Anaerobic	4 (2.5)	<3[b]
Other	9 (5.7)	<3[b]
Negative culture	26 (16.4)	15 (12.2)
Polymicrobial	28 (17.6)	17 (13.8)

DAIR, debridement, antibiotics, and implant retention.
[a] As microbiological findings from the polymicrobial infections are included, the total N is greater than the total N of surgeries performed.
[b] due to Finish legislation, <3 frequencies cannot be reported as exact values.